

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-658**

**CHEMISTRY REVIEW(S)**

## NDA 21-658

### Alvesco (ciclesonide) Inhalation Aerosol 80 and 160 mcg/inhalation (ex-actuation)

#### Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

**Applicant:** Nycomed GmbH

**Indication:** Maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 12 years of age and older.

**Presentations:** 80 mcg and 160 mcg in canisters of 60 and 120 actuations/canister

**Consults:** EER Status: Acceptable. Dec. 13, 2007  
Pharm/Tox: Acceptable. Sept. 22, 2004  
DEMETS: Acceptable. Mar. 29, 2004  
Microbiology: Acceptable. Apr. 04, 2004

**Discussion:** The CMC review for the original application was recommended for approval (see Chem. Review # 1 in DFS). There is also a Chemistry Division Director Review in the DFS dated Oct. 21, 2004 which concluded that the application is recommended for approval from the CMC perspective. However, the application was not approved for clinical reasons. Consequently, the sponsor resubmitted the NDA which contained additional CMC information (amendments) and responses to some CMC requests as outlined in the approvable letter dated June 10, 2004. The additional information and the responses were reviewed and found acceptable.

**Conclusion:** From a CMC perspective the application is recommended for an approval action.

Ali Al-Hakim, Ph.D.  
Branch Chief  
Branch II/DPA I/ONDQA

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/s/

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Ali Al-Hakim  
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**NDA 21-658**

**Alvesco (ciclesonide) Inhalation Aerosol  
80, 160 mcg/actuation**

**b(4)**

**CHEMISTRY DIVISION DIRECTOR REVIEW**

Applicant: Aventis Pharmaceuticals, Inc.

Indication: Proposed: Maintenance treatment of asthma as prophylactic therapy in adult and \_\_\_\_\_, years of age or older. Treatment of pts requiring oral corticosteroid therapy for asthma management.

**b(4)**

Presentations: \_\_\_\_\_, 80 mcg, 160 mcg in canisters of 60 and 120 actuations/canister

EER Status: pending – Inspection of the \_\_\_\_\_ site in \_\_\_\_\_ is scheduled to begin 22-OCT-2004. Due to non-approvability of the NDA (additional clinical trials needed) action may be taken without a final OC recommendation.

**b(4)**

Consults: DMETS – no labeling this cycle  
Statistics – none  
Micro - none  
EA – none – waiver granted

The Alvesco NDA was submitted 23-DEC-2003

**b(4)**

The **drug substance** is manufactured by \_\_\_\_\_  
The manufacturing and controls are adequately described in DMF ' \_\_\_\_\_. The DS is manufactured from \_\_\_\_\_. The specification is adequate, however acceptance will be based upon ID and COA only. The acceptance testing must comport with 21 CFR 211.84. Full testing must be done periodically – this is a GMP issue.

**Conclusion**

Drug substance is acceptable.

The **drug product** is formulated in \_\_\_\_\_, and is manufactured by \_\_\_\_\_  
\_\_\_\_\_. The "packaging" components are all covered by DMFs and all are acceptable. Extractables and leechables issues were exhaustively investigated and adequate controls have been established.

**b(4)**

The Pharmaceutical Development Report establishes good product performance characteristics for all presentations for dose proportionality/actuation, respirable fraction particle size distribution at start and end of actuations, and number of shots /canister. The effect of — content on PSD and DCU is also well established. Justification for critical manufacturing controls was also presented and is acceptable. No performance differences were seen at various canister orientations.

b(4)

Submitted stability data support a 24 month expiry. Note that an increase in — content was observed on stability but had no deleterious effect on impurities and PSD. No differences between clinical vs non-clinical batches were observed. The stability protocol is acceptable.

b(4)

Specifications are considered adequate.

CMC labeling review was done but comprehensive labeling review has been deferred.

All associated DMFs are acceptable.

#### **Conclusion**

Drug product and device are acceptable – several agreements have been made – a time-frame for these agreements needs to be established.

#### **Overall Conclusion**

From a CMC perspective the application is recommended for an approval action.

Eric P. Duffy, PhD  
Director, DNDC II/ONDC

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/s/

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Eric Duffy  
10/21/04 10:00:29 AM  
CHEMIST

# **Chemistry Review Cover Sheet**

**NDA 21-658**

**Alvesco (ciclesonide) Metered Dose  
Inhaler**

**Arthur B. Shaw, Ph.D.**

**ONDQA/DPA1 for DPADP**

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# Chemistry Review Data Sheet

1. NDA 21658
2. REVIEW #:2
3. REVIEW DATE: December 28, 2007
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

Document	Document Date	Comment
Original	23-Dec-2003	None
Chemist's Filing Memo	26-Feb-2004	Acceptable for filing. Additional info requested
74 Day Filing Letter	26-Feb-2004	Request info in Filing Memo
Amendment BC	04-Mar-2004	Response to Filing Letter 26-Feb-2004 Stability info t, Alcohol Content, Impurities
Amendment BC	10-Mar-2004	Response to Filing Letter 26-Feb-2004 Ciclesonide content
Amendment BC	02-Apr-2004	Partial response to Filing Letter 26-Feb-2004 Leachables, Spray Pattern, PSD, Nomenclature
Amendment BC	29-Apr-2004	Additional response to Filing Letter 26-Feb-2004
Memo to File	14-May-2004	Additional info request for PSD. Notification of DMF deficiencies
IR Letter	10-Jun-2004	Info request from 14-May-2004 memo
Amendment BC	08-Jul-2004	Response to 10-Jun-2004 IR Letter
Amendment BC	02-Aug-2004	Notification that amendment submitted to DMF
Amendment BC	04-Aug-2004	Notification that amendment submitted to DMF
Amendment BC	09-Aug-2004	Notification that amendment submitted to DMF
Amendment BC	16-Aug-2004	Notification that amendment submitted to DMF
Amendment BC	16-Sep-2004	Notification that amendment submitted to DMF
Amendment BC	22-Sep-2004	MV Package for Drug substance
Amendment BC	27-Sept-2004	Notification that amendment submitted to DMF
Amendment BC	30-Sep-2004	Change spec for leak rate
Amendment BC	06-Oct-2004	Change PSD spec
Memo to File	04-Oct-2004	Info request following initial complete draft
IR Letter	04-Oct-2004	Info request from 04-Oct-2004 memo (T-con)
AE Letter	21-Oct-2004	Includes commitments in response to IR Letter

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Amendment BL	21-Dec-2007	Revised label, carton and container label (via e-mail)
Amendment AZ	10-Jul-2007	Resubmission including addition of a dose counter
Amendment BC	15-Mar-2007	Change supplier of actuator
Amendment BC	20-Jun-2005	Report amendment to DMF
Amendment BC	19-Jan-2005	Report amendment to DMF

b(4)

## Additional FDA DOCUMENTS

Document	Document Date	Comment
Labeling Fax	14-Dec-2007	Request for target on top of dose counter Amend color of carton and container label
Labeling t-con	20-Dec-2007	Reiterate requests in labeling fax.

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Nycomed GmbH.  
Address: Byk-Gulden-Strasse 2  
D-78467 Konstanz Germany

Representative: George Chen  
Nycomed US Inc.  
210 Park Avenue  
Florham Park NJ

Telephone: 973 514-4271

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Alvesco  
b) Non-Proprietary Name (USAN): ciclesonide  
c) Code Name/# None provided  
d) Chem. Type/Submission Priority
- Chem. Type: 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: N/A

## 10. PHARMACOL. CATEGORY: Corticosteroid

## 11. DOSAGE FORM: Inhalation aerosol

## 12. STRENGTH/POTENCY: 80, and 160 µg/inhalation (ex-actuator)

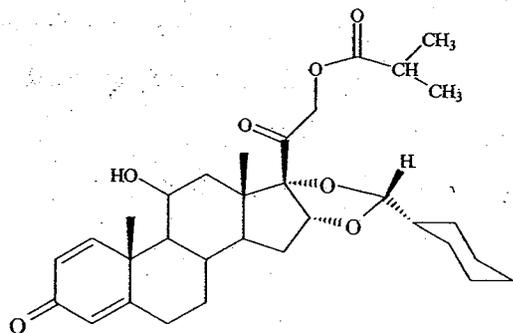
## 13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED:  Rx  OTC

## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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

(2'R)-2'Cyclohexyl-11b-hydroxy-21-isobutyryloxy-16bH-dioxolo[5',4':16,17]pregna-  
1,4-diene-3,20-dione



$C_{32}H_{44}O_7$ . 540.69

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED
_____	II	_____	_____	Adequate	21-Dec-2007
_____	III	_____	_____	Adequate	21-Dec-2007
_____	III	_____	_____	Adequate	30-Nov-2007
_____	III	_____	_____	Adequate	21-Dec-2007
_____		_____	_____	Adequate	06-Dec-2007
16740	III	Trudell Medical International	Top Mount Dose Indicator as Manufactured in Ontario, Canada.	Adequate	Not reviewed

DMF 16740 was not reviewed because none of the parts are in contact with the product. Suitability is determined as part of product performance in the NDA. **ACCEPTABLE**

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	53,391	Ciclesonide MDI

## 18. STATUS:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A		
EES	All sites <b>ACCEPTABLE</b>	13-Dec-2007	N/A
Pharm/Tox	Acceptable for leachables	15-Sep-2004	Huiqing Hao
	Acceptable for S-epimer	01-Sep-2004	
	Acceptable for foreign particulates	22-Sep-2004	
Methods Validation	Not submitted		
DMETS	Proprietary name <b>ACCEPTABLE</b>	29-Mar-2004	Denise Toyer
EA	N/A		
Microbiology	<b>ACCEPTABLE</b>	04-Apr-2004	Bryan Riley

# The Chemistry Review for NDA 21-658

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application may be approved with the dose counter from a CMC point of view.

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

None

### II. Summary of Chemistry Assessments

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

##### 1. Drug Substance

The drug substance is a corticosteroid and is a white to yellowish powder. It is freely soluble in ethanol and is \_\_\_\_\_ It is \_\_\_\_\_

b(4)

##### 2. Drug Product

The drug product is a solution of ciclesonide in \_\_\_\_\_ dehydrated ethanol with HFA-134a (a non-CFC propellant) as the propellant. The solution is filled into an aluminum canister at two different fills (60 actuations and 120 actuations) and sealed with a metering valve. A plastic actuator is included as part of the finished drug product. The valve is designed to deliver the drug accurately at \_\_\_\_\_ different strengths (ex-actuator) 80µg and 160µg/actuation.

b(4)

The Pharmaceutical Development Report (PDR) supports the choice of ethanol content, the number of priming shots required (in the label), and the lack of a need for shaking prior to use (in the label).

The specifications include tests and acceptance criteria for ciclesonide content, leak rate, valve delivery, impurities, Particle Size Distribution (PSD) and delivered dose ex-actuator (Dose Content Uniformity =DCU). All of the acceptance criteria are acceptable. The range of the acceptance criteria for measurement of mean values of the PSD ensures that the amount of drug in a particular size range ( \_\_\_\_\_ µ) is within \_\_\_\_\_ of the label claim. This range is typical of the best MDIs and is well-justified.

b(4)

The acceptance criteria for the leak rate proposed by the applicant are acceptable, with NMT \_\_\_\_\_ out of \_\_\_\_\_ units having a leak rate of more than \_\_\_\_\_ mg/year. The levels of most impurities are below \_\_\_\_\_ % and do not change on storage. The only impurity present on significant amounts, the \_\_\_\_\_ of ciclesonide, has been qualified at \_\_\_\_\_ %.

b(4)

The drug is stable, showing no trends over time for ciclesonide content, impurities, PDS or DCU.

The dose counter added in the July 10, 2007 resubmission has been shown to undercount by more than \_\_\_\_\_ of the cases. This amount of undercounting has been evaluated, taking into account the acceptance criteria for the fill weights, the ciclesonide content, and the leak rate, as well as the process capability of the fill and found acceptable. Investigations by the applicant demonstrated that the undercounting was most likely due to actuating the canister off-center. The instructions to the patient provide clear directions to fire the canister on-center, which will minimize the likelihood of undercounting..

b(4)

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

Maintenance treatment of asthma as prophylactic therapy in adult and adolescent patients 12 years of age and older.

ALVESCO is NOT indicated for the relief of acute bronchospasm.

**C. Basis for Approvability or Not-Approval Recommendation**

The drug product is manufactured and controlled to ensure that an adequate amount of drug will reach its target site in the lung consistently up to the labeled number of actuations on the label.

**III. Administrative**

See DFS

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Chemistry-1

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/s/

Arthur B. Shaw  
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C hen rEview #2

Ali Al-Hakim  
12/31/2007 01:03:17 PM  
CHEMIST

**Chemistry Review Cover Sheet**

**NDA 21-658**

**Alvesco (ciclesonide) Metered Dose  
Inhaler**

**Arthur B. Shaw, Ph.D.  
DNDC2/DPADP**

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NDA 21-658 Chemistry Review #1

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# Chemistry Review Data Sheet

1. NDA or ANDA 21-658
2. REVIEW #:1
3. REVIEW DATE: July 24, 2004
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Comment</u>
Original	23-Dec-2003	None
Amendment BC	04-Mar-2004	Response to Filing Letter 26-Feb-2004 Stability info Content, Alcohol Content, Impurities
Amendment BC	10-Mar-2004	Response to Filing Letter 26-Feb-2004 Ciclesonide content
Amendment BC	02-Apr-2004	Partial response to Filing Letter 26-Feb-2004 Leachables, Spray Pattern, PSD, Nomenclature
Amendment BC	29-Apr-2004	Additional response to Filing Letter 26-Feb-2004
Amendment BC	08-Jul-2004	Response to 10-Jun-2004 IR Letter
Amendment BC	02-Aug-2004	Notification that amendment submitted to DMF
Amendment BC	04-Aug-2004	Notification that amendment submitted to DMF
Amendment BC	09-Aug-2004	Notification that amendment submitted to DMF
Amendment BC	16-Aug-2004	Notification that amendment submitted to DMF
Amendment BC	16-Sep-2004	Notification that amendment submitted to DMF
Amendment BC	22-Sep-2004	MV Package for Drug substance
Amendment BC	27-Sept-2004	Notification that amendment submitted to DMF
Amendment BC	30-Sep-2004	Change spec for leak rate
Amendment BC	06-Oct-2004	Change PSD spec

<u>FDA Documents</u>	<u>Document Date</u>	<u>Comment</u>
Chemist's Filing Memo	26-Feb-2004	Acceptable for filing. Additional info requested
74 Day Filing Letter	26-Feb-2004	Request info in Filing Memo
Memo to File	14-May-2004	Additional info request for PSD. Notification of DMF deficiencies
IR Letter	10-Jun-2004	Info request from 14-May-2004 memo
Memo to File	04-Oct-2004	Info request following initial complete draft
IR Letter	04-Oct-2004	Info request from 04-Oct-2004 memo (T-con)

b(4)

7. NAME & ADDRESS OF APPLICANT:

Name: Aventis Pharmaceuticals, Inc.  
Address: 200 Crossing Blvd., Route 202-206  
P.O. Box 6890  
Bridgewater NJ 08807-0890  
Representative: Daniel Bollag  
Telephone: 908 304-6431

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Alvesco  
b) Non-Proprietary Name (USAN): ciclesonide  
c) Code Name/# None provided  
d) Chem. Type/Submission Priority  
• Chem. Type: 1  
• Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Corticosteroid

11. DOSAGE FORM: Inhalation aerosol (note applicant uses term "Metered Dose Inhaler" in the cover letter and in the 356h but the dosage form name is correct on the label.)

**b(4)**

12. STRENGTH/POTENCY: —, 80, and 160 µg/inhalation (ex-actuator)

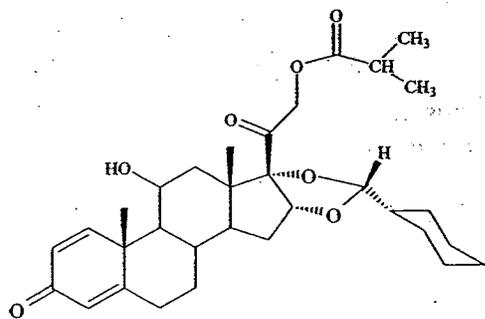
13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED:  X  Rx   OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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

(2'R)-2'Cyclohexyl-11b-hydroxy-21-isobutyryloxy-16bH-dioxolo[5',4':16,17]pregna-1,4-diene-3,20-dione



C<sub>32</sub>H<sub>44</sub>O<sub>7</sub>. 540.69

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>2</sup>	DATE REVIEW COMPLETE D
	II			Adequate *	07-Jul-2004
	III			Adequate*	24-May-2004
	III			Adequate	05-Oct -2004
	III			Adequate	24-May-2004
	IV			Adequate*	04-May-2004

b(4)

\* IR letter sent Response received. Review pending

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	53,391	Ciclesonide MDI

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	All sites ACCEPTABLE except <del>not</del> not inspected yet.	N/A	
Pharm/Tox	Acceptable for leachables	15-Sep-2004	Huiqing Hao
	Acceptable for <del>leachables</del>	01-Sep-2004	
	Acceptable for foreign particulates	22-Sep-2004	
Methods Validation	Not submitted		
DMETS	Proprietary name ACCEPTABLE	29-Mar-2004	Denise Foyer
EA	N/A		
Microbiology	ACCEPTABLE	04-Apr-2004	Bryan Riley

b(4)



# The Chemistry Review for NDA 21-658

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is approvable pending completion of a satisfactory inspection of the manufacturing plant for the \_\_\_\_\_ . The inspection is scheduled for October 22, 2004.

b(4)

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

None

### II. Summary of Chemistry Assessments

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

##### 1. Drug Substance

The drug substance is a corticosteroid and is a white to yellowish powder. It is freely soluble in ethanol and is \_\_\_\_\_

b(4)

##### 2. Drug Product

The drug product is a solution of ciclesonide in \_\_\_\_\_ dehydrated ethanol with HFA-134a (a non-CFC propellant) as the propellant. The solution is filled into an aluminum canister at two different fills (80 actuations and 120 actuations) and sealed with a metering valve. A plastic actuator is included as part of the finished drug product. The valve is designed to deliver the drug accurately at \_\_\_\_\_ different strengths (ex-actuator) \_\_\_\_\_  $\mu\text{g}$ , 80  $\mu\text{g}$ , and 160  $\mu\text{g}$ /actuation.

b(4)

The Pharmaceutical Development Report (PDR) supports the choice of ethanol content, the number of priming shots required (in the label), and the lack of a need for shaking prior to use (in the label).

The specifications include tests and acceptance criteria for ciclesonide content, leak rate, valve delivery, impurities, Particle Size Distribution (PSD) and delivered dose ex-actuator (Dose Content Uniformity =DCU). All of the acceptance criteria are **ACCEPTABLE**. The range of the acceptance criteria for measurement of mean values of the PSD ensures that the amount of drug in a particular size range (\_\_\_\_\_  $\mu\text{m}$ ) is within \_\_\_\_\_ of the label claim. This range is typical of the best MDIs and is well-justified.

b(4)

The acceptance criteria (\_\_\_\_\_ %) for the ciclesonide content are wider than can be justified by the batch data. However since the drug does not exhibit even a mild dose response relationship, releasing drug product that is at the extremes of the acceptance criteria for ciclesonide content is unlikely to cause problems for

efficacy or safety.

The acceptance criteria for the leak rate proposed by the applicant could be a matter of concern because more drug product could leak out of the canister than is permissible to ensure that there is sufficient drug remaining in the canister at the end of shelf life AND when all the labeled shots have been delivered. However since this drug product specifically labeled to NOT be used in cases of acute bronchospasm, this concern does present a safety issue.

The levels of most impurities are below \_\_\_\_\_ and do not change on storage. The only impurity present on significant amounts, the \_\_\_\_\_ has been qualified at - %.

The drug is stable, showing no trends over time for ciclesonide content, impurities, PDS or DCU.

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

The proposed drug product label is for "the maintenance treatment of asthma as prophylactic therapy in adult \_\_\_\_\_ - years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma management....ALVESCO is NOT indicated for the relief of acute bronchospasm."

It is intended for use \_\_\_\_\_ twice daily for patients 12 years old and older.

The drug product is manufactured and controlled to ensure that an adequate amount of drug will reach its target site in the lung consistently up to the labeled number of actuations on the label.

**C. Basis for Approvability or Not-Approval Recommendation**

The drug product is manufactured and controlled to ensure that an adequate amount of drug will reach its target site in the lung consistently up to the labeled number of actuations on the label.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Arthur B. Shaw, PhD., Chemist Name/October 7, 2004

Rik Lostritto, Ph.D., Chemistry Team Leader Name/ October 7, 2004

**C. CC Block**

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229 Page(s) Withheld

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Arthur B. Shaw  
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Richard Lostritto  
10/13/04 04:43:23 PM  
CHEMIST

REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date:** October 1, 2004

**From:** Arthur B. Shaw, Ph.D., Chemist, Division of Pulmonary and Allergy Drug Products,  
HFD-570

**To:** NDA 21-658

**Subject:** Information Request

The following issues have been identified in my initial review of this NDA and should be conveyed to the applicant.

Regarding the drug substance:

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.

Regarding the drug product:

b(4)

3 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**

/s/

-----  
Arthur B. Shaw  
10/1/04 03:40:08 PM  
CHEMIST  
Comments from CMC Initial Review

Richard Lostritto  
10/4/04 05:08:58 PM  
CHEMIST

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This is an electronic record  
of a document that has been  
electronically signed.

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 13, 2004

From: Arthur B. Shaw, Ph.D., Chemist, Division of Pulmonary and Allergy Drug Products,  
HFD-570

To: NDA 21-658

Subject: Mass Balance Request and DMF Deficiencies

In the filing memo dated February 26, 2004, the following discussion of the Particle Size Distribution was presented.

Particle Size Distribution

a. Specifications

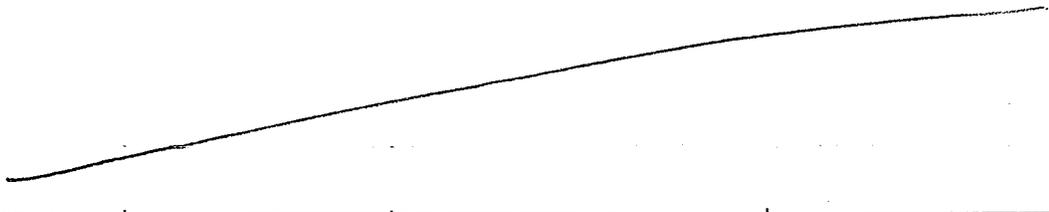
The specifications for the particle size distribution (PSD) are provided with no individual Impactor level data or mass balance data. (Section 3.2.p.5.1 Page 8)

Level 1

Test five units at the start of their label claim.

Compare the results to the level 1 specification limits. If any results fail to meet the level 1 specification limits, proceed to level 2.

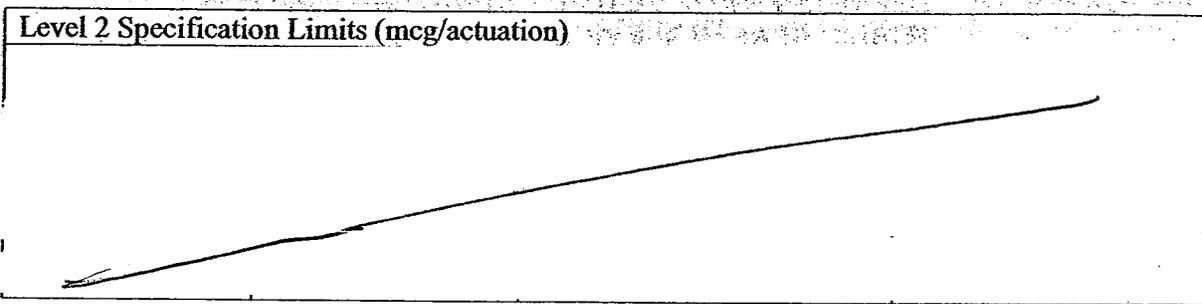
Level 1 Specification Limits (mcg/actuation)



Level 2

Compare the individuals from the level 1 testing to the level 2 specification limits. If NMT two of the five individual results are outside level 2 individual inner limits and none of the individuals are outside level 2 individual outer limits for any groupings, proceed to level 2. Test an additional five units at the start of their label claim.

The mean and all ten individual results (combined level 1 and 2) must meet the level 2 specification limits for all groupings.



b(4)

From Page 23 of the MDI-DPI Guidance:

“At the time of application submission, data for the mass amount of drug substance found on each accessory and each of the various stages of the \_\_\_\_\_ should be reported. In addition, data may also be presented in terms of the percentage of the mass found on the various stages and accessories relative to the label claim.”

In our letter dated March 5, 2004 we asked the applicant to provide the following (Question 7):

“For the Particle Size Distribution assay, provide the data for the mass amount of drug substance found on each accessory (throat, etc.) and each of the various stages of the \_\_\_\_\_ for all batches throughout the stability studies. Individual data points for all the data should be provided in tabular form as SAS transport files. Report the data for each strength (— 80 and 160µg) and fill amount (60 and 120 actuations) for the throat to jet, each numbered stage, and after the filter. In addition, provide the cut-off points in terms of particle diameter for the individual stage.”

We did not ask for any information regarding mass balance.

The applicant provided the particle size data in an amendment dated April 29, 2004. Preliminary analysis of this data set shows that the \_\_\_\_\_ stage numbers are tightly grouped for repeat samples and across the lifetime of the drug. However there are no acceptance criteria for the mass balance. In the calculation part of the procedure there is a calculation for “Material Balance,” defined by the applicant as “Drug recovery as % of delivered dose.”

The procedures are essentially the same for the three strengths. Each includes an equation:

$$Material\ Balance = \frac{T \times 100}{N(mcg)}$$

Where T = The total quantity of CICLESONIDE found in the stem and actuator (mcg).

← Sampler, aerosol valve

N = ← , depending on the strength.

**b(4)**

**APPEARS THIS WAY  
ON ORIGINAL**

The assay procedure calls for taking five shots. Since the dose (ex-valve) is 50, 100 or 200 µg, this is reasonable. Note that this value is not part of the System Suitability nor is it part of the specification. The applicant states that the range should be \_\_\_\_\_% but that is meaningless since it is not used in evaluating the assay.

b(4)

However, there is no calculation of mass balance in terms of the label claim. This information is necessary as part of the specification in order to endure adequate control of the particle size distribution. Furthermore the acceptance criteria should be \_\_\_\_\_.

**COMMENT:** Include acceptance criteria for mass balance as part of the product specification or as part of the System Suitability Test (SST) for the Particle Size Distribution. This should be calculated for particles collected on the \_\_\_\_\_ relevant to the label claim. Provide data to support the acceptance criteria. The expected acceptance criteria should be \_\_\_\_\_%. As part of your response you may include a tiered approach with appropriate actions to be taken if a batch (in the case of a specification) or a particular test run (in the case of an SST) falls outside this range.

b(4)

A number of DMFs used to support this NDA have been found to be deficient and the applicant should be informed.

**COMMENT:** The following DMFs referenced in your DMF have been found to be deficient and the holders informed:

DMF #	Holder Name	Subject of DMF	Date of Deficiency Letter
			05-May-2004
			06-Apr-2004

b(4)

Also a DMF used in support of DMF \_\_\_\_\_ as also been found deficient.

Additional information has been requested for \_\_\_\_\_  
 Manufactured In \_\_\_\_\_ in a letter dated May 14, 2004.  
 When you are notified that a DMF holder has responded to a DMF letter submit an amendment to the NDA stating the date of the DMF holder's response.

b(4)

Draft Letter to the Applicant:

1. Include acceptance criteria for mass balance as part of the product specification or as part of the System Suitability Test (SST) for the Particle Size Distribution. This should be calculated for particles collected on the \_\_\_\_\_ relevant to the label claim. Provide data to support the acceptance criteria. The expected acceptance criteria should be \_\_\_\_\_%. As part of your response you may include a tiered approach with appropriate actions to be taken if a batch (in the case of a specification) or a particular test run (in the case of an SST) falls outside this range.
2. The following DMFs referenced in your NDA have been found to be deficient and the holders informed:

b(4)

DMF #	Holder Name	Subject of DMF	Date of Deficiency Letter
I	_____	_____	05-May-2004
	_____	_____	06-Apr-2004
	_____	_____	

b(4)

Also a DMF used in support of DMF \_\_\_\_\_ has also been found deficient.

Additional information has been requested for DMF \_\_\_\_\_  
 Manufactured In \_\_\_\_\_ in a letter dated May 14, 2004.

b(4)

When you are notified that a DMF holder has responded to a DMF letter submit an amendment to the NDA stating the date of the DMF holder's response.

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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.**  
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/s/

-----  
Arthur B. Shaw  
5/13/04 03:57:03 PM  
CHEMIST  
PM send IR Letter

Richard Lostritto  
5/14/04 03:57:09 PM  
CHEMIST

REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
 PUBLIC HEALTH SERVICE  
 FOOD AND DRUG ADMINISTRATION  
 CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 25, 2004

From: Arthur B. Shaw, Ph.D., Chemist, Division of Pulmonary and Allergy Drug Products, HFD-570

To: NDA 21-658

Subject: Filing Review and Preliminary CMC issues to be communicated to applicant

The CMC section of this NDA is acceptable for filing.

There are a number of issues that should be communicated to the applicant.

1. The  $\curvearrowright$  content increases with time. Section 3.2.P.8.1 Page 32

Table P.8.1.4-4  $\curvearrowright$  Content of Ciclesonide Inhalers: Overall Trend Analysis For Ciclesonide  $\curvearrowright$  80 and 160mcg/actuation Inhaler, 60 Actuation, 25°C/ $\curvearrowright$  RH Inverted

Months on Stability	Mean $\curvearrowright$ Content (ppm)	Number of Individual Data Points	Number of Batches
0		36	9
3		36	9
6		36	9
9		36	9
12		24	6

b(4)

Page 40

Table P.8.1.4-6  $\curvearrowright$  Content of Ciclesonide Inhalers: Overall Trend Analysis For Ciclesonide  $\curvearrowright$  80 and 160mcg/actuation Inhaler, 120 Actuation, 25°C/ $\curvearrowright$  RH Inverted

Months on Stability	Mean $\curvearrowright$ Content (ppm)	Number of Individual Data Points	Number of Batches
0		108	27
3		108	27
6		108	27
9		108	27
12		108	27
18		52	13
24		48	12

b(4)

7 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**

/s/

Arthur B. Shaw  
2/25/04 05:30:12 PM  
CHEMIST

I added "spray pattern" for the specs

Richard Lostritto  
2/26/04 11:00:43 AM  
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21658/000	Action Goal:	
Stamp:	23-DEC-2003	District Goal:	12-NOV-2007
Regulatory Due:	11-JAN-2008	Brand Name:	ALVESCO MDI
Applicant:	NYCOMED US	Estab. Name:	(CICLESONIDE)
	220 PARK AVE	Generic Name:	CICLESONIDE
	FLORHAM PARK, NJ 07932		
Priority:	3S	Dosage Form:	(AEROSOL)
Org Code:	570	Strength:	80, AND 160 MCG

b(4)

Application Comment: RESUBMISSION JULY 7, 2007. ADDED DOES COUNTER AND NEW FUNCTIONS FOR ALTANA SITE RELATED TO DRUG PRODUCT TESTING (on 31-AUG-2007 by A. SHAW () 301-796-1460) STRENGTHS ARE INCORRECT. THEY SHOULD BE 80 AND 160 MCG (on 31-AUG-2007 by A. SHAW () 301-796-1460)

Contacts: A. GREEN 301-796-1219 , Project Manager  
A. SHAW 301-796-1460 , Review Chemist  
R. LOSTRITTO 301-796-2430 , Team Leader

Overall Recommendation: ACCEPTABLE on 13-DEC-2007 by S. ADAMS (HFD-322) 301-827-9051  
ACCEPTABLE on 04-SEP-2007 by S. ADAMS (HFD-322) 301-827-9051  
ACCEPTABLE on 22-OCT-2004 by S. ADAMS (HFD-322) 301-827-9051

Establishment: CFN \_\_\_\_\_ FEI \_\_\_\_\_

b(4)

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_

Responsibilities: \_\_\_\_\_

Profile: ADM OAI Status: NONE

E Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-JAN-2004				SHAWA
SUBMITTED TO DO	13-JAN-2004	PS			ADAMSS
FINISHED INSPECTION T	28-JAN-2004	PS			DAMBROGIOJ
INSPECTION SCHEDULED	11-AUG-2004		27-OCT-2004		ADAMSS
OC RECOMMENDATION	22-OCT-2004			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	
DO RECOMMENDATION	22-OCT-2004			ACCEPTABLE	ADAMSS
				INSPECTION	

BASED ON COMMENTS PROVIDED BY INVESTIGATOR DURING INSPECTION. INSPECTION IS STILL ONGOING HOWEVER AT THE CURRENT TIME NO MAJOR DEFICIENCIES HAVE BEEN FOUND.

SUBMITTED TO OC	03-DEC-2007				SHAWA
SUBMITTED TO DO	04-DEC-2007	GMP			ADAMSS
DO RECOMMENDATION	13-DEC-2007			ACCEPTABLE	ADAMSS

BASED ON FILE REVIEW

PREVIOUS EI COVERED APPLICATION. INSPECTION REQUEST WOULD HAVE BEEN SUBMITTED FOR FOLLOW

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

UP IF NOT FOR LATE SUBMISSION BY REVIEW TEAM AND PENDING PDUFA DATE ON JAN. 11, 2008.

OC RECOMMENDATION 13-DEC-2007 ACCEPTABLE ADAMSS  
DISTRICT RECOMMENDATION

Establishment: CFN 9611622 FEI 3002806615  
ALTANA PHARMA  
ROBERT BOSCH STRASSE 8  
SINGER, , GM D-78224

Responsibilities: AADA:  
DRUG SUBSTANCE OTHER TESTER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: OTHER TESTING IS MICROBIAL TESTING PRODUCT NOT        BUT INTENDED  
FOR INHALATION USE. (on 13-JAN-2004 by A. SHAW () 301-796-1460)  
THIS SITE HAS BEEN ADDED AS AN ALTERNATE DRUG PRODUCT RELEASE AND  
STABILITY TESTING SITE. NOTE THAT THESE ARE VERY DIFFERNT FUCNTIONS  
FORM THE DRUG SUSBTANCE TESTING. ANOTHER NEW FRUNCTION OF THIS SITE IS  
TO ASSEMBLE THE DOSE COUNTER (SECONDARY PACKAGING) (on 31-AUG-2007 by  
A. SHAW () 301-796-1460)

b(4)

stone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-JAN-2004				SHAWA
SUBMITTED TO DO	13-JAN-2004	GMP			ADAMSS
DO RECOMMENDATION	03-FEB-2004			ACCEPTABLE	ADAMSS

OC RECOMMENDATION 03-FEB-2004

BASED ON FILE REVIEW

ACCEPTABLE

ADAMSS

OC RECOMMENDATION 31-AUG-2007

DISTRICT RECOMMENDATION

SHAWA

OC RECOMMENDATION 04-SEP-2007

ACCEPTABLE

ADAMSS

SUBMITTED TO OC 03-DEC-2007

BASED ON PROFILE

SHAWA

OC RECOMMENDATION 04-DEC-2007

ACCEPTABLE

ADAMSS

BASED ON PROFILE

Establishment: CFN

FBI

b(4)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DMF No:

AADA:

b(4)

Responsibilities:

\_\_\_\_\_

Profile:

CSN

OAI Status: NONE

Estab. Comment:

(on 13-JAN-2004 by A. SHAW ( )  
301-796-1460)

PLEASE FORWARD COMPLETED RECOMMENDATION MEMO TO PAI MANAGER WITHIN ONE DAY OF COMPLETION OF INSPECTION. (on 14-JAN-2004 by K. CAMPBELL (HFR-CE140) 215-717-3003)

PLEASE IGNORE PREVIOUS COMMENT BY KARYN CAMPBELL; IT WAS MADE IN ERROR. (on 14-JAN-2004 by K. CAMPBELL (HFR-CE140) 215-717-3003)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-JAN-2004				SHAWA
SUBMITTED TO DO	13-JAN-2004	PS			ADAMSS
ASSIGNED INSPECTION T	09-FEB-2004	PS			DAMBROGIOJ
INSPECTION PERFORMED	26-FEB-2004		26-FEB-2004		ADAMSS
INSPECTION SCHEDULED	19-MAY-2004		26-FEB-2004		ADAMSS
DO RECOMMENDATION	19-MAY-2004			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	19-MAY-2004			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	03-DEC-2007				SHAWA
SUBMITTED TO DO	04-DEC-2007	GMP			ADAMSS
DO RECOMMENDATION	13-DEC-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	13-DEC-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment:

CFN

FEI

b(4)

DMF No:

AADA:

b(4)

Responsibilities:

Profile:

CTL

OAI Status:

NONE

Estab. Comment:

FOR THE 120 PRODUCT

FOR THE 60 PRODUCT

(on 13-

JAN-2004 by A. SHAW () 301-796-1460)

b(4)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-JAN-2004				SHAWA
OC RECOMMENDATION	14-JAN-2004			ACCEPTABLE BASED ON PROFILE	FERGUSONS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21658/000	Action Goal:	
Stamp:	23-DEC-2003	District Goal:	24-AUG-2004
Regulatory Due: (CICLESONIDE)	23-OCT-2004	Brand Name:	ALVESCO
Applicant:	AVENTIS PHARMS	Estab. Name:	
	200 CROSSING BLVD MAILSTOP BX2	Generic Name:	CICLESONIDE
	306C		
Priority:	BRIDGEWATER, NJ 088070890	Dosage Form:	(AEROSOL)
Org Code:	1S	Strength:	<del>                    </del> MCG
	570		

b(4)

Application Comment: STRENGTHS ARE INCORRECT. THEY SHOULD BE  80 AND 160  
MCG (on  
26-FEB-2004 by A. SHAW (HFD-570) 301-827-1050)

FDA Contacts: Manager	A. GREEN	(HFD-570)	301-827-1050	, Project
Chemist	A. SHAW	(HFD-570)	301-827-1050	, Review
Leader	R. LOSTRITTO	(HFD-570)	301-827-1053	, Team

-----  
Overall Recommendation: ACCEPTABLE on 22-OCT-2004 by S. ADAMS  
(HFD-322)301-827-9051  
-----

Establishment: CFN  FEI  b(4)

DMF No:

AADA:

Responsibilities:

Profile:

ADM

OAI Status:

NONE

EMilestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO OC SHAWA	13-JAN-2004			
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SUBMITTED TO DO ADAMSS	13-JAN-2004	PS		
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ASSIGNED INSPECTION T DAMBROGIOJ	28-JAN-2004	PS		
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INSPECTION SCHEDULED ADAMSS	11-AUG-2004		27-OCT-2004	
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OC RECOMMENDATION ADAMSS	22-OCT-2004			ACCEPTABLE
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DO RECOMMENDATION ADAMSS	22-OCT-2004			DISTRICT RECOMMENDATION ACCEPTABLE
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INSPECTION

BASED ON COMMENTS PROVIDED BY INVESTIGATOR DURING INSPECTION. INSPECTION IS STILL ONGOING HOWEVER AT THE CURRENT TIME NO MAJOR DEFICIENCIES HAVE BEEN FOUND.

Establishment: CFN 9611622 FEI 3002806615

ALTANA PHARMA

ROBERT BOSCH STRASSE 8

SINGER, , GM D-78224

DMF No:

AADA:

22-OCT-2004  
2 of 3

FDA CDER EES

Page

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: DRUG SUBSTANCE OTHER TESTER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: OTHER TESTING IS MICROBIAL TESTING PRODUCT NOT INTENDED BUT

b(4)

301-827-1050) FOR INHALATION USE. (on 13-JAN-2004 by A. SHAW (HFD-570)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO OC SHAWA	13-JAN-2004			
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SUBMITTED TO DO ADAMSS	13-JAN-2004	GMP		
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DO RECOMMENDATION ADAMSS	03-FEB-2004			ACCEPTABLE
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OC RECOMMENDATION ADAMSS	03-FEB-2004			ACCEPTABLE
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DISTRICT RECOMMENDATION

Establishment: CFN FEI

b(4)

DMF No:

AADA:

Responsibilities:

Profile:

CSN

OAI Status: NONE

b(4)

Estab. Comment:  
SHAW (HFD-

\_\_\_\_\_," (on 13-JAN-2004 by A.  
570) 301-827-1050)

WITHIN ONE

PLEASE FORWARD COMPLETED RECOMMENDATION MEMO TO PAI MANAGER

(HFR-

DAY OF COMPLETION OF INSPECTION. (on 14-JAN-2004 by K. CAMPBELL  
CE140) 215-597-4390)

IN ERROR.

PLEASE IGNORE PREVIOUS COMMENT BY KARYN CAMPBELL; IT WAS MADE  
(on 14-JAN-2004 by K. CAMPBELL (HFR-CE140) 215-597-4390)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
---------------------------	------	------	------------	-------------------

SUBMITTED TO OC SHAWA	13-JAN-2004			
SUBMITTED TO DO ADAMSS	13-JAN-2004	PS		
ASSIGNED INSPECTION T DAMBROGIOJ	09-FEB-2004	PS		
INSPECTION PERFORMED ADAMSS	26-FEB-2004		26-FEB-2004	
INSPECTION SCHEDULED ADAMSS	19-MAY-2004		26-FEB-2004	
DO RECOMMENDATION ADAMSS	19-MAY-2004			ACCEPTABLE
OC RECOMMENDATION ADAMSS	19-MAY-2004			INSPECTION ACCEPTABLE

Establishment:

CFN

FEI

b(4)

22-OCT-2004  
3 of 3

FDA CDER EES

Page

ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

DMF No:

AADA:

Responsibilities:

Profile:

CTL

OAI Status:

NONE

b(4)

Estab. Comment:  
ALL

FOR THE 120 PRODUCT

FOR THE 60 PRODUCT

(on 13-

JAN-2004 by A. SHAW (HFD-570) 301-827-1050

Milestone Name  
Creator

Date

Type

Insp. Date

Decision & Reason

SUBMITTED TO OC  
SHAWA

13-JAN-2004

OC RECOMMENDATION  
FERGUSONS

14-JAN-2004

ACCEPTABLE

BASED ON PROFILE



0

APPEARS THIS WAY  
ON ORIGINAL



ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application: NDA 21658/000 Action Goal:  
 Stamp: 23-DEC-2003 District Goal: 24-AUG-2004  
 Regulatory Due: 23-OCT-2004 Brand Name: ALVESCO (CICLESONIDE)  
 Applicant: AVENTIS PHARMS Estab. Name:  
 200 CROSSING BLVD MAILSTOP BX2 Generic Name: CICLESONIDE  
 306C  
 Priority: BRIDGEWATER, NJ 088070890 Dosage Form: (AEROSOL)  
 Org Code: 1S Strength: \_\_\_\_\_ MCG  
 570

b(4)

Application Comment: STRENGTHS ARE INCORRECT. THEY SHOULD BE 80 AND 160 MCG (on  
 26-FEB-2004 by A. SHAW (HFD-570) 301-827-1050)

FDA Contacts: A. GREEN (HFD-570) 301-827-5585 , Project Manager  
 A. SHAW (HFD-570) 301-827-1050 , Review Chemist  
 R. LOSTRITTO (HFD-570) 301-827-1053 , Team Leader

Overall Recommendation: ACCEPTABLE on 22-OCT-2004 by S. ADAMS (HFD-322) 301-827-9051

Establishment: CFN \_\_\_\_\_ FEI \_\_\_\_\_

b(4)

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_

Responsibilities: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Profile: ADM OAI Status: NONE

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
NOTED TO OC	13-JAN-2004				SHAWA
SUBMITTED TO DO	13-JAN-2004	PS			ADAMSS
ASSIGNED INSPECTION T	28-JAN-2004	PS			DAMBROGIOJ
INSPECTION SCHEDULED	11-AUG-2004		27-OCT-2004		ADAMSS

OC RECOMMENDATION 22-OCT-2004

ACCEPTABLE

ADAMSS

DISTRICT RECOMMENDATION

DO RECOMMENDATION 22-OCT-2004

ACCEPTABLE

ADAMSS

INSPECTION

ON COMMENTS PROVIDED BY INVESTIGATOR DURING INSPECTION. INSPECTION IS STILL  
ONGOING HOWEVER AT THE CURRENT TIME NO MAJOR DEFICIENCIES HAVE BEEN FOUND.

---

Establishment: CFN 9611622 FEI 3002806615

ALTANA PHARMA

ROBERT BOSCH STRASSE 8

SINGER, , GM D-78224

MF No:

AADA:

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: DRUG SUBSTANCE OTHER TESTER  
 DRUG SUBSTANCE RELEASE TESTER  
 DRUG SUBSTANCE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: OTHER TESTING IS MICROBIAL TESTING PRODUCT NOT "STERILE" BUT INTENDED FOR INHALATION USE. (on 13-JAN-2004 by A. SHAW (HFD-570) 301-827-1050)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-JAN-2004				SHAWA
SUBMITTED TO DO	13-JAN-2004	GMP			ADAMSS
DO RECOMMENDATION	03-FEB-2004			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	03-FEB-2004			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN FEI

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: (on 13-JAN-2004 by A. SHAW (HFD-570) 301-827-1050)

PLEASE FORWARD COMPLETED RECOMMENDATION MEMO TO PAI MANAGER WITHIN ONE DAY OF COMPLETION OF INSPECTION. (on 14-JAN-2004 by K. CAMPBELL (HFR-CE140) 215-597-4390)

PLEASE IGNORE PREVIOUS COMMENT BY KARYN CAMPBELL; IT WAS MADE IN ERROR. (on 14-JAN-2004 by K. CAMPBELL (HFR-CE140) 215-597-4390)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-JAN-2004				SHAWA

b(4)

SUBMITTED TO DO	13-JAN-2004	PS		ADAMSS
ASSIGNED INSPECTION T	09-FEB-2004	PS		DAMBROGIOJ
INSPECTION PERFORMED	26-FEB-2004		26-FEB-2004	ADAMSS
INSPECTION SCHEDULED	19-MAY-2004		26-FEB-2004	ADAMSS
COMMENDATION	19-MAY-2004		ACCEPTABLE	ADAMSS
			INSPECTION	
OC RECOMMENDATION	19-MAY-2004		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	

Establishment:

CFN

FEI

b(4)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Doc. NO:

AADA:

Responsibilities:

\_\_\_\_\_

Profile:

CTL

OAI Status:

NONE

Estab. Comment:

FOR THE 120 PRODUCT

\_\_\_\_\_

FOR THE 60 PRODUCT

b(4)

\_\_\_\_\_  
(on 13-  
JAN-2004 by A. SHAW (HFD-570) 301-827-1050)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-JAN-2004				SHAWA
OC RECOMMENDATION	14-JAN-2004			ACCEPTABLE BASED ON PROFILE	FERGUSONS