

-DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION	
TO (Division/Office): Division Microbial Review Team (Drs. David Hussong and Jim McVey)/OPS		FROM: Prasad Peri, Ph.D. PAL for DPAP in ONDQA/DPA1/Branch 2	
DATE Sept. 17, 2007	NDA. 21-658	TYPE OF DOCUMENT: NDA Resubmission	DATE OF DOCUMENT 10-Jul-2007
NAME OF DRUG Alvesco (ciclesonide) Inhalation Aerosol	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 2	DESIRED COMPLETION DATE Sept 30, 2007
NAME OF FIRM: sanofi aventis			
REASON FOR REQUEST: Evaluation of <u>Evaluation of response to FDA question 3c in the AE letter to applicant.</u>			
COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the response to FDA question pertaining to the validation of the analytical test method _____ for the absence of pathogens. The details of the response are provided in the attached document in the word file. If additional information is needed please feel free to look at the details of the method validation for NDA 21658 at the following link: <u>\\Cdsub1\21658\N_000\2007-07-10 and \\Cdsub1\21658\N_000\2007-07-10\other</u>			

b(4)

In the Approvable letter to the applicant, the Agency requested that the following comment be responded to. The applicant response is listed below. Please evaluate the appropriateness of the response.

Question 3(c) You will provide results for recovery of spiked *Pseudomonas aeruginosa* or *Salmonella abony* in the validation of the Microbial Count Method _____

sanofi -aventis response:

Work was undertaken to support the validation of analytical test method _____ for the absence of pathogens, specifically the organisms *Pseudomonas aeruginosa* and *Salmonella abony*, used for microbiological analysis of Ciclesonide _____ 80mcg and 160mcg inhalers. The validation was performed on _____ and 160mcg inhalers, 120 actuation (batches 1BGA006 and 4BGA006) however, the results may be applied to all three product strengths and the 60 actuation pack size. For the purposes of microbial analysis validation this is appropriate, considering the formulation composition similarities of all product strengths and pack sizes.

Sample Preparation

Ciclesonide inhaler membrane filter samples were prepared according to method _____ for _____ and 160mcg Ciclesonide inhalers, 120 actuation. Test organism culture controls were prepared in accordance with USP <61> guidance, using the reference strains listed in Table 6.

Spiked samples were prepared by _____

Once incubation was complete, the samples and controls were inspected, and the results for each strain recorded.

b(4)

Table 6 - Reference Strains Used in the Validation of the Method for the Microbial Analysis of Ciclesonide Inhalers

Name	Strain Number	Abbreviated Reference
<i>Pseudomonas aeruginosa</i>	ATCC 9027	<i>Ps. aeruginosa</i>
<i>Salmonella abony</i>	NCTC 6017	<i>S. abony</i>

Results

Inoculum Count

The results for inoculum count are presented in Table 7. The results for the inoculum count confirm suitability for use in the recovery experiments.

Table 7 - Results for Inoculum Count

Organism	Suspension Count	Mean Calculated Values of Suspension (cfu/unit)
<i>Ps. aeruginosa</i>	40, 37	3.9×10^1
<i>S. abony</i>	75, 114	9.5×10^1

Total Viable Count

Validation of Total Viable Count was assessed by recovery of the micro-organisms listed in Table 8.

Table 8 - Micro-organisms used for Recovery

Organism
<i>Ps. aeruginosa</i>
<i>S. abony</i>

The results for the control and inhaler samples are presented in Table 9.

Table 9 - Results for Total Viable Count

Organism	Inoculum (control) Sample	Ciclesonide 40mcg Sample		Ciclesonide 160mcg Sample	
	Mean Calculated values of 10^1 suspension (cfu/unit)	Count (cfu/unit)	Mean Count (cfu/unit)	Count (cfu/unit)	Mean Count (cfu/unit)
<i>Ps. Aeruginosa</i>	3.9×10^1	35, 51	4.3×10^1	34, 19	2.7×10^1
<i>S. abony</i>	9.5×10^1	137, 107	11.7×10^1	49, 53	5.1×10^1

The results for Total Viable Count demonstrate that the method is validated with respect to Total Viable Count and is acceptable for use on Ciclesonide inhalers.

Specific Micro-organism Validation

Validation of the method for suitability for determining absence of specific micro-organisms was conducted using the micro-organisms listed in Table 10.

Table 10 - Micro-organisms Used for Specific Validation

Organism
<i>Ps. aeruginosa</i>
<i>S. abony</i>

A positive growth of each organism listed in Table 10 was recorded for each sample of Ciclesonide inhaler analyzed as part of this experiment. Specific micro-organism validation is satisfactory.

Conclusions

Test method _____, shown to be suitable for microbial assessment of Ciclesonide _____, 80mcg and 160mcg inhalers, 60 and 120 actuations. No inhibition of test organism growth was observed during the validation process. The method is validated in accordance with USP monograph <61>.

The method is validated for the Total Viable Count and absence of pathogens, inclusive of the organisms *Pseudomonas aeruginosa* and *Salmonella abony*. The sensitivity of the method is determined to be _____fu/unit.

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/s/

Ali Al-Hakim

9/17/2007 04:56:04 PM

REQUEST FOR CONSULTATION

TO (Division/Office):

**Division of Drug, Marketing, Advertising and
Communication (DDMAC)**
O Bldg 22 Rm. 1400

FROM:

Colette Jackson
Project Manager
Division of Pulmonary and Allergy Products

DATE
July 25, 2007

IND NO.

NDA NO.
21-658

TYPE OF DOCUMENT
N

DATE OF DOCUMENT
July 10, 2007

NAME OF DRUG

ALVESCO (ciclesonide)

PRIORITY CONSIDERATION

Standard

CLASSIFICATION OF DRUG

Pro-corticosteroid

DESIRED COMPLETION DATE

October 10, 2007

NAME OF FIRM: Sanofi-Aventis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Labeling Review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for an evaluation and review of the labeling for ALVESCO (ciclesonide).
 This is a re-submission in response to our 10/21/2004 AE Letter
 This submission is electronic only and is located in the EDR in the submission dated July 10, 2007.

PDUFA DATE: January 11, 2008

CC:

Archival NDA 21-658
 HFD-570/Division File
 HFD-570/Jackson

TITLE OF REQUESTER

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

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/s/

Colette Jackson
7/25/2007 10:41:47 AM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 21, 2006

To: Frances Barbone	From: Colette Jackson
Company: Sanofi-Aventis Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 908-541-5274	Fax number: 301-796-9718
Phone number: 908-304- 6431 7210	Phone number: 301-796-1230
Subject: NDA 21-658	

Total no. of pages including cover: 3 (4)

Comments:

Document to be mailed: YES xNO

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NDA 21-658
Ciclesonide MDI

We have completed our review of your submission to NDA 21-658 dated February 7, 2006, which contains the following questions regarding your new efficacy studies:

Question 1. *The safety data from studies XRP1526B/3030 and RP1526B/3031 will be integrated with the 12-week placebo-controlled studies previously submitted under NDA 21-658. Does the Agency concur with the proposal to integrate these data as stated?*

Agency Response:

It is acceptable to combine the results from studies of equal duration and dosage. Therefore adverse events observed in studies 3030 and 3031 during 12-weeks of treatment, with once daily dosage, forms can be combined with the results of the studies submitted with the original NDA .

Question 2. *Studies XRP1526B/343, XRP1526B3027 and XRP1526/3028 will be provided as stand-alone CSRs and electronic datasets, without further integration. Does the Agency concur with the proposal to submit these data as stand-alone CSRs without further integration?*

Agency Response:

This is acceptable.

Question 3. *Does the Agency agree that the Altana Pharma CSRs can be submitted as supportive information without further integration?*

Agency Response:

Uncontrolled studies may be submitted as part of the safety update for this NDA, however, the Division does not consider data from uncontrolled studies as supportive evidence for efficacy.

Question 4. *Does the Agency agree with the Sponsor's plan to utilize the same dataset structure and format as the original NDA submission, for the NDA amendment-response to the Approvable Letter?*

Agency Response:

This is acceptable.



If there are any questions, please contact Ms. Colette Jackson, Project Manager, at 301-796-1230.

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/s/

Colette Jackson
3/21/2006 02:17:56 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 10, 2005

To: Dan Bollag	From: Colette Jackson
Company: Aventis	Division of Pulmonary and Allergy Drug Products
Fax number: 908-541-5274	Fax number: 301-827-1271
Phone number: 908-304-6431	Phone number: 301-827-9388

Subject: NDA 21-658 2/2/05 submission

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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NDA 21-658

Alvesco (ciclesonide)

Aventis Pharmaceuticals

We have completed our review of your submission dated February 1, 2005. We have the following response to your question (in bold italics) posed in your submission:

If the proposed additional clinical studies in adults and adolescents confirm the efficacy of Alvesco, does the FDA agree that the available data can support a claim in _____ ?

No, we do not agree. The additional studies #3030 and #3031 may provide adequate information to evaluate the safety of ciclesonide 160 mg daily administered as 80 mcg twice daily or 160 mcg once daily in adults. However, the studies do not address the efficacy of the 80 mcg daily dose. _____

_____ The Division maintains that efficacy of the 80 mcg daily dose has not been established in adults since efficacy was demonstrated in only one study (study # 322).

b(4)



Drafted: CCJ/May 4, 2005

Initialed:

Barnes/May 4, 2005

Bosken/May 4, 2005

Gilbert-McClain/May 4, 2005

Finalized: CCJ/May 10, 2005

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/s/

Colette Jackson
5/10/05 12:49:45 PM
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Food and Drug Administration
 Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2005

To: Dan Bollag	From: Colette Jackson
Company: Aventis	Division of Pulmonary and Allergy Drug Products
Fax number: 908-541-5274	Fax number: 301-827-1271
Phone number: 908-304-6431	Phone number: 301-827-9388

Subject: NDA 21-658 Responses to 7/18/05 Type A meeting questions

Total no. of pages including cover: 4

Comments:

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NDA 21-658
Alvesco (ciclesonide)
Aventis Pharmaceuticals

Attached are the FDA responses to your questions (in bold italics) regarding Alvesco. You have the option of canceling our teleconference of July 18, 2005, if these answers are clear to you. If you choose to have the teleconference, notify the Division of the specific questions for discussion and we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please notify the Division as soon as possible whether you are canceling the meeting.

Question 1: If studies #3030 and #3031 in adults and adolescents confirm the efficacy and safety of 160 mcg Alvesco, does the FDA agree that evaluation of pediatric efficacy and safety can proceed at the 160 mcg dose? Since the 40 mcg dose was not shown to be effective in children, evaluation of efficacy at the 80 mcg dose will be a review issue.

Division Response:

The terms "evaluation" and "proceed" are vague. You will have to explain if you are referring to additional clinical trials, additional analysis, or some other form of evaluation.

Question 2: If studies #3030 and #3031 in adults and adolescents confirm the efficacy and safety of 160 mcg Alvesco, does the FDA agree that the pre-specified integrated analysis of studies #341 and #342 in children 4 to 11 years old can be employed to assess pediatric efficacy? If not, please explain.

Division Response:

Nowhere in the SAP for study #341 or #342 does it state that an integrated analysis would supersede the analysis of the primary trials, and the FDA never agreed that the combined data set could be used for the primary analysis. The FDA maintains that the primary analysis is that of the individual studies and the integrated analysis is viewed as exploratory.

Question 3: If studies #3030 and #3031 in adults and adolescents confirm the efficacy and safety of 160 mcg Alvesco and FDA does not agree that the pre-specified integrated analysis of studies #341 and #342 can be employed to assess pediatric efficacy, does the FDA agree that an extrapolation of the adult results, supported by the individual results of studies #341, #342, and #343 can support e

b(4)

Division Response:

As long as the lowest effective dose in adults has been identified, extrapolation of the adult results supported by the individual results of studies # 341 and # 342 could potentially support _____

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If there are any questions, please contact Colette Jackson, Regulatory Project Manager, at 301-827-9388.

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/s/

Colette Jackson
7/15/05 11:15:06 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 30, 2004

To: Daniel Bollag, Ph.D.	From: Colette Jackson
Company: Aventis	Division of Pulmonary and Allergy Drug Products
Fax number: 908-541-5274	Fax number: 301-827-1271
Phone number: 908-304-6431	Phone number: 301-827-9388
Subject: 12/3/04 Meeting Minutes for NDA 21-658	

Total no. of pages including cover:

Comments:

Document to be mailed: YES NO

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 3, 2004

TIME: 2:30 PM

LOCATION: Food and Drug Administration/ Chesapeake Conference Room

APPLICATION: NDA 21-658/ Alvesco (ciclesonide)/Aventis Pharmaceuticals

TYPE OF MEETING: Advice/Type A Meeting

FDA ATTENDEES, DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

Robert J. Meyer, MD, Director, Office of Drug Evaluation II
Badrul A. Chowdhury, M.D., Ph.D., Division Director
Carol Bosken, M.D., Clinical Reviewer
Lydia Gilbert-McClain, M.D., Clinical Team Leader
Sandra Suarez, Ph.D., Clinical Pharmacology/Biopharmaceutics
Emmanuel Fadiran, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader
Sue Jane Wang, Ph.D., Acting Statistical Team Leader
Ted Guo, Ph.D., Statistical Reviewer
Colette Jackson, Project Manager

EXTERNAL ATTENDEES AND TITLES:

Aventis Pharmaceuticals

Daniel Bollag, Ph.D., Regulatory Affairs
Jon Villaume, Ph.D., Regulatory Affairs
Steve Caffé, MD, Regulatory Affairs
Don Banerji, MD, Clinical Pulmonology
Stephane Kirkesselli, MD, Clinical Pulmonology
Sudeep Kundu, Ph.D., Biostatistics
Larry Roi, Ph.D., Biostatistics
James Williams, MD, Global Project Team Leader
Sol Rajfer, MD, Clinical Development

Altana

Tushar Shah, MD, Scientific and Clinical Development

BACKGROUND: The purpose of this Type A meeting is to discuss Deficiency #1 from the Agency's October 22, 2004, action letter. On November 23, 2004, the Division sent written responses to the questions posed in the meeting package via facsimile (see

attachment). On December 2, 2004, Aventis sent their corresponding clarifications (in bold italics) below via secure e-mail. (**POST-MEETING NOTE:** Aventis officially submitted their clarifications in a letter dated December 2, 2004).

DISCUSSION:

NDA 21-658 - Ciclesonide

**December 3, 2004
Carol H. Bosken, MD**

Introduction

- The following responses are based on our analysis of the results of the studies submitted in the original NDA. In that data set replicated efficacy was shown in the adult population for dose regimens of 320 mcg once daily and 320 mcg twice daily. Lower doses were not shown to be effective. Efficacy was not demonstrated for any dose in the pediatric population. We emphasize that the Agency will not rely on *post hoc* meta-analysis or integrated analyses in preference to the data as analyzed in the original clinical trials.

December 3, 2004

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Question 1

- If the data demonstrate that a once-daily regimen is superior to placebo and similar to a twice-daily dosing regimen Aventis believes that the proposed clinical study will support

- Does the FDA concur?

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b(1)
b(4)

Answer 1



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The Division stated that, in general, the recommendation for two clinical trials prior to approval of a drug is based on the need for replication. Unintentionally biased selection of patients can affect the results of any one study. This is very much less likely to be a factor if the same results are found in two studies. If a drug is effective, it should be possible to demonstrate this in two separate studies. Studies 321 and 322 were adequately powered to detect a statistically significant effect. According to the statistical analysis that was submitted with the NDA, the efficacy of ciclesonide was only replicated for the 320 mcg daily dose in the adult population. According to the step-down procedure, efficacy of the 80 and 160 mcg doses was not replicated. The secondary outcomes are considered to be supportive of the primary efficacy findings. Aventis referred to their clarification response regarding question 1 below.

Regarding Question 1

Aventis contends that the totality of the data from Studies 321 and 322 support the efficacy of all _____ ciclesonide doses (80, 160 _____ μg _____) in the overall population. Additionally, all _____ doses provided similar numerical benefits relative to placebo without a clear dose-response relationship. If Study 3030 confirms that 160 μg of ciclesonide once daily is superior to placebo and similar to 80 μg of ciclesonide twice daily, Aventis contends that these data further support _____

b(4)

Please explain the rationale for not accepting t _____

The Division stated that we do not agree that the _____
_____ Studies 321 and 322 are separate studies, each powered to show a superior Ciclesonide effect, and should be analyzed separately. These studies did not show _____

_____ The Division stated that we will not accept a conclusion _____ based upon the pooling of data from studies 321 and 322. Aventis asked the Division what is necessary for proof of efficacy, and whether the Division required replication of every dose. The Division stated that in order to show that the drug is effective in a particular patient population, replication is necessary. For the purposes of replication, extrapolation of efficacy cannot be made from a higher dose to a lower dose. However, replication of efficacy for a higher dose may not be necessary if replication of efficacy has already been demonstrated for the lower dose.

b(4)

Aventis stated that upon review of their studies in which the Division has interpreted no efficacy of the 160 mcg dose, the 160 mcg dose was significantly better than placebo based upon the primary and secondary endpoints. The Division stated that the secondary endpoints are supportive but they do not constitute the primary evidence of efficacy. In addition, the secondary efficacy data for the 160 mcg once daily dose in studies 321 and 322 have many notable discrepancies and our conclusion is that the data in totality do not support efficacy of the 160 mcg once daily dose.

Aventis stated that their data has some value and asked the Division what additional work is necessary in order to support efficacy of the drug. The Division re-emphasized that additional studies needed to be conducted to evaluate the efficacy of the 160 and the 80 mcg doses.

Question 2

- If the data demonstrate that a twice-daily regimen is the only regimen superior to placebo, Aventis believes that the proposed clinical study will support twice-daily dosing recommendations in adults and adolescents with mild to moderate asthma.
- Does the FDA concur?

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Answer 2

The proposed study may be sufficient to support dosing recommendations for ciclesonide 80 mcg and 160 mcg twice daily. The proposed study will not support _____

b(4)

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Aventis referred to their clarification for question #2.

Regarding Question 2

Considering our view that the totality of the data in the completed studies 321 and 322 support the efficacy of all _____ ciclesonide doses and due to the flat dose response relationship for inhaled corticosteroids including ciclesonide in this patient population, Aventis considers that the results from Study 3030 with the 160 µg daily dose comparing the once daily and twice daily regimens can be extrapolated to the other two doses. Please clarify the rationale if this approach is not accepted.

b(4)

b(4)

Aventis noted that if BID is the preferred dosing regimen, is it acceptable to divide the dose. The Division explained that the proposed study would support a dosing regimen of 80 mcg twice daily, and 160 mcg twice daily, however the _____ would not be supported.

Question 3

If the data demonstrate that a twice-daily regimen is the only regimen superior to placebo, and that patients on a twice-daily regimen remain stable when switched to a once-daily regimen, then Aventis believes that the proposed clinical study will support twice-daily dosing recommendations _____

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b(4)

Answer 3

The treatment period of the proposed study design is of insufficient duration to support dosing recommendations to _____ dosing regimen. If this claim is being sought then a study should be designed to demonstrate asthma stability in patients treated for at least _____

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b(4)

b(5)

The Division referred to Aventis' clarification for question #3.

Regarding Question 3

Aventis recognizes that Pulmicort (budesonide) received labeling for once daily administration based on data from a subset of patients who were already well

controlled on inhaled corticosteroids in a study randomizing patients to 200 or 400 µg budesonide once daily for 6 weeks, followed by treatment with 200 µg budesonide for 12 weeks. Aventis has already conducted two studies (321 and 322) in which the subset of patients previously controlled on inhaled corticosteroids (Stratum 1, integrated data) were treated for 12 weeks with once daily ciclesonide, and in whom efficacy was clearly demonstrated. The improvement observed for ciclesonide in predose FEV₁ compared to placebo was comparable to the improvement seen with the two doses of budesonide (see table), although the study designs were different:

<u>Regimen</u>	<u>FEV1 improvement from placebo</u> <u>(p-value)</u>	<u>number of patients</u>
Ciclesonide 80 µg QD	170 mL (0.0002)	142
Ciclesonide 160 µg QD	170 mL (0.0004)	139
Ciclesonide 320 µg QD	190 mL (<0.0001)	142
Budesonide 200 µg QD	190 mL (0.007)	44
Budesonide 400 µg QD	220 mL (0.002)	42

In Study 3030, in addition to the analysis of patients receiving once daily ALVESCO for 12 weeks (many of whom will previously have been taking twice daily controller therapy). Aventis proposes to demonstrate that patients stabilized on t _____

_____ This will provide substantially more data than the Agency previously considered acceptable for budesonide's once daily labeling option for patients on prior controller therapy.

While initially we proposed a _____

The Division again clarified that from our analysis of the data efficacy was not demonstrated for the 80 mcg and the 160 mcg dose. Additionally, Aventis' initial proposal was if _____

_____ Therefore, Aventis' contention that they have more data than what was accepted by the Agency for the budesonide once daily regimen is inaccurate. The table provided by Aventis comparing ciclesonide c _____

_____ since these data are from different studies with very different study designs. The Division explained that the dosing recommendation of _____

b(5)

_____. The initial period of stabilization on the twice daily regimen could be shorter and at the discretion of Aventis. At least 12 weeks of treatment on the once daily regimen is necessary in order to allow an appropriate evaluation of destabilization when _____

Question 4

- Aventis believes that the proposed clinical study including patients taking prior reliever or prior controller therapy, will support appropriate dosing recommendations for ciclesonide in patients with mild to moderate persistent asthma. Based on asthma guidelines and current clinical practice standards, Aventis considers that a primary efficacy analysis that demonstrates efficacy in the intention-to-treat (ITT) patient population of patients with mild to moderate asthma will support dosing recommendations in these patients.
- Does the FDA concur?

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Answer 4

We concur that an inhaled corticosteroid should be effective in subjects with asthma regardless of their prior therapy. We note, however, that the efficacy of ciclesonide in adult asthmatic subjects not previously treated with ICS was not demonstrated at any dose in the two studies in which this analysis was performed. Therefore, an appropriate study should be done to support efficacy in the sub-populations defined by prior corticosteroid use so that the label can contain recommendations for each patient group.

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Answer 4 (con't)

- The resulting label will then be consistent with the format of all labels of inhaled corticosteroids approved for treatment of asthma in the United States.

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Aventis referred to their clarification for question #4.

Regarding Question 4

Aventis notes that previous sponsors have enrolled patients on prior reliever therapy having average FEV₁ percent predicted values in the 60 – 70% range. Due to the increased acceptance of inhaled corticosteroid therapy and adoption of treatment guidelines, it has become much more difficult to identify patients with such low FEV₁ values who have only received prior reliever therapy. For example, the prior reliever subset of patients in Studies 321 and 322 had a mean baseline FEV₁ percent predicted value of 73.4%. Therefore, based on this modest impairment in lung function, demonstrating statistically significant improvements in FEV₁ has become a far greater challenge, and, in Aventis's view, a less pertinent measure of efficacy in this population. Aventis proposes that for the evaluation of patients on prior reliever therapy, a measure other than FEV₁ (either an individual or composite endpoint) would be more meaningful in determining the effectiveness of an inhaled corticosteroid for this subpopulation. Can the FDA comment on this proposal and clarify its views with regard to the analysis of prior reliever patients?

The Division stated that we would be willing to evaluate alternate primary endpoints if Aventis proposes them. The Division stated that the endpoints would need to be clinically meaningful but whatever Aventis decides, they need to allow for efficacy to be demonstrated in the steroid naïve patient population. Patients with mild to moderate

asthma who require treatment with inhaled corticosteroids need assurance that the dose is effective. Aventis asked the Division if statistical significance would need to be demonstrated with the steroid naïve population and asked the Division if the study should be powered to demonstrate statistical significance in the steroid-naïve population. The Division noted that the concern is that efficacy was virtually nil for the steroid-naïve group and whatever study design Aventis decides on should be such that efficacy is demonstrated convincingly for the steroid-naïve population. Aventis stated that this is a difficult subgroup and asked about conducting a study in a patient population comprised of only steroid-naïve patients. The Division noted that such a study design may limit Aventis' ability to make determinations of once daily dosing in other patient populations since it is possible that the twice daily dosing regimen may be efficacious in one subgroup whereas the once daily dosing regimen may be effective in another. The Division stated that we are open to consideration of other study design options but couldn't make agreements on proposals raised at the meeting without internal review of the protocols.

Question 5

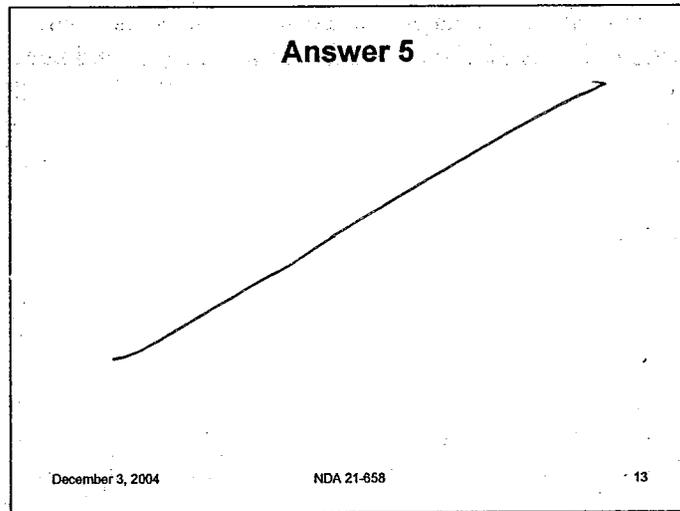
If the data demonstrate that a once-daily regimen is superior to placebo and similar to a twice-daily regimen, Aventis believes that the proposed clinical trial will support _____

b(4)

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b(5)

b(4)

The Division noted that study 3030 will not _____
Aventis should determine the lowest effective dose for adults and then evaluate that dose in children less than 12 years of age. The Division noted that from a safety standpoint we do not want to overdose the children and we want to establish the lowest effective dose to limit systemic exposure and side effects.

The Division also stated that the plan to perform an integrated analysis on studies 341 and 342 was not communicated to the Agency prior to the submission of the NDA. **(POST-MEETING NOTE:** Furthermore, the term “integrated analysis” did not appear in the study report until the section Discussion and Overall Conclusions. The sponsor merely indicated, in Appendix B.1 (of every pivotal study), that an integrated analysis was performed. It doesn’t lead us to believe that the sponsor’s original intent was to let the integrated analyses (results) supersede those drawn from the individual studies. The integrated analyses, like analyses of secondary efficacy variables, play no more than a “supporting role.” Please note, in the study report for Studies 321, 322, 341, 342, the sponsor stated, “After discussion with the Food and Drug Administration (FDA) (Byk Gulden Pharma Group End of Phase II Meeting, October 22, 1999) [27], it was agreed that patients be stratified based on prior inhaled corticosteroids use (patients taking inhaled corticosteroids, and patients not taking inhaled corticosteroids). It was further agreed that this design would be replicated in 2 studies.” Therefore, we conclude that although such analysis was planned and done, it was never part of the discussions in either the sponsor’s investigational plan or the statistical methodology section. It can only serve as secondary and for exploration purposes.)

The Agency approved combining study 323 and 324, but this issue was not raised for any other set of studies. The results of study 341 and 342 did not demonstrate efficacy, therefore, they can not be used to support a dosing regimen in children.

Aventis referred to their clarification for question #5.

Regarding Question 5

1. We interpret your response to imply that if the adult data under the first scenario (Question 1) support the effectiveness of 80 µg and 160 µg ALVESCO once daily, then the Agency will allow _____
_____ Please confirm if our interpretation is accurate and also takes into consideration the phrase _____

b(4)

2. It is important for Aventis to emphasize that the combined analysis of pediatric data from studies 341 and 342 was pre-specified in the Statistical Analysis Plan, and therefore this was not a post hoc analysis. In addition, Aventis notes that the Division has previously approved inhaled corticosteroids for use in children based on a single clinical study. Given the scenario for Question 5, does FDA agree that approval in _____ of studies #341 and #342, data from Study 3030? Will the data from studies 341 and 342 be adequate to address the statement _____

Aventis stated that if _____
_____ The Division stated that _____

_____ Aventis stated that since 160 mcg dose is effective in adults, they anticipate that half of that dose (i.e. 80 mcg once daily) would be effective in _____. Aventis stated that prior to unblinding the data for pediatric studies 341 and 342, they submitted their final Statistical Analysis Plan (SAP) to the IND to the Agency in which they stated that they will be combining the two studies in an integrated analysis for efficacy. Aventis stated that their rationale for combining the studies was based on the fact that the two studies were identical in design and that with demonstration of efficacy in adults, only one efficacy study was needed in the pediatric population. The Division noted that we were not aware of a decision to pool the data from the two studies. Aventis provided a handout from that particular submission (see attachment) and focused on the Integrated Analysis of Efficacy, to note that the integrated data meets the primary and secondary endpoints. The Division stated that adding the 2 studies together still is dependent upon the support of adult efficacy. _____

b(5)

_____ If the integration of the 2 studies is accepted, then an adult study that supports a robust finding of efficacy would be required.

Question 6

- If the data demonstrate that a twice-daily regimen is the only regimen superior to placebo, Aventis believes that the proposed clinical study will support _____
- Does the FDA concur?

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b(4)

Answer 6

Refer to the answer to question 5

December 3, 2004

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Aventis clarification for question #6.

Regarding Question 6

1. *Our interpretation of your response to Question 6 is that if Study 3030 demonstrates BID to be the preferred regimen, the Agency will allow*

_____ We recognize that acceptance of the _____ μg BID dose by the Agency depends on the acceptance of efficacy of the 80 μg daily dose in adults (see clarification responses to Questions 1 and 2 above). Does the FDA concur?

b(4)

2. For this scenario, please clarify what is meant by '_____'

b(4)

Additional Comment

Depending on the final outcome of the proposed clinical study (ies), the dose selection chosen for the pediatric growth study (#343) may not be appropriate and the growth study may need to be repeated.

December 3, 2004

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Aventis clarification for additional FDA comment.

Regarding the Additional FDA Comment

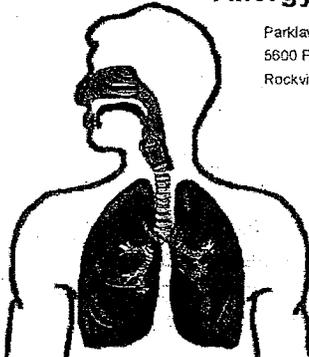
1. In the event that the preferred regimen is twice daily and total daily doses of 80 μg and 160 μg ciclesonide are accepted by the Agency in adults _____, Aventis believes that the results of the growth study (#343) with once daily administration of 160 μg ciclesonide will satisfy the FDA requirements for growth velocity safety data. Please clarify your rationale if this is not the case.

The Division stated that the ongoing growth studies need to be conducted at the highest recommended dose in children. Thus, if the recommended dose is higher than the dose studied in the growth study, then the growth study may need to be repeated. However, if

the results of the ongoing growth study (study 343) are positive, then the growth study may not need to be repeated.

Aventis inquired as to what they needed to do next to address these clinical deficiencies and suggested another submission of proposals with subsequent discussion with the Division. The Division stated that another meeting was not necessary and that Aventis should design their studies and submit them to the Division for review and comment.

**Division of Pulmonary and
Allergy Drug Products**



Parklawn Building, Room 10B-45
5600 Fishers Lane, HFD-570
Rockville, MD 20857

December 3, 2004

NDA 21-658

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Phone: 301-827-1650
Fax: 301-827-1271

Colette Jackson
Minutes Preparer

Attachments:

Aventis Handout
November 23, 2004, facsimile sent to Aventis

9.4 Interim analyses

No interim analyses were planned, and no interim analyses were performed for this study.

9.5 Changes from the statistical section in the protocol

The analysis of the primary endpoint (Section 9.1) described in the Statistical Analysis Plan is the same as the one described in the statistical section of the protocol. There have been no major changes from the analyses or the methods described for other endpoints in the protocol to those described in the Statistical Analysis Plan.

9.6 Integrated Analysis of Efficacy

An integrated analysis of covariance of the primary efficacy endpoint, FEV₁ percent predicted, will be performed and the results of the analysis provided in the Clinical Summary of Efficacy in the Common Technical Document (CTD) by combining the intent-to-treat (ITT) patient population from this study (XRP1526B-341) with that from a study with identical design (XRP1526B-342). The analysis of covariance (ANCOVA) model for this integrated analysis will include factors for study, treatment, center (pooled), previous therapy (based on Stratum 1 and Stratum 2), and the following covariates: gender, baseline FEV₁ percent predicted, and age. The pooling of centers will be done within each individual study and the same pooled centers will be used for the integrated analysis.

The efficacy of ciclesonide treatment will be assessed by comparing the ciclesonide dose regimens against placebo (i.e., ciclesonide 160 µg/day versus placebo, ciclesonide 80 µg/day versus placebo, and ciclesonide 40 µg/day versus placebo comparisons). A step-down procedure will be utilized to address the issue of multiplicity. The ciclesonide 160 µg/day group will be compared with placebo first. If that comparison is statistically significant at a significance level of $\alpha=0.05$, then the ciclesonide 80 µg/day group will be compared with placebo at a significance level of $\alpha=0.05$. If that comparison is statistically significant at a significance level of $\alpha=0.05$, then the ciclesonide 40 µg/day group will be compared with placebo at a significance level of $\alpha=0.05$.

The above integrated analysis will be done for the combined ITT patient population from both studies, and then for each previous therapy stratum separately. Analyses of covariance of secondary and other endpoints will be also performed on the integrated data from these two studies in the CTD.

10. ANALYSIS AND PRESENTATION OF SAFETY DATA

Safety and tolerability will be evaluated by statistical and clinical review of all safety parameters, including adverse events, laboratory values, vital signs, and oropharyngeal examination.

Statistical hypothesis testing for safety parameters must be interpreted cautiously since the analysis of safety data is essentially a screening experiment. Should a particular safety concern

b(4)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: November 23, 2004

To: Dan Bollag	From: Colette Jackson
Company: Aventis	Division of Pulmonary and Allergy Drug Products
Fax number: 908-541-5274	Fax number: 301-827-1271
Phone number: 908-304-6431	Phone number: 301-827-9388

Subject: NDA 21-658 Responses to Meeting Questions

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES xNO

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NDA 21-658
Alvesco (ciclesonide) Metered Dose Inhaler
Aventis Pharmaceuticals

Attached are the FDA responses to your questions (in bold italics) regarding Alvesco (ciclesonide) Metered Dose Inhaler. You have the option of canceling our meeting of December 3, 2004, if these answers are clear to you. If you choose to have the meeting (or change it to a telecon), we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please notify the Division as soon as possible whether you are canceling the meeting.

The following responses are based on our analysis of the results of the studies submitted in the original NDA. In that data set replicated efficacy was shown in the adult population for dose regimens of 320 mcg once daily and 320 mcg twice daily. Lower doses were not shown to be effective. Efficacy was not demonstrated for any dose in the pediatric population. We emphasize that the Agency will not rely on *post hoc* meta-analysis or integrated analyses in preference to the data as analyzed in the original clinical trials.

Question #1: *If the data demonstrate that a once-daily regimen is superior to placebo and similar to a twice-daily regimen, Aventis believes that the proposed clinical study will support _____*

b(4)

Does the FDA concur?

The proposed study may support _____ / dosing recommendations for ciclesonide 160 mcg and 320 mcg daily. This would be a review issue.
The proposed study will _____ dosing recommendations for ciclesonide _____

Question #2: *If the data demonstrate that a twice-daily regimen is the only regimen superior to placebo, Aventis believes that the proposed clinical study will support twice-daily dosing recommendations in adults and adolescents with mild to moderate persistent asthma.*

Does the FDA concur?

The proposed study may be sufficient to support dosing recommendations for ciclesonide 80 mcg and 160 mcg twice daily. The proposed study will not support dosing recommendations for ciclesonide _____ mcg daily.

b(4)

Question #3: *If the data demonstrate that a twice-daily regimen is the only regimen superior to placebo, and that patients on a twice-daily regimen remain stable when _____*

b(4)

Does the FDA concur?

The treatment period of the proposed study design is of insufficient duration to support dosing recommendations to _____ .. If this claim is being sought then a study should be designed to demonstrate asthma stability in patients treated for at least _____

b(4)

Question #4: *Aventis believes that the proposed clinical study including patients taking prior reliever or prior controller therapy will support dosing recommendations for ciclesonide in patients with mild to moderate persistent asthma. Based on asthma guidelines and current clinical practice standards, Aventis considers that a primary efficacy analysis that demonstrates efficacy in the intention-to-treat (ITT) patient population of patients with mild to moderate asthma will support dosing recommendations in these patients.*

Does the FDA concur?

We concur that an inhaled corticosteroid should be effective in subjects with asthma regardless of their prior therapy. We note, however, that the efficacy of ciclesonide in adult asthmatic subjects not previously treated with ICS was not demonstrated at any dose, in the two trials in which this analysis was performed. Therefore, an appropriate study should be conducted to support efficacy in the sub-populations defined by prior corticosteroid use so that the label can contain recommendations for each patient group. The resulting label will then be consistent with the format of all labels of inhaled corticosteroids approved for treatment of asthma in the United States.

Question #5: *If the data demonstrate that a once-daily regimen is superior to placebo and similar to a twice-daily regimen, Aventis believes that the proposed clinical study will _____*

b(4)

Does the FDA concur?

In principle, efficacy in subjects

b(4)

Question #6 *If the data demonstrate that a twice-daily regimen is the only regimen superior to placebo, Aventis believes that the proposed clinical study will support twice-daily dosing recommendations in — patients.*

b(4)

Does the FDA concur?

Refer to the answer to question 5.

Additional FDA comment:

Depending on the final outcome of the proposed clinical study (ies), the dose selection chosen for the pediatric growth study (#343) may not be appropriate and the growth study may need to be repeated.

If there are any questions, please contact Colette Jackson, Regulatory Health Project Manager, at 301-827-9388.

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

/s/

Colette Jackson
11/23/04 03:25:07 PM
CSO



Drafted: December 7, 2004

Initialed by:

Bosken/December 10, 2004

Gilbert-McClain/ December 10, 2004

Suarez/ December 14, 2004

Fadiran/ December 14, 2004

Wang/ December 14, 2004

Guo/ December 14, 2004

Chowdhury/December 15, 2004

Finalized: CCJ/December 30, 2004

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Colette Jackson
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: September 23, 2002

To: Dr. Eric Floyd	From: Colette Jackson
Company: Aventis Pharmaceuticals.	Division of Pulmonary and Allergy Drug Products
Fax number: 908-541-5274	Fax number: 301-827-5586
Phone number: 908-231-2474	Phone number: 301-827-5580

Subject: August 29, 2002 Meeting Minutes

Total no. of pages including cover: 12

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Byk Gulden Pharma Group
IND 53,391
End-of-Phase 2 (EOP2) Meeting
October 22, 1999

Memorandum of Telephone Facsimile Correspondence

Date: November 17, 1999
To: Cynthia I. Renger
Associate Director, Regulatory Affairs
From: LCDR James Lindsay Cobbs
Project Manager
Subject: Meeting minutes.

Reference is made to the meeting held between representatives of your company and this Division on October 22, 1999. Attached is a copy of our final minutes for that meeting. These minutes will serve as the official record of the meeting. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

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Thank you.

LCDR James Lindsay Cobbs
Project Manager
Division of Pulmonary & Allergy Drug Products

Date

Byk Gulden Pharma Group
IND 53,391
End-of-Phase 2 Meeting
October 22, 1999
Page 2

Representing Division of Pulmonary & Allergy Drug Products (DPADP)

Craig Bertha, Chemistry Reviewer
Lindsay Cobbs, Regulatory Project Manager
Young Moon-Choi, Clinical Pharmacology & Biopharmaceutics Reviewer
Badrul Chowdhury, Acting Clinical Team Leader
Robert Meyer, Director DPADP
Guirag Poochikian, Chemistry Team Leader
Joe Sun, Pharmacology Team Leader
Mark Vogel, Pharmacology Reviewer
Ramana Upoor, Clinical Pharmacology & Biopharmaceutics Team Leader

Representing Byk Gulden

Mohamed Baccouche, Regulatory Affairs
Klaus Dietzel, Project Leader
Renate Engelstaetter, Clinical Development Phase II and III Europe
Gerd Kassel, Pharmacovigilance
Joerg Kemkowski, Toxicology
Helgert Mueller, Drug Product Manufacturing Development
Gunter Stingel, CMC dossier
Klaus Tuch, Toxicology
Petra Willersin-Kern, Regulatory Affairs
Karl Zech, Pharmacokinetics

Representing Altana, Inc.

Cynthia I. Renger, Regulatory Affairs
Kerry Whitehead, Regulatory Affairs

Representing _____

b(4)

b(4)

Background: Altana requested an EOP2 meeting for ciclesonide MDI, on behalf of Byk Gulden. Byk has proposed the indication, "Maintenance treatment of mild, moderate, and severe asthma as prophylactic therapy down to 4 years of age." Please see the meeting request package dated September 21, 1999, for details.

The Agenda of the meeting follows.

AGENDA

Introduction	Lindsay Cobbs, R.Ph.	5 min
Chemistry	Craig Bertha, Ph.D.	30 min
Pharm/Tox	Mark Vogel, Ph.D.	10 min
Biopharmaceutics	Young Moon Choi, Ph.D.	10 min
Clinical	Badrul Chowdhury, M.D., Ph.D.	30 min
Conclusion		5 min

Chemistry, Manufacturing, & Controls (CMC)

The Division referenced the IND reactivation letter dated April 10, 1998, and provided the following additional comments.

Drug Substance (DS)

1. The Division recommended that the specifications for the DS include a test and acceptance criteria for the melting point (p. 181).
2. The Division recommended a quantitative test and acceptance criteria for color of the

drug substance instead of a description (e.g., APHA color, p. 181).

3. The Division stated that _____ is not considered a starting material for the _____ of the ciclesonide, but is considered an intermediate (p. 171). b(4)
4. It appears that since 1997 the _____ is supplied by _____ (provided by _____ prior to 1997). If any other supplier of this intermediate is used in the future, a DMF from that supplier describing all the details and controls for the manufacture of this material should be provided (p. 173).
5. Based on the structures of some of the impurities (in particular "impurity _____ and "impurity _____) that are identified as having the _____ moiety at the _____ position, the Division noted that it would be prudent to look for the corresponding _____ because of the toxicity potential. This may also require input from Pharm/Tox (p. 174).
6. Qualification data for the impurities with acceptance limits _____ in the DS should be provided for review by pharm/tox (p. 181). b(4)
7. The Division noted that the limits for residual _____ in the DS are extremely wide relative to the data and should be more reflective of the data and therefore tightened significantly (p. 186).
8. The Division recommended that microbial testing for the DS on stability be performed annually for 25°C/60%RH storage conditions (p. 190).
9. The Division recommended that the sponsor perform the _____ test for _____ on the DS samples stored under conditions of 40°C/75%RH for 6 months for submission of the NDA (p. 191).

Drug Product (DP)

The Division referenced the IND reactivation letter dated April 10, 1998, and the draft guidance Metered Dos Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products and provided the following additional comments.

10. The Division stated that drug product manufacturing (with representative batch records) should be included in the submission of the NDA (pp. 192 and 193). Also, test methods and acceptance criteria for the DP components (excipients, DS,

container, and closure system components) should be included in the application.

11. The Division stated that there should be DMF references for the manufacturing and controls for the various container and closure components (i.e., canister, valve, actuator, etc.) and the noncompensial propellant excipient.
12. The Division noted that USP leakage rate acceptance criteria are typically too broad in terms of the leakage observed for current MDIs. These specifications should be tightened to be reflective of actual data (p. 197, 200, 203). b(4)
13. The Division stated that the mean for the beginning, middle, and end individual doses for Medication Delivery/Through Life should be controlled separately to _____ (p. 198, 201, 204). Alternatively, the sponsor may propose alternate n numbers to those in the package for the unit-life measurements.
14. The Division stated that the PSD data for the DP collected by _____ should be collected in terms of the amounts on the individual plates and accessories instead of as groupings of plates (p. 198, 201, 204). You may propose to control the amounts found on various groups of plates and accessories but individual data should be submitted in the application for review. b(4)
15. The Division stated that the qualification information should be available for the impurity _____, that is allowed at a level > the ICH qualification threshold for review by pharm/tox (p. 199, 202, 205). b(4)
16. The Division stated that foreign particulates in the respirable size range (e.g., < 10 μ m) should be controlled (p. 199, 202, 205).
 - The sponsor noted that they might have problems if < _____ are required. The Division stated that if this were the case all of the data should be provided for review and a decision would be based on the actual data. b(4)
17. The Division stated that the drug product tests and specifications should control leachables emanating from the container and closure components (p. 199, 202, 205). Also, leachables should be monitored on stability (p. 218, 220). The sponsor was referred to the draft guidance for details on the control of extractables from incoming container/closure components and leachables appearing in the drug product formulation.

18. The Division stated that data should be provided in the application to support the "one collection distance" used for the spray pattern testing is the optimal one, i.e., most discriminating (p. 209).
19. The Division stated that the tail-off study should also examine the PSD by _____ (p. 222). b(4)
20. The Division referred the sponsor to the draft MDI/DPI guidance for the Division's expectations in terms of studies designed to characterize the drug product (p. 221).
21. The Division reminded the sponsor that there should be _____ for _____ for the DP with a _____.
22. Questions from p. 229.
 - a. The acceptability of the protocols to provide data to support an NDA.
 - The Division stated that the sponsor should consider the above comments and revise the stability protocols accordingly so that the necessary data will be available for the NDA.
 - b. Assuming that all results and trend analyses are within expected limits, will the proposed testing at _____ years be sufficient in order to claim a _____ month shelf-life? b(4)
 - The Division asked for clarification of this question. The sponsor stated that they would like to know if the proposed testing/data provided would support a _____ month shelf-life for this product. The Division noted that shelf-life is dependent on the data provided in the application at the time of submission and that the shelf-life for most products approved vary up to 24 months. Data provided in the application must adequately address the shelf-life proposed at the time of submission.
 - c. With regards to through life medication delivery testing, historically, the middle position has in light of the draft guidance document (2180dft), is it acceptable to continue this practice?
 - The Division stated that for this product with 120 labeled actuations, it

would be acceptable to continue using the 60 actuation point as the middle position for through life medication delivery testing.

Pharmacology/Toxicology

23. The Division concurred with the change in rat strain (Sprague Dawley vs Wistar) between DPI and MDI studies.
24. The Division stated that based on historical data, Alveolar histiocytosis is no longer an Agency concern, therefore the 6-month rat study with HFA formulation is not necessary.
25. The Division stated that histological re-analysis and historical control data alleviate the Division's concern for the nasal cavity observations in the 1-year dog DPI study. The sponsor was also referred to the correspondence dated March 18, 1999.
26. The Division stated that the 1-year dog oral study to demonstrate that nasal effects are not "systemic" is no longer a Division concern for the same reason as stated in comment 26.
27. The Division stated that the design of the 3-month dog study (rat vs dog in "definitive" 3-month bridging study) is appropriate and referred the sponsor to the correspondence dated March 18, 1999.
28. The Division requested that the 3-month dog HFA study report be submitted before initiating clinical studies > 3-months.
29. Rodent carcinogenicity protocols.
 - a. The Division noted that that the CAC dose recommendations were not incorporated into the ongoing rat carcinogenicity study and stated that the final rat carcinogenicity study, once completed, should be provided for CAC recommendation and can be submitted to the IND.
 - b. The Division noted that the high dose in mice has been reduced to 900 $\mu\text{g}/\text{kg}$ in accordance with CAC recommendation.
30. The Division stated that the carcinogenicity dose-ranging studies (if seeking CAC concurrence) are preferably conducted by GLP. The Division indicated that this

should not be a problem unless there is some indication that the doses in final study were inappropriate.

31. The Division stated that the juvenile animal studies are not needed to support clinical studies in children ≥ 2 years of age.
32. Does the pre-clinical data support the proposed high clinical dose of 1600 $\mu\text{g}/\text{day}$?
The following table was presented during the meeting.

AUC for metabolite ($\mu\text{g}\cdot\text{hr}/\text{L}$)		
Dog	mild reversible GC effect at 18 $\mu\text{g}/\text{day}$	1.95
Rat	minimal GC effects at 16 $\mu\text{g}/\text{kg}$	1.12
	moderate GC effect at 47 $\mu\text{g}/\text{kg}$	2.83
Human	4 x 200 μg	3.07
	proposed high dose 1600 $\mu\text{g}/\text{day}$	

- a. The Division stated that monitorable glucocorticoid effects would be expected based on the pre-clinical data and noted that human safety data must also be considered.
- b. The sponsor stated that, for rats, plasma levels during inhalation exposure were not incorporated into the reported AUCs and that they are generating data for more accurate estimates.
- c. The Division stated that "bridging" PK studies are appropriate for estimating exposure in pivotal toxicology studies to be incorporated in the labeling (e.g., reproductive toxicity and carcinogenicity).
33. The Division noted that including reprotox findings in the Investigator's Brochure & Informed Consent were appropriate revisions.
34. The Division stated that the pre-clinical program is sufficient pending successful completion of the following studies.
- a. Peri-, post-natal developmental toxicity (segment-III).
- b. Rat carcinogenicity *in vivo* completed (analysis ongoing).
- c. Mouse carcinogenicity.

- d. Lower dose rabbit embryo-fetal development (to define NOAEL).
- e. Qualification of degradation products (if dictated by stability results).

Clinical Pharmacology & Biopharmaceutics

35. Questions from Volume 2 p. 80.

- a. Metabolism in humans: Does the agency agree if we characterize the metabolic pathway of ciclesonide in humans with *in vitro* techniques only?
 - (1) Based on the rationale provided in the meeting request package the Division agreed that the metabolic pathway of ciclesonide in humans could be characterized with *in vitro* techniques only.
 - (2) The Division stated that the human *in vitro* metabolism results should be provided in Item 6, and the relative activity of parent drug and metabolites should also be included.
- b. Chronopharmacokinetics: Does the agency agree that we will rely on PK information from a steady state study with daily morning inhalation even if we administer the drug in the evening during phase III in the US?
 - The Division concurred and added that pharmacokinetic (PK) data should also be collected in the phase III studies as it is important to obtain more information on drug-drug interaction, gender effect, and special populations at the recommended dosing regimen. This may be a subset of the planned studies and a sparse sampling method may be used. This will also provide information on the PK/PD relationship.
- c. Drug-Drug Interaction: Is any further drug-drug interaction study needed?
 - The Division noted that no additional studies are needed and reiterated comment b. above.

Additional Biopharmaceutics Comments

36. The Division stated that the sponsor should collect systemic exposure PK data in the "Pediatric studies." This may be a subset of the planned studies and a sparse sampling

method may be used.

37. The sponsor was reminded that protein-binding information should be included in the NDA.
38. The sponsor was referred to the guidance "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design" for statistical analysis method and predefined equivalence acceptance limits for bioequivalence (for criteria for bioequivalence). Also, if the confidence interval of the natural log mean ratio of test/reference appear to be out of range (80 – 125 %), then the clinical relevance of the difference and the rationale of the acceptance should be provided in the NDA.
39. The Division stated that the data regarding the potential interconversion of R to S epimer and the activity difference of R and S forms should also be provided in the NDA.

Clinical

40. Clinical Questions from Volume 1 p.37.
 - a. Does the Agency agree that the safety and efficacy results from the Phase Ia/II studies conducted in adults by Byk Gulden are sufficient to support initiation of the Phase III U.S. program in adults, adolescents and children 4years and older (Question 3.6.1)?
 - (1) The Division noted that previous data support initiation of the proposed studies.
 - (2) The Division recommended that some PK data should be collected from the proposed pediatric studies.
 - b. Will the proposed III U.S. program in adults/adolescents and pediatric asthmatics, if successful, enable the sponsor to obtain the proposed labeling for dosing and administration (Question 3.6.2)?
 - (1) The Division stated that the proposed labeling for dosing is reasonable, however, the ultimate labeling for dosing will depend on results of the studies.
 - (2) The Division noted that there does not appear to be a planned

replication in the program for dose, device, and indication.

The sponsor's proposed plan is as follows.

Adult program:

Study 301 (efficacy study)
Study 302 (efficacy study)
Study 303 (CS sparing study)

Pediatric program:

Study 305 (efficacy study)

b(4)

The Division recommended that the following be addressed in the clinical program.

- (1) Once daily vs. twice daily dosing should be compared (e.g. 200 mcg QD vs 100 mcg BID).
 - (2) The dose proportionality of various devices should be established.
 - (3) The major efficacy claims (studies 301, 302, 305) should be replicated.
 - (4) The proposed dose regimens, particularly for patients who were previously on inhaled corticosteroids and those who were not on inhaled corticosteroids should be replicated.
- c. We think the data basis is appropriate for receiving an approval up to 1600 µg/day as the highest dose will usually not be needed for chronic maintenance treatment but for intermittent treatment over several weeks, with dose titration to lower doses. Does the Agency agree (Question 3.6.3)?
- (1) The Division noted that the proposed database might not be adequate for the higher doses of 800 mcg/day and 1600 mcg/day. The database will have enough number of patients but may not have enough at the higher doses.
 - (2) The Division stated that safety data from at least 300 patients exposed for at least 6 months with 100 completing one year is required. The sponsor was referred to the Draft Guidance for Industry Document

“Clinical Development of Metered Dose Inhaler and Dry Powder Products for Pulmonary Indications,” or see the FDA website address (www.fda.gov/cder/guidance/index.htm).

b(4)

d. Does the FDA accept the submission in the _____
_____ (Question 3.6.4)?

• _____

b(5)

e. If the company accepts the class labeling that growth velocity can be decreased in children, is it then possible to obtain an _____ before the 1 year growth study (including an additional 6-months baseline) is finalized? Or does the Agency principally not accept to give an approval without having seen the results of the long term growth study (Question 3.6.5)?

- (1) The Division stated that the pediatric growth study may be submitted after submission of the NDA. The class labeling will indicate the known growth suppressing effects of inhaled corticosteroids.
- (2) The Division recommended the sponsor consider a knemometry study with a positive control prior to submission.

Additional Clinical Comments

42. The Pediatric Rule.

- b. The Division recommended that the sponsor plan to conduct studies in patients below the age of 4 years and down to the age of 6 months.
- c. The Division stated that due to safety and dosing concerns, it may be appropriate for the Sponsor to delay initiation of the studies in very young children pending efficacy determination in patients 4 years of age and older.

- The sponsor noted that "...6 years...." is a typographical error.
- e. The sponsor was reminded that approved US formulations should be used as active comparators as well as US approved and marketed devices for PEFV measurements.
- f. The Division recommended that the ACTH stimulation test be performed in a subset of patients enrolled in the Phase 3 studies.
- g. Since the low dose of ACTH (proposed 10 mcg dose) is not commercially available, the Division recommended that uniformity of the administered dose be ensured and stated in the protocol.
- h. The Division reminded the sponsor that study 302 can not be used for comparative claims with fluticasone because a single study can not be used for comparative claims.
- i. The Division stated that since some of the studies, particularly 303 (steroid sparing study) has complex design features, the Division recommended that full protocols be submitted for review and comment before initiating the studies. The sponsor stated that the new objective of study 303 was to obtain a relative safety claim for ciclesonide as compared to fluticasone based on HPA axis studies. The Division pointed out that such a study would be problematic because such a comparison is only relevant if equally effective doses are examined. Identifying such doses may be difficult due to the problem with a relatively "flat" dose response curve for ICS. The Division referred to a published study on Flovent to support this position. The burden on the sponsor will be to identify doses of ciclesonide and the comparator inhaled corticosteroid that have identical efficacy and then compare the two for safety. Furthermore, such a comparative claim must be replicated.

Post meeting note: During the meeting Byk referred to the Guidance "Formats and

Byk Gulden Pharma Group
IND 53,391
End-of-Phase 2 Meeting
October 22, 1999
Page 15

Specifications for Submission of Animal Carcinogenicity Study Data”(March 12, 1997), and stated that 2 formats for data submission are referenced in the guidance. The sponsor asked which format the Division preferred for data submission. The Division noted that either format could be used but agreed to get back to the sponsor after following up with the Division of Biometrics. The Division of Biometrics stated that format (a) the Divisions of Biometrics Formats and Specifications for Submission of Animal Carcinogenicity Study Data, is preferred.



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Page 16

DIVISION FILE
HFD-570/COBBS
HFD-570/BERTHA/10-28-99
HFD-570/POOCHIKIAN
HFD-570/NICKLAS
HFD-570/CHOWDHURY/10-27-99
HFD-570/UPPOOR/10-28-99
HFD-570/MEYER/11-12-99
HFD-570/ CHOI/10-28-99
HFD-570/VOGEL/11-1-99
HFD-570/SUN/10-27-99



DRAFT BY: LCOBBS/OCTOBER 27, 1999
MY DOCUMENTS/3391BYK.DOC

CORRESPONDENCE

ADRA Review #1 of Action Package for NDA 21-658, Alvesco (ciclesonide) Metered-Dose Inhaler

Reviewer: Lee Ripper, HFD-102

Date received: October 15, 2004

Date original NDA received: December 23, 2003

UF GOAL DATE: October 22, 2004

Proposed Indications: Maintenance Tx of asthma as prophylactic therapy in adult

Action type: AE

RPM: Colette Jackson

Drug Classification: 1S
505(b)(1) application

Patent Info: AC

Debarment Certification: AC

Safety Update: Dated 4/26/04. MOR, page 56

Clinical Inspection Summary: 6 sites inspected, AC, 9/17/04; addressed in MOR, page 21

ODS/DMETS Review of Trade Name: AC 3/29/04

DSRCS Review of PPI: Nothing in pkg

DDMAC Review: 10/12/04 Memo to File by Dr. McClain states that comments were recd from DDMAC for the PI and the Patient Instructions for Use

EA: Request for categorical exclusion was AC; CMC Rev#1, page 239

EER: 3 of 4 sites AC; inspection of _____, scheduled for 10/22/04. AC 10/22/04

Financial Disclosure: MOR, page 22, FD info recd for all essential studies.

CMC section to Eric Duffy, 10/15/04

P/T section to Ken Hastings (Ken on leave Fri, 10/15, and on travel M-W 10/18-20)

1. 9/15/04 P/T review of leachables recommends that specs (found in DMF) for _____ compounds be lowered from less than _____ ug/unit to less than _____ g/unit. Page 101 of the CMC review gives the limits as less than _____ ug/unit. I did not see the P/T review addressed in the CMC review. The CMC review states that the DMF was AC on 5/24/04 which was before the P/T consult was completed. F/U: Colette forwarded a Memo of TC on these specs. A Post-Mtg Note states that _____ submitted a 9/22/04 amendment to the DMF revising the leachables spec for the / compounds in question to not mor than _____ mg/unit. NOTE: Anybody reading the CMC review will think the limits are not more than 0.1 mg/unit. Discussed documentation of leachables with Eric Duffy.

Lee Ripper
ADRA, ODE II
10/15/04

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/s/

Leah Ripper
10/25/04 01:45:05 PM
CSO



NDA 21-658

INFORMATION REQUEST LETTER

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

10/4/04

Attention: Dr. Daniel Bollag
Director, US Regulatory Affairs

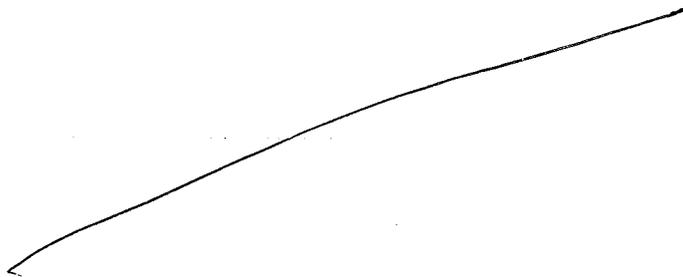
Dear Dr. Bollag:

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

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following request pertains to the drug substance.
 - a. 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.
2. The following requests pertain to the drug product.
 - a. In regard to the Pharmaceutical Development Report:
 - (1) 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(4)

(2) Provide an explanation for the increase in _____ content on storage. Explain whether _____ is leaking through the seal or if the _____ is _____ from the valve components.

(3) Provide the details of the time course of the temperature cycling experiment reported in Section 3.2. P.2.2.1.8. Explain:

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

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

(c) If a cycle is constituted with : _____

b(4)

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

b(4)

b(4)

(5) Provide data to justify choice of _____ time and temperature in the manufacturing procedure, providing data showing the effects of these parameters on leak rate and valve performance.

(6) Provide the procedures used to determine the amount of _____ in the foreign particulates. Provide the data resulting from this determination. Provide the data and calculations that form the basis for the assertion that the mass per actuation of particulates is _____ mcg/actuation (Page 18 in Section 3.2.P.2.4.4.2.).

b(4)

b. In regard to the Drug Product Manufacturing:

(1) Provide details of the manufacturing procedure for the _____ and _____ steps.

b(4)

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative- 1

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/s/

Richard Lostritto
10/4/04 04:33:22 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-658

10/1/04

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

Attention: Dr. Daniel Bollag
Director, US Regulatory Affairs

Dear Dr. Bollag:

Please refer to your submission dated March 22, 2004, requesting a partial waiver for pediatric studies for Alvesco (ciclesonide) Metered Dose Inhaler (MDI).

We have reviewed the submission and agree that a waiver is justified for pediatric studies in patients zero to less than 6 months of age for Alvesco (ciclesonide) MDI for asthma because the disease is unlikely to exist or is difficult to diagnose in this age range.

Accordingly, at this time a waiver for pediatric studies for this application is granted under Pediatric Research Equity Act (PREA) for Alvesco (ciclesonide) MDI for asthma in children zero to less than 6 months of age.

If you have questions, please call Colette Jackson, Project Manager, at 301-827-9388.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
10/1/04 10:51:17 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-658

Supplement #

SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Alvesco™

Generic Name: ciclesonide

Dosage Form: Metered Dose Inhaler

Strengths: — mcg, 80 mcg, and 160 mcg

b(4)

Applicant: Aventis Pharmaceuticals

Date of Application: December 22, 2003

Date of Receipt: December 23, 2003

Date clock started after UN: N/A

Date of Filing Meeting: February 10, 2004

Filing Date: February 21, 2003

Action Goal Date (optional): October 9, 2004 User Fee Goal Date: October 23, 2004

Indication(s) requested: Asthma

Type of Application: Original (b)(1) NDA X Original (b)(2) NDA
(b)(1) Supplement (b)(2) Supplement
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S X P
Resubmission after a withdrawal? No Resubmission after a refuse to file? No
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) No

User Fee Status: Paid X Waived (e.g., small business, public health)
Exempt (orphan, government)

Form 3397 (User Fee Cover Sheet) submitted: xYES NO

User Fee ID # 4548

Clinical data? YES x NO, Referenced to NDA # Monograph

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES xNO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES xNO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES xNO
 If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? xYES NO

• Was form 356h included with an authorized signature? xYES NO
 If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? xYES NO
 If no, explain:

• If an electronic NDA, does it follow the Guidance? xYES NO
 If an electronic NDA, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Modules 1 through 5 were submitted electronically.

Additional comments:

Module 1 provided also in paper.

• If in Common Technical Document format, does it follow the guidance? xYES NO

• Is it an electronic CTD? (~~eCTD not currently available~~) xN/A YES NO
 If an electronic CTD, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information included with authorized signature? xYES NO

• Exclusivity requested? YES, _____ years xNO
 Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? xYES NO
 If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge"

• Financial Disclosure information included with authorized signature? xYES NO
 (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO
 Field copy retained by Aventis until FDA notifies Aventis of the assigned investigator in the Division of Field Investigations. It will then be forwarded to the assigned field investigator.

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: IND 53,391
- End-of-Phase 2 Meeting(s)? YES NO
 Date(s) 10/22/99
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? YES NO
 Date(s) 8/29/02
 If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? YES NO
 xN/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? YES NO
 xN/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO
 xN/A
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO
 xN/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? xYES NO
- If no, did applicant submit a complete environmental assessment? YES NO
- If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? xYES NO
- If parenteral product, consulted to Microbiology Team (HFD-805)? YES xNO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications

that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

• EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

YES, IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

• Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT
Biopharmaceutics
MEMO OF FILING MEETING

DATE: February 10, 2004

BACKGROUND:

NDA 21-658 is a new molecular entity. IND 53,391 is the referenced IND for ciclesonide.

ATTENDEES:

10B45 Attendees:

Badrul A. Chowdhury, M.D., Ph.D., Division Director, DPADP
Lydia Gilbert-McClain, M.D., Acting Clinical Team Leader, DPADP
Carol Bosken, M.D., Clinical Reviewer, DPADP
Richard Lostritto, Ph.D., Supervisory Chemist
Art Shaw, Ph.D., Chemistry Reviewer
Huiqing Hao, Ph.D., Pharmacology/Toxicology Reviewer
Joseph Sun, Ph.D., Pharmacology/Toxicology Team Leader
Shinja Kim, Ph.D., Clinical Pharmacology/Biopharmaceutics
Sayed Al Habet, Ph.D., Clinical Pharmacology/Biopharmaceutics
Yaning Wang, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer
Ted Guo, Ph.D., Statistical Reviewer
James Gebert, Ph.D., Statistical Team Leader
Colette Jackson, Project Manager
Carol Hill, Project Manager
Brenda Marques, DDMAC reviewer
Elenita Ibarra Pratt, DSI officer

ASSIGNED REVIEWERS:

Discipline

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemist:
Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
Regulatory Project Manager:
Other Consults:

Reviewer

Carol Bosken
Lydia Gilbert-McClain,
Ted Guo
Huiqing Hao

Art Shaw

Yaning Wang /Sandra Suarez

Colette Jackson

Per reviewers, are all parts in English or English translation?

xYES

NO

If no, explain:

CLINICAL FILE REFUSE TO FILE _____

- Clinical site inspection needed: xYES NO
- Advisory Committee Meeting needed? YES, date if known _____ xNO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

xN/A YES NO

CLINICAL MICROBIOLOGY FILE _____ REFUSE TO FILE _____ xN/A

STATISTICS FILE REFUSE TO FILE _____

BIOPHARMACEUTICS FILE REFUSE TO FILE _____

- Biopharm. inspection needed: YES xNO

PHARMACOLOGY FILE REFUSE TO FILE _____

- GLP inspection needed: YES xNO

CHEMISTRY FILE REFUSE TO FILE _____

- Establishment(s) ready for inspection? xYES NO
- Microbiology xYES NO N/A

ELECTRONIC SUBMISSION:

Any comments:

Data format for stats requested at February 3, 2004, teleconference. None submitted to date. Biopharmaceutics and Clinical are having problems accessing data.

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

_____ Filing issues to be communicated by Day 74.

ACTION ITEMS:

1. Document no filing issues conveyed to applicant by Day 74.

Colette Jackson
Regulatory Project Manager, HFD-570

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/s/

Colette Jackson
9/30/04 04:27:44 PM
CSO

Alvesco was studied in varying doses between 80 µg QD to 640 µg BID in adolescents and adults and between 40µg to 160µg in children given once daily for 12 weeks. The primary efficacy endpoint for most of the pivotal studies, with exception to study 325, was the change from baseline to Week 12 (end of study) in forced expiratory volume in one second (FEV1). Safety assessments included HPA axis evaluations, eye exams, and adverse events. The pivotal trials in support of the safety and efficacy of Alvesco include adolescent and adult subjects in studies 321 (n=526), 322 (n=489), 323/324 (n=297) and 325 (n=141), and studies 341 (n=514) and 342 (n= 517) in children. Sites 28, 40, 83 and 160 were selected for auditing due to high enrollment and sites 132 and 150 were inspected in response to a complaint received by DSI.

II. RESULTS (by site):

Name (site no.)	City, State	Country	Protocol	Insp. Date	EIR Recd.	Classn.
Edwin Kerwin, MD (28)	Medford, OR	USA	321, 323, 341	4/29/5/6/2004	8/31/2004	NAI
Michael Noonan, MD (40)	Portland, OR	USA	322, 323/324, 342	4/19-4/28/2004	8/31/2004	NAI
Lawrence Sher, MD (160)	Rolling Hills, CA	USA	322, 323/324, 342	4/13-23/2004	5/10/2004	NAI
Jonathan Bernstein, MD (83)	Cincinnati, OH	USA	322, 323/324, 342	5/10-5/20/2004	7/1/2004	NAI
Kenneth Kim, MD (150)	Long Beach, CA	USA	323/324, 341	2/19-3/2/2004	3/10/2004	VAI-RR
Harold Nelson, MD (132)	Denver, CO	USA	321	2/17-3/15/2004	4/14/2004	VAI-RR

Protocols Inspected

Study Protocol: XRP1526B-321: “A Phase III Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Efficacy, Safety and Dose Response Study of Ciclesonide Metered Dose Inhaler 100µg/day, 200 µg/day, and 400 µg/day (Ex-Valve) Administered Once Daily for 12-Weeks in the Treatment of Mild to Moderate Persistent Asthma in Adolescents and Adults”

This was a multicenter, double-blind, randomized, placebo-controlled, stratified, parallel-group, efficacy, safety, and dose-response study in patients with asthma; sites were all from the United States. The primary objective of the study was to compare safety, efficacy and dose-response of ciclesonide 100 µg/day, 200 µg/day, and 400 µg/day (ex-valve) once daily dosing with placebo in patients with mild to moderate persistent asthma 12 years of age and older. The primary outcome measurement was the change from baseline to Week 12 (end of study) in forced expiratory volume in one second (FEV1). A total of 1082 subjects were screened; 526 were randomized.

Study Protocol: XRP1526B-322: “A Phase III Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Efficacy, Safety and Dose Response Study of Ciclesonide Metered Dose Inhaler 100 µg/day, 200 µg/day, and 400 µg/day (Ex-Valve) Administered Once Daily for 12-Weeks in the Treatment of Mild to Moderate Persistent Asthma in Adolescents and Adults”

This was a multicenter, double-blind, randomized, placebo-controlled, stratified, parallel-group, efficacy, safety, and dose-response study in patients with asthma; sites were all from the United States. The primary objective of the study was to compare safety, efficacy and dose-response of ciclesonide 100 µg/day, 200 µg/day, and 400 µg/day (ex-valve) once daily dosing with placebo in patients with mild to moderate persistent asthma 12 years of age and older. The primary outcome measurement was the change from baseline to Week 12 (end of study) in forced expiratory volume in one second (FEV1). A total of 1070 subjects were screened; 489 were randomized.

Study Protocol: XRP1526B-323/324: “A Phase III Double-Blind, Double-Dummy, Parallel-Group, Multicenter, Placebo-Controlled, Efficacy, Safety and Dose Response Study of Ciclesonide MDI 400 µg/day, 800 µg/day (Ex-Valve), and Flovent MDI (Fluticasone Propionate) 880 µg/day (Ex-Actuator) Administered Twice Daily for 12-Weeks in the Treatment of Severe Persistent Asthma in Adolescents and Adults”

This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, stratified, parallel-group, efficacy, and safety in patients with severe persistent asthma; sites were all from the United States. The primary objective of the study was to compare safety and efficacy of BID dosing of ciclesonide 400 µg/day and 800µg/day (ex-valve) with placebo and an active comparator, fluticasone propionate MDI 1000 µg/day in patients with severe

persistent asthma 12 years of age and older. The primary outcome measurement was the change from baseline to Week 12 (end of study) in forced expiratory volume in one second (FEV1). A total of 1225 subjects were screened; 531 were randomized.

Study Protocol: XRP1526B-341: "A Phase III Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Efficacy, Safety and Dose Response Study of Ciclesonide Metered Dose Inhaler 50 µg/day, 100 µg/day, and 200 µg/day (Ex-Valve) Administered Once Daily for 12 Weeks in the Treatment of Children with Persistent Asthma"

This was an international, multicenter, randomized, double-blind, placebo-controlled, stratified, parallel group, efficacy, safety, and dose-response study conducted in Mexico and the United States. The primary objective of the study was to compare safety and efficacy of once daily dosing of ciclesonide 50 µg/day, 100 µg/day and 200µg/day (ex-valve) with placebo in patients with mild, moderate, and severe persistent asthma 4-11 years of age. The primary outcome measurement was the change from baseline to Week 12 (end of study) in forced expiratory volume in one second (FEV1). A total of 1109 subjects were screened; 514 were randomized.

Study Protocol: XRP1526B-342: "A Phase III Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Efficacy, Safety and Dose Response Study of Ciclesonide Metered Dose Inhaler 50 µg/day, 100 µg/day, and 200 µg/day (Ex-Valve) Administered Once Daily for 12 Weeks in the Treatment of Children with Persistent Asthma"

This was an international, multicenter, randomized, double-blind, placebo-controlled, stratified, parallel group, efficacy, safety, and dose-response study conducted in Poland and the United States. The primary objective of the study was to compare safety and efficacy of once daily dosing of ciclesonide 50 µg/day, 100 µg/day and 200µg/day (ex-valve) with placebo in patients with mild, moderate, and severe persistent asthma 4-11 years of age. The primary outcome measurement was the change from baseline to Week 12 (end of study) in forced expiratory volume in one second (FEV1). A total of 913 subjects were screened; 517 were randomized.

Site Inspections

The medical officer selected the following domestic sites based on high enrollers and inspectional histories. No significant issues were identified as criteria for selection, with exception to site 28. Site 28 was selected because of high enrollment and a subject death occurred in protocol 341L, the long term study. DSI also audited sites 132 and 150 since for-cause inspections were already scheduled for those sites in response to complaints.

Data listings that were sent to DSI by Dr. Carol Bosken, HFD-570 reviewing medical officer, were sent to the respective field investigators for 100% verification with source documents on site.

- (1) **Edward Kerwin, M.D. (site 28)**
Clinical Research Institute of Southern Oregon, LLC
3850 Crater Lake Avenue, Suite B
Medford Oregon, 97504

The inspection reviewed case report forms, data listings and source documents. Source documents included screening records, lab reports, vital signs, concomitant medications, medical history records, subject diaries and quality of life questionnaires, physical exams, laboratory reports, and pulmonary function tests. Each data point listed on the data listings received from the review division and selected sponsor-submitted case report tabulations were also compared to the case report forms and source documents; no discrepancies were found. The following clinical studies were inspected:

Protocol 321: A total of 57 subjects were screened and consented, 35 randomized; 4 subjects prematurely discontinued—#6 & #17 due to lack of efficacy and #36 & #45 due to prohibited concomitant medication, 30 subjects completed study, and one subject reported a serious adverse event (#22 reported ruptured appendicitis). All

subjects exists and met eligibility criteria. Therefore, the inspection is classified NAI. Data at this site is acceptable.

(3) Lawrence Sher, M.D. (site 160)

Peninsula Research Associates
501 Deep Valley Drive, Suite 210
Rolling Hills Estates, California 90274

The inspection reviewed case report forms, source documents such as study visit records, lab reports, prior history records, study worksheets, subject diaries, and pulmonary function tests. The data listings from the sponsor-submitted case report tabulations were also compared to the case report forms and source documents. The following clinical studies were inspected:

Protocol 322: A total of 38 subjects were screened and consented, 5 were screen failures, 6 prematurely discontinued (3 withdrew consent, one subject put herself back on old study medication and another lacked transportation), 27 subjects were randomized and completed study. No serious adverse events or deaths reported. A total of 15 subject records were reviewed during the inspection and did not reveal any significant findings.

Protocol 323: A total of 7 subjects were screened and consented, 3 were screen failures, 4 were randomized and completed study. No serious adverse events or deaths were reported. A total of 6 subject records were reviewed during the inspection and did not reveal any significant findings.

Protocol 342: A total of 23 subjects were screened and consented, 5 were screen failures, one prematurely discontinued due to exacerbation of asthma, and 17 subjects completed study. No serious adverse events or deaths were reported. A total of 15 subject records were reviewed during the inspection and did not reveal any significant findings.

The inspection found that Dr. Sher was in compliance with applicable regulations and no 483 was issued. In general, the inspection of documents support that audited subjects exists and met eligibility criteria. Therefore, the inspection is classified NAI. Data at this site is acceptable.

(4) Jonathan Bernstein, M.D. (site 83)

Bernstein Clinical Research Center
8444 Winton Road
Cincinnati, Ohio 45231

The inspection reviewed case report forms, data listings and source documents. Source documents included screening records, lab reports, vital signs, concomitant medications, medical history records, study worksheets, subject diaries and quality of life questionnaires, physical exams and pulmonary function tests. The data listings from the sponsor-submitted case report tabulations were also compared to the case report forms and source documents. The following clinical studies were inspected:

Protocol 322: A total of 27 subjects were screened and consented; 7 were screen failures, 3 prematurely discontinued (one subject was lost to follow-up and 2 were due to lack of efficacy). A total of 10 subject records were reviewed during the inspection and no significant discrepancies were found.

Protocol 323/324: A total of 40 subjects were screened and consented; 14 were screen failures, one did not want to continue on study, one was lost to follow-up, and 6 discontinued early due to lack of efficacy. A total of 12 subject records were reviewed during the inspection and no significant discrepancies were found.

Protocol 342: A total of 46 subjects were screened and consented; 16 were screen failures, 6 did not want to continue on study, 4 was lost to follow-up, 2 discontinued early due to lack of efficacy, and 2 discontinued to due an adverse event. A total of 10 subject records were reviewed during the inspection and no significant discrepancies were found.

(6) Harold Nelson, M.D. (site 132)
National Jewish Medical and Research Center
1400 Jackson Street
Denver, Colorado 80206

DSI issued a for-cause inspection for Dr. Nelson in response to a complaint received from a former employee (anonymous). The complainant alleged that the clinical investigator, in general, was not involved with the conduct of the study, did not train or supervise study personnel, unqualified staff performed PFTs and PDS (pulmonary data systems) tests when the protocol states that the investigator must be there, and performed inappropriate randomization procedures. The complainant also alleged that he/she was asked to do the methacholine challenge test using a profile for another qualified personnel. The protocols in question include, but not limited to, _____ and another study sponsored by _____ which were audited. In addition, the inspection included a review of studies in support of NDA 21-658 (ciclesonide) since the inspector was located on site during site selection. The following study, in support of NDA 21-658, was reviewed:

b(4)

Protocol 321: Approximately 49 subjects were screened; 19 randomized. Observations were based on a review of records from 15 of 19 randomized subjects. Four subjects withdrew from the study due to an upper respiratory infection, two asthma exacerbations, and one withdrew consent.

Data for protocol 321 from this site was compared to the data listings obtained from the EDR that was submitted by the sponsor. **The only significant discrepancies noted include: a head cold for subject 32 (12/20/01), yeast infection (10/24/01) for subject 21, and an eye infection for subject 34 (2/19/02) that were not reported on the AE data listing and the start date for asthma exacerbation for subject 47 should read 4/7/02 and not 4/15/02.**

The following protocol violations (21 CFR 312.60) were cited:

1. Protocol 321 required that all adverse events be documented on the case report form. Subjects 21 and 34 reported in their diaries a yeast infection and an eye infection, respectively, that required treatment. However, these adverse events were not reported on the case report form.
2. Protocol 321 required a pre-dose, 20-minute, 30-minute, and 60-minute post-stimulation blood draw for serum cortisol was required at study visits 2 and 8. The required blood draw at 20 minutes for subject 32 at study visit 8 was not collected.

The following recordkeeping violations [21 CFR 312.62(b)] were cited:

1. The Previous and Concomitant Medications case report forms were not accurately completed for subjects 34, 39, and 46. For subject 34, Claritin D and Advil were reportedly taken by the subject during the study but were not reported on the case report form. For subject 39, Flovent, Terazosin and Lovastatin were initiated prior to the study and continued while on study but were not reported on the case report form. For subject 46, Serevent, Allegra, and ibuprofen were not reported at baseline on the case report form.
2. There were two different source documents that listed medications for subject 45 and the listings were inconsistent with one another.
3. The case report form did not accurately reflect the time of the last dose of albuterol administration that was recorded in the Asthma Diary for subjects 34, 35 at study visit 6, and subject 46 at study visits 4-8.

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The inspection confirmed the complaint that another person's user profile was used to access the study spirometry in order to conduct the methacholine challenge test for protocol _____ .6. The user name and password of _____ was used inappropriately by _____ to perform the methacholine challenge test. _____ is a

Page 9 of 9-NDA 21-658 Alvesco® (ciclesonide)
Summary Report of Domestic Inspections

HFD-45/Laddon

HFD-47/Pratt/Ball/GCPB2 Files #11140/11138/10576/7036/11186/11224

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/s/

Elinita Ibarra-Pratt
9/15/04 12:09:59 PM
CSO

Leslie Ball
9/17/04 10:53:56 AM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-658

Aventis Pharmaceuticals
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Francis P. Barbone, Ph.D.
Corporate Regulatory Affairs

Dear Dr. Barbone:

We acknowledge receipt on July 11, 2007, of your July 10, 2007, resubmission to your new drug application for ALVESCO™ (ciclesonide MDI).

We consider this a complete, class 2 response to our October 21, 2004, action letter. Therefore, the user fee goal date is January 11, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the partial waiver granted on October 1, 2004, and the deferral granted on January 21, 2004, for the pediatric study requirement for this application.

We note that you have submitted pediatric studies for patients \geq years of age and older with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

b(4)

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-658

Page 2

U.S. Postal Service/ Courier/Overnight Mail:
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Colette Jackson, Regulatory Project Manager, at (301) 796-1230.

Sincerely,

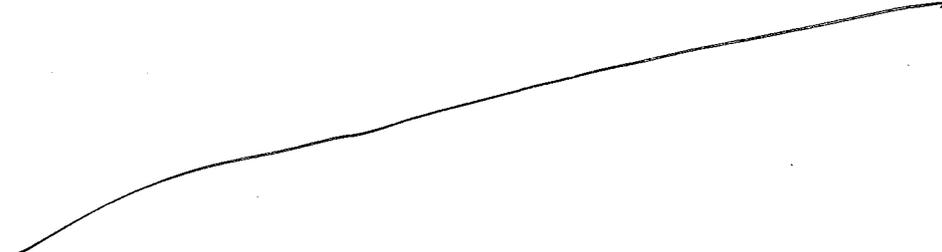
{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
8/9/2007 10:29:48 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION	
TO (<i>Division/Office</i>): Division of Pulmonary Drug Products, Pharmacology/Toxicology Review Team		FROM: Arthur Shaw, Review Chemist, Division of New Drug Chemistry 2, collocated Division of Pulmonary Drug Products	
DATE July 20, 2004	NDA. 21-658	TYPE OF DOCUMENT: Original	DATE OF DOCUMENT December 22, 2003
NAME OF DRUG Alvesco	PRIORITY CONSIDERATION: S	CLASSIFICATI ON OF DRUG: 1	DESIRED COMPLETION DATE Sept 1, 2004
NAME OF FIRM: Aventis			
REASON FOR REQUEST: <u>SAFETY ASSESSMENT</u>			
COMMENTS/SPECIAL INSTRUCTIONS: In section 3.2.P.5.5.6.1 Qualification of Drug Substance Process Impurities , the applicant states:			
			

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/s/

Arthur B. Shaw
7/20/04 05:41:17 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2004

To: Dan Bollag	From: Colette Jackson
Company: Aventis	Division of Pulmonary and Allergy Drug Products
Fax number: 908-541-5274	Fax number: 301-827-1271
Phone number: 908-304-6431	Phone number: 301-827-9388

Subject: Pediatric Waiver Request Letter

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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NDA 21-658

INFORMATION REQUEST LETTER

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

7/8/04

Attention: Dr. Daniel Bollag
Director, US Regulatory Affairs

Dear Dr. Bollag:

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

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. For studies 321, 322, 323/324, 323/324lt, 326, 341, 342, 102, and 103 reanalyze the cosyntropin stimulation tests results excluding all of the subjects with serious medication violations. This includes any subject with your violation codes ACAA, ADAA, AEAA, AEAB, AFAA, AGAA or any combination of these codes or combinations of these codes with other violations. Provide the point estimates and the 90% CI of the ratio of the Geometric means (corrected for baseline) for ciclesonide/placebo and ciclesonide/active comparator (where appropriate). Identify the subjects included in the analyses.
2. In the proposed PI, reference is made to urinary free cortisol corrected for creatinine. Reanalyze the data from this study (study 102) without correction for creatinine. Correction for creatinine assumes continuous and unvarying excretion of cortisol, as opposed to its known physiologic pattern, which is diurnal. Exclude from the reanalysis patients who have incomplete urine collections as assessed by urine volume and 24-hour creatinine excretion, patients with serious medication violations as noted in comment #3, patients with urine collection times outside of the collection time intervals, and patients with any other confounding factor that could affect interpretation of the result.
3. Provide the following information as SAS transport files for study 49/2000 (Effect of inhaled ciclesonide on cortisol levels and hypersensitivity to AMP in subject with bronchial asthma):
 - a. Individual AUC_{0-24} hour serum cortisol for each treatment.

- b. Point estimates and 90% confidence intervals of the geometric mean ratio of AUC_{0-24} for test vs. placebo and test vs. active comparator.
- c. Individual 24 hour urine cortisol corrected and un-corrected for creatinine for each treatment.

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

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sandra Barnes

7/8/04 12:24:47 PM



Food and Drug Administration
Rockville, MD 20857

NDA 21-658

INFORMATION REQUEST LETTER

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

6/10/04

Attention: Dr. Daniel Bollag
Director, US Regulatory Affairs

Dear Dr. Bollag:

Please refer to your December 22, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alvesco (ciclesonide) Inhalation Aerosol.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

b(4)

- 2. The following DMFs referenced in your NDA have been found to be deficient and the holders informed:

DMF #	Holder Name	Subject of DMF	Date of Deficiency Letter
		_____	May 5, 2004 and June 8, 2004
		_____	April 6, 2004

b(4)

- 3. Also a DMF used in support of DMF _____ has also been found deficient.

4. Additional information has been requested for the following DMFs

DMF #	Holder Name	Subject of DMF-	Date of Deficiency Letter
			May 14, 2004
			June 8, 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.

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

Sincerely,

{See appended electronic signature page}

Richard Lostritto, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Brian Rogers
6/10/04 12:05:15 PM

Executive CAC
June 8, 2004

Committee: Abby Jacobs, Ph.D., HFD-024, Acting Chair
Joseph Contrera, Ph.D., HFD-901, Member
Al DeFelice, Ph.D., HFD-110, Alternative Member
Joseph Sun, Ph.D., HFD-570, Team Leader
Huiqing Hao, Ph.D., HFD-570, Presenting Reviewer

Author of Draft: Huiqing Hao

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21658
Drug Name: Alvesco™ (Ciclesonide)
Sponsor: Aventis Pharmaceuticals

Background:

Ciclesonide is a glucocorticoid steroid intended for treatment of asthma by the inhalation route. The toxicity profile is typical for corticosteroids. Genotoxicity studies revealed it was negative in the Ames test, CHO-HGPRT mammalian mutation assay, for in vitro chromosomal aberrations in human lymphocytes and in the in vitro micronucleus test. However, it was positive in mouse micronucleus tests.

Mouse Carcinogenicity Study

Mice in the 2-year carcinogenicity study were given ciclesonide by oral gavage at doses of 150, 450, and 900 mcg/kg/day in polyethylene glycol. (The executive CAC had concurred with the dose selection). Decreased body weights in high dose animals (9-15% of untreated and 6-7% of vehicle) were observed by the end of the study.

The only possibly drug related tumor finding was adenoma in stomach antrum (HD: females, 3/50; male, 1/50; MD: male, 1/50). Statistical analysis revealed a significant positive trend test for females, but the results of the pair-wise Fishers Exact test comparing high dose females to vehicle controls were not statistically significant. The historical range at the study laboratory for adenomas of the stomach antrum is 0-2.1%. No other tumors (single or combined) were significantly increased.

Rat Carcinogenicity Study

Rats in the 2-year carcinogenicity study were given ciclesonide by inhalation at delivered doses of 30, 76 and 193 mcg/kg/day. (The executive CAC did not provide a recommendation on the dose-selection because a different rat strain was used in the dose-ranging study). An MTD was reached in this study based on the decreased body weights in high dose animals relative to those of controls (17-20% of air control and 15-18% of vehicle control).

There were no drug-related increases of benign or malignant tumors in this study. Statistical analysis revealed no positive trends for any single tumor or combined tumors in male or female rats.

Executive CAC Recommendations and Conclusions:

Mouse Study:

The Committee agreed that the study was adequate and that there were no drug-related neoplastic findings.

Rat Study:

The Committee agreed that the study was adequate and that there were no drug-related neoplastic findings.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

Cc:\n
/Division File, HFD-570
/Team Leader, Joseph Sun, HFD-570
/Reviewer, Huiqing Hao, HFD-570
/CSO/PM, Colette Jackson, HFD-570
Adele Seifried, HFD-024

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/s/

Abby Jacobs

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION	
TO (<i>Division/Office</i>): Division of Pulmonary Drug Products, Pharmacology/Toxicology Review Team		FROM: Arthur Shaw, Review Chemist, Division of New Drug Chemistry 2, collocated Division of Pulmonary Drug Products	
DATE March 17, 2004	NDA. 21-658	TYPE OF DOCUMENT: DMF 1 —	DATE OF DOCUMENT December 8, 2003
NAME OF DRUG Alvesco	PRIORITY CONSIDERATION: S	CLASSIFICATION OF DRUG: 1	DESIRED COMPLETION DATE May 1, 20043
NAME OF FIRM: Aventis is the sponsor of the NDA. _____ is the DMF holder			
REASON FOR REQUEST: <u>SAFETY ASSESSMENT</u>			
COMMENTS/SPECIAL INSTRUCTIONS: The DMF holder has proposed specifications for leachables from the valve assemblies used for the actuators for this drug product. These specifications are NOT in the NDA. Hard copy of information from the DMF will be provided.			
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER	

b(4)

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/s/

Arthur B. Shaw
3/17/04 03:34:22 PM
Tox consult on leachables



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 10, 2004
FROM: Carol H. Bosken, MD
Division of Pulmonary and Allergy Drug Products, HFD(570)
THROUGH: Lydia I Gilbert-McClain, MD
Team Leader, Division of Pulmonary and Allergy Drug Products, HFD(570)
TO: Ele Ibarra-Pratt
Division of Scientific Investigations
SUBJECT: NDA 21,658 Audit

It has come to our attention that Site 58, which was included in our previous request for auditing for the above referenced NDA, has recently been audited by DSI. In that case, we are in agreement that Site 160, which is already scheduled for auditing, can be substituted. In addition we would like to have Sites 40 and 83 included in the audit because of the large number of subjects that they enrolled.

We have previously indicated that the FEV₁ as a measure of pulmonary function, cataracts on physical exam, and cortisol measurements were the important outcome measures that we were interested in auditing. It would also be important to assure that patient accrual and enrollment was according to protocol. The enrollment criteria were complicated and it would have been easy to overlook some of the details. To be specific in studies, 321 and 322 patients were assigned to one of two strata on the basis of their prior asthma medications. Patients were stratified at screening, and their eligibility for randomization was dependent upon their response to placebo treatment during run-in.

Stratum 1: Patients who had been on inhaled corticosteroids &/or leukotriene inhibitors for the 30 days prior to screening. At screening they were required to have a FEV₁ of 65-100% predicted. After 5-28 days of single-blind placebo treatment they had to have a FEV₁ of 60-85% predicted and the post-placebo FEV₁ had to have been at least 10% less than the screening FEV₁.

Stratum 2: Patients who had not been on inhaled corticosteroids &/or leukotriene inhibitors for the 30 days prior to screening. They could have been treated with long or short acting β -agonists or methylxanthines. At screening they were required to have a FEV₁ of 60-85% predicted. After 5-28 days of single-blind placebo treatment they were still required to have a FEV₁ of 60-85% predicted. However, they were also required to have an asthma severity score ≥ 3 for 3 out of the 7 days prior to randomization, OR PEF variability of $\geq 20\%$ for 3 out of the 7 days prior to randomization, OR to have used albuterol ≥ 2 puffs/days for 3 out of the 7 days prior to randomization.

The relevant variables are "Stratad" for the stratum after manual review (1 or 2), "periodz" for time period coded as "screening", "baseline" or "double-blind", and "Dosevsdy", which is the days before (negative numbers) or after (positive number) the first dose of study medication was given. The visit number is listed as variable "vsno". The visit (vsno) 2 is equivalent to screening and should occur between 5 and 28 days before the first dose of medication. Vsno 3 is the visit of randomization and dosevsdy should be close to 0.

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/s/

Lydia McClain
3/10/04 05:17:41 PM
I concur



FILING REVIEW LETTER

NDA 21-658

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

3/5/04

Attention: Dr. Daniel Bollag
Director, US Regulatory Affairs

Dear Dr. Bollag:

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

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 21, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. _____ in the early Phase 1 PK studies used a _____, after which a modification was made to replace the _____ with a _____ in order to improve performance of the product. Indicate if an *in vitro* and/or *in vivo* link was provided in this submission and the location of it. b(4)
2. Explain the increase in _____ content. Provide data to demonstrate the effect of the increase _____ content on ciclesonide content and impurity levels. b(4)
3. Provide information to show the source of the potential leachables, _____ and _____.
4. Regarding the stability data:
 - a. Submit the stability data for the following test parameters: ethanol, water, ciclesonide content (assay), impurities. We propose the following data format which must be submitted as a SAS v.5 transport file.

Name	Label	Type
BATCH*	Batch	Character
TIME*	Time in months	Numeric
LEVEL*	Measurement	Numeric
TEMPER	Temperature	Character/Numeric
RH	Relative humidity	Character/Numeric
PACKAGE	Package	Character/Numeric
STRENGTH	Strength	Character/Numeric
CLLEVEL	1-Confidence level	Numeric
CLSIDE	#sides of confidence limits	Numeric
LOWSPEC	Lower specification	Numeric
UPPSPEC	Upper specification	Numeric

- b. Submit statistical analyses of the data, showing the criteria used for pooling in each case.
5. Describe the difference between the " _____ " and the " _____ ". Specify the studies in which the _____ was used.
 6. Include testing and acceptance criteria for "Spray Pattern" in the Specifications. b(4)
 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 cascade impactor 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.
 8. Provide data to demonstrate the consistency of the Particle Size Distribution (PSD) from beginning to end of actuator emptying.
 9. The test method for PSD (LCCIC007 Section 3.2.p.5.2, Page 179) includes options to measure either "only start Particle Size Distribution" or "start and end Particle Size Distribution" but the specification for PSD (Section 3.2.p.5.1 Page 8) does not specify which option to choose. Include specific directions as to which option to use. If the second option is used as part of routine testing, report data from "Start" and End" as requested above in Comment 7: _____
 _____ (for the 60 Actuation Products) or _____ (for the 120 Actuation Products). b(5)
 10. Use a consistent nomenclature for impurities and the parent compound throughout the NDA. Explain why the impurity ' _____ ' is named " _____ " with _____
 This is ciclesonide. Provide a link between the names of the impurities in the NDA and in DMF _____

NDA 21-658

Page 3

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

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

Sincerely,

{See appended electronic signature page}

Badru A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
3/5/04 12:35:53 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 1, 2004

To: Dan Bollag	From: Colette Jackson
Company: Aventis	Division of Pulmonary and Allergy Drug Products
Fax number: 908-541-5274	Fax number: 301-827-1271
Phone number: 908-304-6431	Phone number: 301-827-9388

Subject: February 13, 2004, teleconference

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-1050. Thank you.

MEMORANDUM OF TELECON

DATE: February 3, 2004

APPLICATION NUMBER: NDA 21-658/Alvesco

AVENTIS PHARMACEUTICALS PARTICIPANTS:

Eric Floyd, MBA, Ph.D., Regulatory Liaison
Daniel Bollag, Ph.D., Regulatory Liaison
Donald Banerji, M.D., Global Clinical Development
Sudeep Kundu, Ph.D., Global Biostatistics
Xiaoping Zhand, Ed.D., Global Biostatistics
Rosemary Crew, M.S., Publishing & Electronic Submissions

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS, HFD-570

Carol Bosken, M.D., Clinical Reviewer
Lydia Gilbert-McClain, M.D., Clinical Team Leader
Kathy Szema, M.D., Medical Officer
Ted Guo, Ph.D., Statistical Reviewer
James Gebert, Ph.D., Statistical Team Leader
Donald Collier, Office of Information Management
Colette Jackson, Project Manager

SUBJECT: Electronic submission problems

The Division informed the sponsor of the navigational difficulty of the clinical portion of their electronic submission due to electronic links which do not work and difficulty within the table of contents. The sponsor noted that they have identified the problems and have rectified the problem. They will submit a forthcoming tape to the electronic document room in the very near future.

The Division commented on the potential problems regarding the data submissions using Study 321 as an example. The Division pointed out that the Quality Of Life data files are all labeled as "continued," leaving doubts regarding the whereabouts of the first data file. Another example is that the datafile effpft.xpt does not come with a SAS-format catalog. Therefore, the Division suggested that the labels for the data files need a re-examination and the SAS-format catalogs need to be submitted. The sponsor stated that the files are large and needed to be broken down into separate diaries. However, it agreed that "continued" should not have been used to describe the first file and they will correct this with the forthcoming tape to be submitted.

The Division requested that the sponsor submit the SAS format catalogs to the same folders as those in which at least one data file needs a format link. It may start with its pivotal studies, due to the large number of data files in the submission. The sponsor agreed to submit the format

catalog as an amendment to the application as soon as possible and no specific timeline was mentioned.

Colette Jackson
Project Manager



cc:

Gilbert-McClain/February 9, 2004
Bosken/February 9, 2004
Guo/ February 9, 2004
Gebert/ February 9, 2004
Collier/ February 9, 2004

Drafted: February 8, 2004
Finalized: February 27, 2004



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/s/

Colette Jackson
3/3/04 12:20:44 PM
CSO

MEMORANDUM OF TELECON

DATE: February 3, 2004

APPLICATION NUMBER: NDA 21-658/Alvesco

AVENTIS PHARMACEUTICALS PARTICIPANTS:

Daniel Bollag, Ph.D., Regulatory Liaison

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS, HFD-570

Colette Jackson, Project Manager

SUBJECT: Biopharmaceutics electronic submission problems

The Division asked Aventis Pharmaceuticals if it is possible to submit the following to the electronic document room:

RAWNONMEM/ASCII files for both program code and data for the two files/studies studydmpkus01_085.pdf and studydmpk2003_0019.pdf.

Dr. Bollag willingly agreed to submit the required information as soon as possible.

Colette Jackson
Project Manager

Drafted: CCJ/February 27, 2004
Finalized: CCJ/March 1, 2004

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/s/

Colette Jackson
3/3/04 12:22:49 PM
CSO

REQUEST FOR CONSULTATION

TO (Division/Office):
New Drug Microbiology Staff HFD-003

FROM:
Arthur B. Shaw, Ph.D., HFD-570

DATE
January 26, 2004

IND NO.

NDA NO.
21-568

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
22-Dec-2003

NAME OF DRUG
Alvesco (ciclesonide) MDI

PRIORITY
CONSIDERATION
S

CLASSIFICATION OF
DRUG
1

DESIRED
COMPLETION DATE
March 1, 2004

NAME OF FIRM: Aventis

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | New NDA |

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 - PHARMACOLOGY
 - BIOPHARMACEUTICS
 - OTHER (SPECIFY BELOW):
- Microbiology**

COMMENTS/SPECIAL INSTRUCTIONS: The applicant has performed a microbiological challenge for this MDI (attached). They claim that the drug solution does not support microbial growth. Is this information adequate to support their conclusion?

See \\Cdsesub1\21658\N_000\2003-12-22\cmclproduct Section 3.2.p.2.5

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)
X MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Arthur B. Shaw
1/28/04 03:38:19 PM
Micro consults

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM:
Colette Jackson
Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

DATE January 22, 2004	IND NO.	NDA NO. 21-658	TYPE OF DOCUMENT N	DATE OF DOCUMENT December 22, 2003
NAME OF DRUG Alvesco (ciclesonide)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Inhaled Corticosteroid	DESIRED COMPLETION DATE September 9, 2004

NAME OF FIRM: Aventis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
---	--

IV. DRUG EXPERIENCE

<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS
--	---

V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
-----------------------------------	--------------------------------------

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This is a request for a nomenclature consult to evaluate the acceptability of Alvesco (ciclesonide).
This submission is electronic only and is located in the EDR in the submission dated December 22, 2003.

PDUFA DATE: October 23, 2004

CC:
Archival NDA 21-658
HFD-570/Division File
HFD-570/Jackson

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Colette Jackson
1/22/04 09:10:24 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-658

1/21/04

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

Attention: Dr. Daniel Bollag
Director, US Regulatory Affairs

Dear Dr. Bollag:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Alvesco (ciclesonide) Metered Dose Inhaler

Review Priority Classification: Standard (S)

Date of Application: December 22, 2003

Date of Receipt: December 23, 2003

Our Reference Number: NDA 21-658

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 23, 2004.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until October 23, 2007. However, in the interim, please submit your pediatric

drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Pulmonary and Allergy Drug Products, HFD-570

Attention: Division Document Room, 8B-45

5600 Fishers Lane

Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.

Director

Division of Pulmonary and Allergy Drug Products, HFD-570

Office of Drug Evaluation II

Center For Drug Evaluation and Research

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/s/

Badrul Chowdhury
1/21/04 09:37:08 AM



November 24, 2003

Mellon Bank
Three Mellon Bank Center
27th Floor
(FDA 360909)
Pittsburgh, PA 15259-0001

RE: User Fee for Ciclesonide NDA 21-658

To Whom It May Concern:

Please find enclosed the required User Fee payment in the amount of **\$573,500.00** for the upcoming **Ciclesonide; NDA 21-658**, and **User Fee ID No. 4548**.

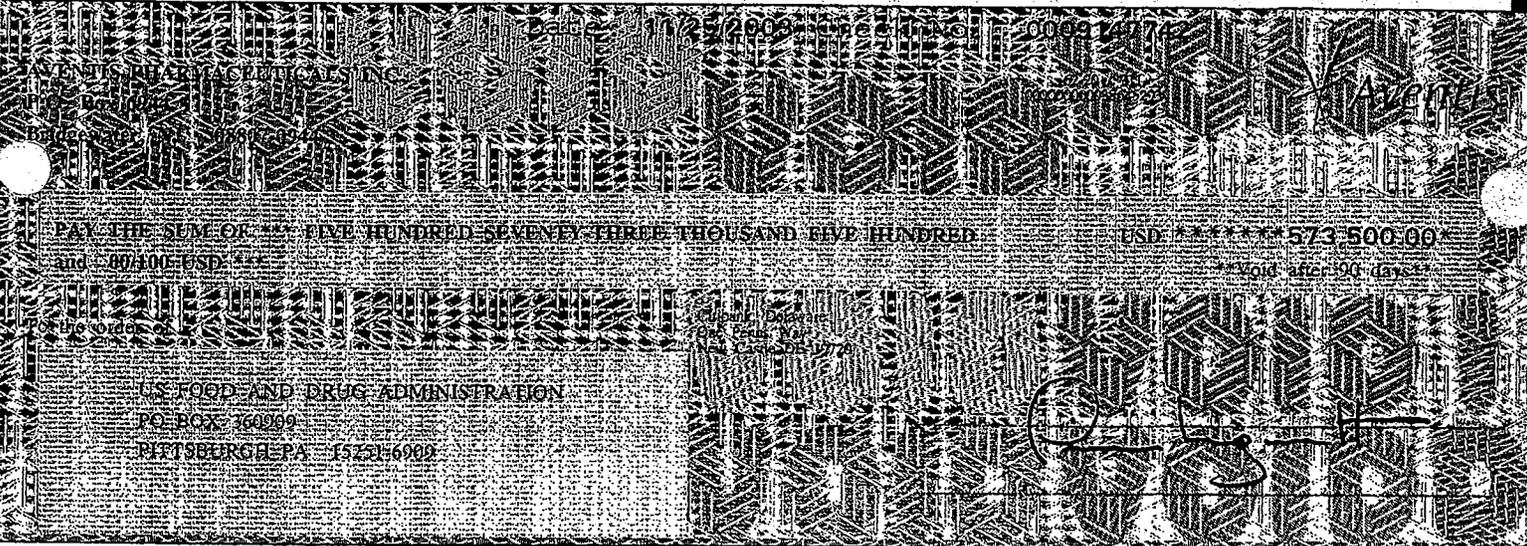
If you have any questions or if I can be of further assistance please contact me at (908) 304-6315.

Sincerely,
Aventis Pharmaceuticals Inc.

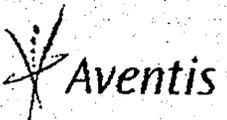
A handwritten signature in cursive script that reads "Stephanie Sterling".

Stephanie Sterling
Senior Administrative Assistant
US GRAMS Regulatory

Enclosure



⑈0009147742⑈ ⑆031100209⑆ 38645293⑈



Date :
11/25/2003

Vendor:
10155891

Page :
1/ 1

Check No.:
0009147742

Date	Reference/	Document	Text	Gross Amount	Discount	Net Amount
11/25/2003	INV112403	1900649411	Give: F.Lee- ⁴⁵⁴⁸ user fee NDA 2 1-658 Ciclesonide	573,500.00	0.00	573,500.00

*****573,500.00*

**ASHOK R. PATEL, MD
CAROLINE A. TOLOSA - GLORIA, MD
ACADEMY ALLERGY ASTHMA AND
IMMUNOLOGY**

Regina Flores, MA, CRC
Patricia Clark, MA, CRC
Phone (719) 744-0699
Fax (719) 542-5034

Research Department
3116 N. Elizabeth St.
Pueblo, CO 81008
ReginaFlores777@msn.com
Patjclarkcrc123@msn.com

October 15, 2003

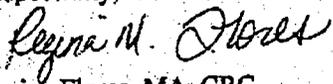
RE: Protocol: XRP1526B-341LT
Site: 9-267
DEA # _____

b(4)

To Whom It May Concern,

This letter is in correspondence to clarification of Principal Investigator Dr. Ashok R. Patel. Apparently there are two investigators with identical names. Dr. Ashok R. Patel has never been disbarred from participation in any study. The DEA number is listed above for your reference. If you should have any further questions, please call me at (719) 744-0699 ext. 104

Respectfully,


Regina Flores, MA, CRC

**ACADEMY ALLERGY ASTHMA &
IMMUNOLOGY CENTER**

**ASHOK R. PATEL M.D.
CAROLINE A. TOLOSA-GLORIA M.D.
CESAR J. GLORIA M.D.**

3116 North Elizabeth Street
Pueblo, CO 81008
Office: (719)542-7222
Fax: (719) 542-5034

TO: _____	FROM: Regina Flores MA, CRC
ATTENTION: _____	PHONE: FAX: 904-231-4280

b(4)

Total number of pages: 2
(Total includes cover sheet)

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PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Aventis Pharmaceuticals Inc.

Headquarters:
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021658

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(908) 304-6431

3. PRODUCT NAME

Ciclesonide

6. USER FEE I.D. NUMBER

4548

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Senior VP, Head of GRAMS

DATE

11/24/2003



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 1, 2004

To: Dan Bollag	From: Colette Jackson
Company: Aventis	Division of Pulmonary and Allergy Drug Products
Fax number: 908-541-5274	Fax number: 301-827-1271
Phone number: 908-304-6431	Phone number: 301-827-9388

Subject: February 3, 2004, teleconference

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES xNO

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 29, 2002
TIME: 9:30 AM
LOCATION: Food and Drug Administration/ Chesapeake Conference Room
APPLICATION: IND 53,391 Ciclesonide /Aventis Pharmaceuticals
TYPE OF MEETING: Pre-NDA Meeting

FDA ATTENDEES, DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

Robert J. Meyer, MD, Director, Office of Drug Evaluation II
Marianne Mann, MD, Deputy Division Director
Mary Purucker, MD, Ph.D., Clinical Team Leader
Raymond Anthracite, MD, Clinical Reviewer
Joseph Sun, Ph.D., Pharmacology/Toxicology Team Leader
Huiqing Hao, Ph.D., Pharmacology/Toxicology Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader
Sandra Suarez-Sharp, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer
Eric Duffy, Ph.D., DNDC II, Director
Guirag Poochikian, Ph.D., Chemistry Team Leader
Craig Bertha, Ph.D., Chemistry Reviewer
James Gebert, Ph.D., Biostatistics Reviewer
Don Collier, Project Manager
Colette Jackson, Project Manager
Craig Ostroff, PharmD., Regulatory Management Officer
Justina Molzon, CDER Associate Director for International Programs

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Aventis Pharma

Dr. Eric Floyd - Regulatory Affairs
Dr. Steve Caffè - Regulatory Affairs
Dr. Daniel Bollag - Regulatory Affairs
Dr. Pascale Vintezou - Regulatory Affairs
Dr. James Williams - Clinical Development
Dr. Donald Banerji - Clinical Development
Dr. James Fish - Clinical Development
Dr. Shashank Rohatagi - DMPK
Dr. Peter Glascott. - DSE/Toxicology
Dr. Sudeep Kundu - Biostatistics
Dr. Jim Cassaday - Data Management

Dr. Thomas Friebe - Regulatory Coordinator
Dr. Thomas Monticello - Head, Pathology (US), DSE
Mr. Jeffrey Dixon - Global Project Management
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Dr. Volkmar Zingel - Head, Dossier Management CMC
Dr. Klaus Dietzel - Project Leader

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BACKGROUND: The purpose of this meeting is to review the status of the Clinical development program, the CMC development program, and the proposed format of the forthcoming Common Technical Document (CTD) submission.

DISCUSSION:

The FDA addressed the following questions, in bold italics, posed in the sponsor's meeting package:

MODULE 2 – OVERALL SUMMARIES

- 1. Does the proposed Table of Contents for Module 2 (Tab 4) fulfill the requirements of the Agency reviewers(s)?***

The Division indicated that it is difficult to determine from the limited information presented. Safety reports from the prior developer of this drug under this IND were censored by attribution. If the primary safety data also suffers from this reporting bias, it will be largely unusable. The sponsor will need to explain how to address this specific concern. The sponsor was advised to address this in the NDA submission, and to clarify which studies had adverse events censored by attribution and which studies had more traditional adverse event reporting.

Assuming the prior concern is managed, we prefer to see the Integrated Safety Summary (ISS) lump all study results from all developers into two groups, all controlled trials and all uncontrolled trials. The Division would also prefer separation of studies that censored adverse events from studies that did not censor in the ISS. Justina Molzon noted the placement of the Integrated Safety Summary and the Integrated Summary of Efficacy can be confusing and suggested that, if either summary is too large, to place them into Module 5.

MODULE 3 - QUALITY

1. Drug Substance Impurities: Is the submitted response to FDA's EOP-II request for search of _____ acceptable?

The Division relayed to the sponsor that the information provided indicates that the impurities methodology is able to detect the _____ that would be formed from oxidation of the _____ key intermediate _____, and that this impurity has not been seen at levels above _____ % in any of the production-scale batches. The sponsor infers that the formation of the _____ corresponding to the _____ impurities _____ and _____ is therefore also unlikely. This investigation and argument is reasonable. The Division raised this issue because the _____ group would be a structural alert for mutagenicity. Therefore, it is important that the method chosen be able to detect and quantify these potential degradants. The summary of the method in the meeting package indicates these impurities can be detected if they were to form. The Division wanted to make sure that the sponsor was aware of this potential safety issue. When the application arrives, we will be applying the principles set up by the ICH in terms of the reporting, identification, and qualification of drug substance impurities.

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2. Impurities Qualification in Drug Product: Does the Agency concur that the _____ impurity at NMT _____ % (w/w) and the _____ at NMT _____ % (w/w) are not of toxicological concern and are qualified?

The Division indicated that the drug substance qualification threshold for impurities is _____ % or _____ mg/day (whichever is lower) when MDI is ≤ 2 g. _____, at _____ % in the drug substance is much higher than the threshold of _____ %. Therefore, qualification of _____ is needed. To qualify the _____, which does not constitute a structural alert, general toxicity in one animal species for 90 days is desirable. The 28-day dog study that has been performed is not adequate to qualify this impurity. Similarly, other impurities in the drug substance need to be qualified if their levels exceed _____ %. The sponsor questioned whether the 90-day study would show additional toxicity compared to the already performed 28-day dog study. The sponsor noted that there was a 6-month inhalation rat study performed and the impurity was present in complex with the parent compound. The sponsor asked whether the 6-month inhalation rat study could qualify the impurity. The Division informed the sponsor that if the impurity was complexed with the drug substance, the 6-month rat study may be sufficient as long as the NOAEL was defined and as long as enough safety margin was provided. The sponsor asked if the threshold for the impurity has some flexibility. The Division informed the sponsor that if the impurity had a similar toxicity profile as the parent compound, then the threshold would have some flexibility. The sponsor questioned if the 6-month data is deemed unacceptable, could they

b(4)

The Agency informed the sponsor that this would not likely be deemed acceptable, since the study is a critical part of the application process.

The Division indicated the drug product qualification threshold for degradants is \leq _____ or _____ mcg (whichever is lower) for MDI _____ mg. The specification of NMT _____% for _____, a degradant, in the drug product is therefore acceptable. The same policy is applicable to all other degradants that are not structural alerts for mutagenicity in the drug product.

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3. Shelf-Life Determination for Ciclesonide MDI: Based on the amount and type of data planned to be submitted in the original application, does the Agency concur with the provision of a 24-month shelf life for the 60 and 120 actuation products?

The Agency relayed that without an actual evaluation of the data and trends, it is not possible to answer this question at the current time. However, the expiration-dating period will be based on a statistical analysis of the available stability data once an agreement has been made on the acceptance criteria for the related parameters. There will be certain key parameters that the Agency will always include in our request to our statistical colleagues and we will also include parameters that are "trending." The Agency will typically look at assay, degradant impurities and leachables, emitted dose, aerodynamic particle size distribution, weight loss due to leakage, and moisture uptake. The sponsor inquired as to the requirements to achieve a 24-month shelf life. The Agency informed the sponsor that 24-months will not be granted with only 12-months of data. Full term data is needed.

4. Demonstrated Equivalence of the 60 and 120 Actuation Pack Sizes: Does the data proposed to be presented in the NDA sufficiently support equivalence between the 60 actuation and 120 actuation products?

The Division requested a brief description of the configuration of the 60 count versus the 120 count unit since it was not clearly stated in the meeting package. The sponsor displayed a picture of the sleeved can to be used with the 60 count version. This unit consisted of a shorter canister for maintenance of internal headspace with a lesser fill volume but with an external "sleeve" can fit onto the bottom that will render the overall dimensions as that for the 120 count fill version. The Division noted that there will be no contact of the formulation with the additional "sleeve" can.

The Division suggested that the sponsor should compare the levels of leachables and foreign particulates between the two sizes (i.e., the gaskets are probably of the same mass for both counts although the fill is obviously less for the 60 count version potentially leading to higher levels of leachables in the smaller count product). Also, there may be differences in terms of _____ uptake, and therefore _____ content should be evaluated.

b(4)

The Division indicated that this may be more of a statistical issue subject to review, but that it should be understood that depending on the differences seen between the 60 count data and the 120 count data, it may not be justified to pool these data to determine a joint expiration dating period determination.

5. Dose Counter Amendment: Aventis plans to submit the dose counter documentation package after the initial NDA filing. Can this information be submitted during the NDA review cycle period without resetting the review clock?

The Division questioned why there is a delay expected the submission of the dose counter documentation package. The Division indicated that the sponsor should submit the pertinent documentation as soon as possible following the NDA submission. If the material is submitted too late in the review cycle, the Agency may not have enough time for review before the goal date for action. If that occurs, the product may still potentially be approved, but it would not be approved with the dose counter. The sponsor noted that the delay is expected due to the lack of availability of the data. The dose counter is in the process of development

6. Dose Counter Comparability Data: Does the Agency concur that the CMC and clinical use study data package proposed to support the use of a dose counter is appropriate?

In reference to CMC, the Division noted that the sponsor will be doing in vitro tests of the units with the counter examining the force to count versus actuate. The Division informed the sponsor that they should institute an acceptance specification for the "force to actuate" for the valve when these drug product components are accepted from the supplier. The Division confirmed that there will be tests to assess the ruggedness of the counter to drop and impact as well as temperature cycling. The Division also confirmed that there will be in vitro tests on counters to make sure they "stop" or "lock out" when you reach the labeled claim number of actuations. In addition, the sponsor will be comparing the key performance parameters of dose content uniformity (DCU) and particle size distribution (PSD) by cascade impactor for MDI units both with and without a counter in a one-time study. The Division's main concerns are that there are no "fire not count" issues, in other words the counter should always record an actuation when one is performed. The Division also requests that the counter be rugged.

The Division noted that the information outlined in the meeting package appears to provide the necessary data to address the CMC concerns. The Division also added that for the proposed in-use study, any counters that are reported by patients to be problematic (counter-related or otherwise) should be returned, examined, and tested to determine the cause of the problem, and that this information be included with the other data in the NDA. The Division suggests the returned units should also be tested for performance as well (e.g. DCU and PSD testing).

In reference to Clinical, the in-use study was submitted as a synopsis. The Division failed to identify a "data package" associated with it.

The Division requested that the sponsor submit data to validate the assumption that weight changes are a sensitive indicator of the number of actuations and to quantify the accuracy and variability of this measurement prior to using it in the clinical trial. It is likely that the weight changes noted in the clinical trial will not correlate entirely with the number of reported actuations reported by patients and the number of actuations reported by the dose counter.

The Division also suggested that the in vitro testing, recommended in the draft guidance to assess reliability and lack of undercounting during simulated use and abuse, be studied. The Division

would like to know how this trial will "...obtain information on the technical function and the perceived utility for patients of the counters..." [draft Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products]. The Division inquired whether the sponsor intends to utilize a questionnaire and, if so, it would need to be provided in the final protocol. The sponsor indicated their intention of using a questionnaire, and agreed to submit it with the final protocol.

7. CTD Format and Content: Does the proposed Table of Contents for Module 3 - CTD Quality section fulfill the requirements of the Agency reviewer(s)?

The Division noted that under the section dealing with the DP characterization, plume geometry and microbial challenge testing should be included, as recommended in our draft CMC guidance. In reference to Module 3, the Division suggested change in the numbering pattern utilized in the submission and referred the sponsor to the ICH website and the CTD guidance documents

The Division had the following additional comments (not necessarily all inclusive) on other CMC information provided in the meeting package:

1. In v001:p038, DS specifications: Any individual impurity found at a concentration of 0.10 percent or 1.0 mg per daily intake (whichever is lower), relative to the parent drug substance, should be identified.
2. In v001:pp. 038-039, DS specifications: Some of the limits that are currently proposed for dealing with the purity of the DS looked wide. The acceptance criteria proposed for the impurities, degradants, organic volatile impurities, and heavy metals will be assessed relative to the data provided and should be reflective of that data from a QC perspective. It is not acceptable to have an upper limit of $\frac{1}{100}$ ppm for the ethanol content in the DS when quantitated levels are 1 or 2 orders of magnitude lower. **b(4)**
3. In v001: pp. 047-048, as already mentioned, DP expiration dating period calculations: Leachables and weight loss due to leakage should be included in the assessment.
4. In v001: pp. 052-053, in terms of the dose proportionality study for the $\frac{1}{100}$ different strengths ($\frac{1}{100}$, 80, and 160 mcg emitted), this should include a comparison of both the emitted dosing performance as well as the particle size distribution by CI, as recommended in our draft CMC guidance.

The following comments relate to your brief summary provided for how you will address past CMC issues from the EOP2 meeting. **b(4)**

5. In v001: p. 032, in terms of the foreign particulates in the DP (solution based), the typical ranges that are characterized are for particles $\frac{1}{100}$ μm , $\frac{1}{100}$ μm , and $\frac{1}{100}$ μm .
6. In v001: p. 033, in terms of the $\frac{1}{100}$ applied to 100% of the manufactured filled canisters, the application should include complete validation data for this process (e.g., including data supporting the attainment of an $\frac{1}{100}$ **b(4)**

for at least 3 minutes). The quarantine or equilibration period after 1 _____ should be at least 3 weeks (an upper limit to this period should also be proposed as well).

7. In v001: p. 032, it is stated that extractables controls will be applied to the CCS and that the relationship to leachables will be supported with data in a DMF. Leachables in the DP need to be determined for product stored on stability. There should be specifications for DP leachables regardless of whether or not an adequate correlation is established with CCS extractables.

Leachables studies for the DP should be performed on an adequate number of batches (e.g., primary stability batches) with enough time points to characterize the progression and allow the data to be used in the statistical analysis for expiration dating period calculations, as we have already discussed.

MODULE 4 – NONCLINICAL STUDY REPORTS

1. *Does the proposed Table of Contents for Module 4 – NonClinical section fulfill the requirements of the Agency reviewer(s)?*

The Division indicated that the proposed Table of Contents for Module 4 does fulfill the requirements of the reviewer, however, issues that may be identified during the reviewing of these studies including pre- and post-natal developmental toxicity study, second Seg II study in rabbits at a lower dose to define a NOAEL, and carcinogenicity studies in rats and mice. Additionally, the Division expects the sponsor to provide (or cross-reference to) complete Pharmacology/Toxicology data to support the use of HFA 134a.

2. *With completion of the studies discussed at the End-of-Phase II meeting and the Aventis response to the FDA regarding the 12-month inhalation dog study, it is our understanding that the non-clinical toxicology package for Ciclesonide is sufficient for registration and all outstanding questions are resolved. Does the FDA concur with this?*

The Division indicated non-concurrence due to the fact that spermiogenic disturbance observed in the 12-month dog study has not been clarified. No such "artifacts" were observed in the control in the 12-month study nor in the control and the two lower doses in the 3-month study. The sponsor needs to provide historical control data to support their assertion that this represents artifact. The sponsor acknowledged this issue, noting it was an unusual determination to them as well. The Division indicated that the term of spermiogenic disturbances was used as a synonym for dyspermia by Byk-Gulden in another study. The sponsor suggested contracting an independent, international pathology panel to review the dog test slides in order to resolve what is perceived as a "terminology" issue, since Byk-Gulden utilized coding unfamiliar to national toxicological societies. The sponsor indicated there is no other historical data to provide. The Division indicated its willingness to review data from the independent pathology panel, but if the

review of the re-submission of the report does not resolve this issue and a NOAEL is not identified, it will be a concern of considerable toxicological significance.

CLINICAL PHARMACOLOGY

The Division relayed the following Clinical Pharmacology comments to the sponsor:

1. It is not clear from the package submitted on July 29, 2002, if the effect of gender on the PK of ciclesonide and its metabolites has been addressed. It is recommended that appropriate analysis be done to address this. The sponsor noted that gender was included as a covariate in population PK analysis.
2. For population PK and PD studies, include program code, data sets (ID, time, dose, concentration, covariates), model building information, and output of final model (refer to Population Pharmacokinetics Guidance for Industry). Submit the data as SAS transport files. The sponsor indicated that they have followed the Population Pharmacokinetics Guidance for Industry as close as possible and that they will submit the data requested as SAS transport files.
3. The sponsor has stated in a previous meeting that sparse sampling with population PK analysis is planned to be conducted in young children. The Agency questions whether the sponsor has developed an analytical method sensitive enough to detect the drug and the metabolites in plasma. The sponsor mentioned that the assay sensitivity, although improved, still cannot detect the parent compound since it is not available long enough in plasma for its characterization.

MODULE 5 – CLINICAL STUDY REPORTS

1. *Does the proposed Table of Contents for Module 5 – Clinical section fulfill the requirements of the Agency reviewer(s)?*

The Table of Contents appears acceptable. Under 21 CFR(d)(5)(vi)(a) there is no requirement to submit safety data for a different drug product, but we would appreciate the Altana Pharma AG's () safety data as "...data from...studies of related drugs" [1:83]. The sponsor indicated their intention to submit the summary of the actual () data and its data sets separately.

b(4)

A prototype CSR is presented in Tab 7. This prototype CSR illustrates the proposed organization of the CSR's that will be included in our NDA submission.

2. *Does the Agency agree with the presentation and documentation of efficacy and safety data as displayed in the prototype CSR?*

The Division indicated general agreement with the CSR, but specifically requests that all safety analyses also be done on subsets of race, gender and age. The Division also requested that laboratory safety variables also be summarized as shift tables [1:140-1, 195-6]. There should be one table for each lab value and study arm, showing patient counts in categories of below the predefined low abnormal (PLA), between PLA and lower limit of normal (LLN), within the normal range, above the upper limit of normal (ULN) but below predefined high abnormal (PHA) and above the PHA. These counts should be tallied at baseline and at the end of treatment exposure. For example, let "v" be a laboratory value, and each table should look like this:

TREATMENT 'A' LAB VALUE = HEMATOCRIT						
Baseline	End of Treatment	$v \leq \text{PLA}$	$\text{PLA} < v \leq \text{LLN}$	$\text{LLN} < v \leq \text{ULN}$	$\text{ULN} < v \leq \text{PHA}$	$\text{PHA} < v$
$v \leq \text{PLA}$						
$\text{PLA} < v \leq \text{LLN}$						
$\text{LLN} < v \leq \text{ULN}$						
$\text{ULN} < v \leq \text{PHA}$						
$\text{PHA} < v$						
v = a laboratory value PLA = predefined low abnormal LLN = lower limit of normal ULN = upper limit of normal PHA = predefined high abnormal						

The dark vertically hatched cells represent categorical shifts up from baseline and the lighter diagonally hatched cells are the shifts down. For a three-armed trial, there should be three such tables for each laboratory value.

TAB 8 - SUMMARY OF SAFETY / SAFETY TABLES

The ISS tables will follow a format consistent with the tables for the individual CSRs. Sample tables are provided under Tab 8.

3. Does the Agency concur with the approach to the data displays summarized in Tab 8?

The table presented appears acceptable. . Please refer to our request for an additional display of laboratory data explained in the response to the prior query.

4. Does the Agency concur with Aventis' plans for the presentation of overall safety data and summary of safety (ISS) within Module 2 of the CTD?

The Division indicated that this may be presented anywhere the sponsor deems suitable. The Division noted that the sponsor will need to address the pediatric rule. The sponsor indicated their intention to currently address the adult population enrollment issue, and address the pediatric issues at a later time.

TAB 9 - STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) provided under Tab 9 (previously submitted on May 29, 2002 (Serial #145)), outlines the statistical plans for the Phase III severe persistent asthma studies (Protocols 323/324 combined). This plan conforms generally to all prior agreements reached between Aventis and the Agency and established principles of clinical trial analysis. An additional SAP will be submitted under separate cover, prior to unblinding, outlining the statistical analysis plans for the Phase III mild to moderate persistent asthma studies (Protocols 321 and 322).

5. Is the format of the plan provided acceptable? Are the two planned analyses sufficient to support the filing provided the results are consistent with the respective study hypotheses?

The Division agreed that these are acceptable, but noted that the program is minimal and problems could occur if certain doses are not efficacious. The sponsor indicated there are 2 studies with mild to moderate patients and that data will not be pooled. Protocols 323 and 324 will pool data, but for efficacy only.

TAB 10 - PLANS FOR ELECTRONIC SUBMISSION

The proposed electronic submission of this NDA will utilize the ADOBE Acrobat and SAS platforms previously established with the Agency. Case Report Tabulations and Case Report Forms will be submitted in electronic format only.

6. Does the electronic submission plan fulfill the requirements of the Agency reviewer(s)?

The electronic submission plan is acceptable.

Minutes Preparer _____
Colette Jackson, Project Manager

cc: Original

HFD570/Div. Files
HFD-570/Meeting Minutes files
HFD-570/Jackson
HFD-570/Mann
HFD-570/Purucker
HFD-570/Anthracite
HFD-570/Bertha
HFD-570/Poochikian
HFD-570/Sun
HFD-570/Hao
HFD-570/Fadiran
HFD-570/Suarez
HFD-570/Gebert
HFD-570/Meyer

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MEETING MINUTES



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