

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II



TO: Kathy Creeden
Phone Number: 908-277-3245
Fax Number: 908-277-4751
FROM: Perinde Jane

DIVISION OF PULMONARY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 2 Date: 7-10-98

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COMMENTS:

Memorandum

Date: July 9, 1998
To: Parinda Jani
From: Tracey Zoetis
RE: NDA 20-831

In reply to the inquiry from Novartis regarding item B.10 of the June 26, 1998 letter, here is a list of the inhalation studies for which the deposition factor should be provided.

Study	Study No.
(Dry Powder Formulation 1:1000): 13-Week Inhalation Toxicity Study in Dogs	906155
(Dry Powder Formulation 1:69): 4-Week Inhalation Toxicity Study in Rats	926111
(Dry Powder Formulation 1:1000): 13-Week Inhalation Toxicity Study in Rats	906154
13-Week Inhalation Toxicity Study in Rats	906224
(1:73 Powder Formulation): 26/52-Week Inhalation Toxicity Study in Rats	936115
(Dry Powder Formulation 1:69): Preliminary Inhalation Toxicity Study in Dogs	926109
Inhalation Feasibility Study in Dogs	936077
(Dry Powder Formulation 1:69) 4-Week Inhalation Toxicity Study in Dogs	926074
(1:73 Powder Formulation): 52-Week Inhalation Toxicity Study in Dogs	936116

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ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II



TO: Dan Lettrich

Phone Number: 908-277-5804

Fax Number: 908-277-5989

FROM: Parinele Jam

DIVISION OF PULMONARY DRUG PRODUCTS

CDER Pulmonary Group (HFD-570), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-1050 FAX: (301) 827-1271

Total number of pages, including cover sheet: 3 Date: 4-29-98

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COMMENTS:

M E M O R A N D U M

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

DATE: April 28, 1998

FROM: John C. Leak, Ph.D., chemist HFD-570

/S/
U

THROUGH: G. Poochikian, Ph.D., chemistry team leader HFD-570

/S/

SUBJECT: Novartis 4/22/98 FAX - questions on our 3/25/98 letter

TO: File

Attached is a copy of the FAX to NDA 20-831 and this reviewer's response to the questions in the FAX. The CSO (project leader) should FAX our response to the applicant's questions.

cc: NDA 20-831
HFD-570
HFD-570/JLeak/GPoochikian
HFD-570/PJani

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ON ORIGINAL**

2 PAGE(S) REDACTED



Daniel G. Lettrich
Associate Director

Novartis Pharmaceuticals Corporation

Tel 800-277-8804
Fax 800-277-8888
Internet: daniel.lettrich
@pharma.novartis.com

Fax
301-827-1271
3 pages

Attention

Ms. P. Janl, Project Manager
Food & Drug Administration Division of Pulmonary Drug Products/HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Date 22-Apr-98

Subject Foradil™ NDA 20-831 - Clarification of 25-Mar-98 FDA Questions

Dear Parinda,

As agreed by your voicemail message to me on Friday, 17-Apr-98, a meeting at FDA for full discussion of FDA's 25-Mar-98 questions regarding our original NDA for Foradil Dry Powder Capsules will be delayed until late May. The purpose of this meeting is for FDA to fully explain their concerns to Novartis and for both parties to agree upon what course of action Novartis will take to satisfy these concerns.

In the meantime, we would like to receive some direction about the following questions, so that we might start generating data in order to have more information available for discussion at the May meeting.

[]

I will phone you on Thursday, 23-Apr to discuss the possibility of a telecon or written communication regarding these questions of primary concern.

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2 PAGE(S) REDACTED

Printed by Parinda Jani
Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 22-Apr-1998 11:31am
From: Tracey Zoetis
ZOETIST
Dept: HFD-570 PKLN 10B45
Tel No: 301-827-1050 FAX t-

TO: Parinda Jani

(JANIP)

Subject: Questions for Novartis

Parinda,

Could you please contact the Sponsor to find out the answers to the attached questions. Let me know how quickly I can get these answers.

Thank you,
Tracey

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ON ORIGINAL**

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II**



DIVISION OF PULMONARY DRUG PRODUCTS

**CDER Pulmonary Group (HFD-155), 5600 Fishers Lane
Rockville, Maryland 20857**

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PHONE: (301) 827-1050 FAX: (301) 827-1271

TO: Cathy Creeden

FROM: Parvada Jauri

Total number of pages, including cover sheet: 2

Date: 4-23-98

COMMENTS:

1. Please clarify the AUC data for mice. In study no. DM1/1991 (NDA volume 64, pp. 277 - 319), AUC for mice dosed orally are reported to be 33.48 $\mu\text{mol.h/l}$ for the 6 mg/kg group and 315.5 $\mu\text{mol.h/l}$ for the 60 mg/kg/day group (page 301). The table in the Comprehensive Summary of Nonclinical Absorption, Distribution, Metabolism and Excretion Studies (NDA volume 11, pp. 265 - 377) reports AUC data for mice as 300 and 4300 nmol.h/l for these same groups, respectively (p. 303). On the next page, AUC data are reported as 130 and 1100 (no reported units) for these groups, respectively (page 304).

Please clarify this discrepancy and provide re-calculations of human equivalent oral and inhaled doses as well as the multiple of the maximum daily inhalation dose as reported in Table 25 (page 304) of the NDA (vol. 11, p. 304).

2. Please clarify the types of liver tumors that were combined mouse dietary carcinogenicity study. In the statistical analysis of the carcinogenicity study, "hepatocellular tumors" were combined (see NDA vol. 49, pp. 430 and 440). Please specify the tumor types that were included in this analysis and the rationale for combining the tumors.

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: July 25, 2000

Time: 11:00 – 12:30

Location: Conference Room "10B45"

IMTS #: 6023

Sponsor: Novartis Pharmaceuticals Corporation

NDA: 20-831

Product: Foradil Aerolizer (formoterol fumarate inhalation powder)

Type of Meeting: Chemistry, Manufacturing, and Controls (CMC)

FDA Attendees:

Parinda Jani	Project Manager
John Leak, Ph.D.	Consultant, Chemistry Reviewer
Robert Meyer, M.D.	Division Director, DPADP
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Kevin Swiss, Ph.D.	Chemistry Reviewer

Novartis Attendees:

Stephanie Barba	Executive Director, Global Therapeutic Area Head
Hartmut Bethke	Technical Operations
Kathleen Creedon, Ph.D.	Assistant Director, Therapeutic Area
Barbara Haeberlin	Technical Research and Development
Ian Hassan	Project Management
Yatindra Joshi, Ph.D.	Vice President, US Analytical Research and Development
Thomas Koestler	Global Head, DRA and CS&E
Sharon Olmstead	Assistant Director, Regulatory Liaison, Washington D.C.
Glenn Thompson	Technical Research and Development

Background: The original NDA for Foradil Aerolizer was submitted June 26, 1997. An "Information Request" letter was sent to the sponsor on March 25, 1998. The Agency sent an "approvable" letter to the sponsor On June 26, 1998. The Agency received a "complete response" for the "approvable" letter on November 23, 1999. A second "approvable" letter was sent to the sponsor on May 24, 2000. For additional information refer to the minutes of the meetings/teleconferences dated December 14, 1998, February 24 and March 4, 1999, and April 6 and July 6, 2000 and the submission dated July 17, 2000.

Purpose: The purpose of the meeting was to discuss the issues related to Foradil Aerolizer for-1) shelf-life and storage conditions; 2) mass balance deficit; 3) variability and stability related to the fine particle fraction; 4) variability of the emitted dose; and 5) secondary protective packaging.

Discussion:

Shelf-life and storage conditions

Novartis stated that for the marketing and patients' compliance purposes, it would prefer that patients be allowed to store this product at room temperature. Novartis is planning to submit stability data for three lots and two packaging sites _____ up to 12 months at 5°C/60% and 75% RH, 25°C/60% and 75% RH, 30°C/60% RH, up to 6-7.5 months of data at 40°C/75% RH, and up to 24 months of data at 25°C/60% RH and 12 months at 30°C/60% - 80%RH (original NDA stability data). Novartis believes that the data to be submitted to the

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Agency with the "complete response" would justify _____ expiration dating period, refrigerated storage conditions prior to dispensing, and after dispensing to the patient up to 6 months of storage at room temperature.

The Agency stated that the final conclusion regarding the expiration dating period and the storage conditions before and after dispensing will be a review issue.

Mass balance deficit

Novartis questioned whether mass balance would be still an issue, if the recommended storage conditions for Foradil are under refrigeration. Novartis stated that the degradation products were all accounted for with the C-14 study. Novartis has conducted several toxicology studies in which the animals were exposed to 10 – 300 times the recommended doses, and there were no safety implications. The batches used in the pivotal clinical studies were stored at room temperature, and based upon the degradation profile, estimated mass balance deficit would have been up to 8% in the pivotal clinical studies.

The Agency stated that the submitted data suggest that the storage conditions have significant impact on the mass balance. The cumulative effect of chronic administration of Foradil was not studied in the clinical trials. There are no data available for the impact of secondary packaging. Novartis needs to place proper controls in the process for batch-to-batch reproducibility.

Fine particle fraction (FPF)

Novartis stated that the FPF is comparable for the clinical and commercial batches. The analysis submitted for FPF includes accelerated stability data (40°C/75% RH). Novartis has conducted extensive investigation including instrumentation, training of the technicians, and the environmental controls of the testing laboratory, to determine the trends observed for FPF. The testing of the samples from _____ packaging sites is conducted at the same commercial laboratory.

The Agency stated that the proposed approach is acceptable. The FPF data should be presented separately for _____ for each packaging site.

Emitted dose

Novartis agrees to accept the release and controls specifications for emitted dose recommended by the Agency.

Secondary Protective Packaging

Novartis stated that there are limited data available for the secondary protective packaging. Novartis is willing to commit to launch the product with overwrap, put the first three commercial batches on stability with and without overwrap, evaluate the data, and if the overwrap does not improve the stability of the product, request removal of it. Additional data for the overwrapped product will be provided during the review process.

The following additional issues were discussed and/or agreed upon.

- Novartis will conduct stability testing of first three commercial batches. The number of batches to be tested annually will depend on the rate of productions (testing of only one batch would not be acceptable). Novartis should propose as to how many batches (percent of the number of batches to be manufactured annually) will be tested annually.
- Novartis will make a proposal as to how many batches would be tested annually and what parameters will be tested.
- The concept of refrigeration plus room temperature storage would be acceptable. The duration of refrigeration and room temperature storage would be a review issue.
- Novartis will provide appropriate DMF references that would include the composition and components for the secondary packaging.
- Novartis will provide individual plate data for the _____ testing for _____ packaging sites.
- Novartis is planning to submit a "response" to the May 24, 2000, "approvable" letter by second week of August.
- Novartis will submit additional secondary packaging data for 2 months time point by end of August. It was agreed that the "User Fee" review clock will start upon receipt of this submission, as this submission would be considered a "complete response".

/S/

Parinda Jani
Project Manager

CC:
ORIG NDA 20-831
DIV FILE/HFD-570
HFD-570/JANI
HFD-570/POOCHIKIAN/8-8-00
HFD-570/MEYER/8-21-00
HFD-570/SWISS/8-8-00

**APPEARS THIS WAY
ON ORIGINAL**

Meeting Minutes

Meeting Date: April 6, 2000

Time: 9:30-11:00 AM

Location: Conference Room "M"

IMTS #: 5425

Applicant: Novartis Pharmaceuticals Corporation

NDA: 20-831

Product: Foradil Aerolizer (formoterol fumarate powder for inhalation)

Type of Meeting: CMC, Stability data

FDA Attendees:

Craig Bertha, Ph.D.	Chemistry Reviewer
Parinda Jani	Project Manager
John Jenkins, M.D.	Office Director, ODE-II
John Leak, Ph.D.	Consultant, Chemistry Reviewer
Robert Meyer, M.D.	Division Director, DPADP
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Steve Wilson, Ph.D.	Team Leader, Biometrics

Novartis Attendees:

Stephanie Barba	Executive Director, DRA, Global Therapeutic Area Head
Robert Clark	US Head DRA-CMC
Barbara Haeberlin, Ph.D.	Team Project Leader, Basle Analytical Research and Development
Yatindra Joshi, Ph.D.	Vice President, US Analytical Research and Development
Thomas Koestler, Ph.D.	Global Head, DRA and CS&E
Glenn Thompson, Ph.D.	Senior Scientist III, US Analytical Research and Development

Background: Refer to the following documents:

March 25, 1998:	IR letter
June 26, 1998:	Action letter (AE)
December 14, 1998:	Meeting minutes
January 21, 1999:	IR letter
February 24, 1999:	Teleconference minutes
March 4, 1999:	Meeting minutes
February 16, 2000:	6-month stability data update submission

This meeting was scheduled to discuss the updated stability data and to reach an agreement for the expiration dating period and storage conditions for Foradil.

Novartis presented an overview of the new stability data and described the differences between the original stability studies submitted in the NDA and the data in the recent submission.

Novartis stated that:

- The stability studies are still ongoing and the 9-month time point data are being analyzed and will be available soon for the Agency's review.
- There are some marginal changes observed for 25⁰C/60% RH and 25⁰C/75% RH conditions between the 6-month and the 9-month time point.
- There are changes observed for 30⁰C/60% RH condition between the 6-month and the 9-month time point. Additional testing is still ongoing.

- It appears to Novartis that the new assay data as a function of time are consistent with the data provided in the original NDA submission.
- It is Novartis' observation that the stability trends for _____ packaging _____) are similar and consistent as they were observed with the original data.
- Novartis believes that the data supports room temperature storage and _____ shelf-life.

The Agency has evaluated the submitted data and has made the following observations in regard to the emitted dose, mass balance which includes assay and degradation, and fine particle size distribution.

- There is relatively high variability in the observed data.
- It is still not clear whether the high variability and certain trends are due to the environmental conditions (i.e., temperature or humidity, or combination), and/or are independent of these conditions.
- There is significant drop in assay and fine particles (30% and 50%, respectively) at 40°C. Similar trends are observed at 30°C and 25°C, but to a lesser degree.
- Once the product is released, it will be stored at various temperature and/or other conditions, which may have an impact on the performance of the product.

In response, Novartis stated that because of the limited new data, they were unable to conduct the _____ analysis, which was discussed at the previous meetings. Novartis believes that the only time the product will be exposed to the uncontrolled conditions, when it will be dispensed to the patients. Generally, the storage conditions in the warehouses, wholesalers, pharmacies etc. are at controlled room temperature, between 20°C - 25°C. In their opinion, the impact on the performance of the product may be minimal.

The Agency questioned whether Novartis has conducted any experiments with any kind of secondary protective packaging as it is difficult to make an assessment whether the effect is due to humidity, temperature, or combination of both.

Novartis stated that the packaging leak testing is performed with a very sensitive assay. Novartis has not explored whether a secondary protective packaging decrease the variability, but is willing to conduct additional studies with a secondary protective packaging.

The issue of 5°C stability data, and whether storage under refrigeration is feasible was discussed. Since Novartis has requested room temperature storage condition, the Agency has not analyzed the refrigeration temperature data in detail. Novartis clarified the following points with regard to the particle size distribution data obtained by _____

- Each data point is an average of analysis of 20 capsules.
- The variability for single capsule is not known.
- Novartis believes that similar variability would have been observed in clinical trials under actual patient use conditions.

The Agency responded that in clinical trials, the responses measured are "means." Individual data, such as the dose a patient receives, variability of the doses, and drug delivery are not measured. It is still not clear whether the molecule is affected by higher temperature and if any effect is enhanced by increased humidity. There is a significant amount of product degradation observed at 40°C/75% RH. If in fact temperature is causing the degradation, refrigeration storage conditions may need to be considered.

In response, Novartis stated the following.

- At least _____ shelf-life expiration dating period is needed for the product to be commercially viable.
- It is possible to control the storage conditions from manufacturing to dispensing.
- Novartis is willing to ship the product under refrigerated conditions.
- Novartis is concerned that if patients are asked to store this product under refrigeration, patients may end up storing the device under refrigeration, and then there would be a possibility of moisture condensation in the device.
- It was clarified that a new device will be dispensed every time a prescription is filled (the product will have a device and packages containing a total of 60 blisters in a box).
- Novartis is willing to consider instructing patients to store the blister packages under refrigeration (removing the device from the box and storing it separately).

The Agency presented its analysis of the fine particles distribution data under various conditions and time points (time points 0, 3, and 6-month/25°C/75% RH, 25°C/60% RH, 30°C/60% RH, and 40°C/75% RH). The Agency has noted that there is a significant drop and shift for fine particles distribution in various _____ at 40°C/75% RH that is not fully explained by loss of substance in the assay. Based on these data, whether a secondary packaging would make any difference can not be determined and it would be difficult for the Agency to establish an appropriate expiration dating period and storage condition.

Novartis stated that there were marketing reasons for not using the secondary packaging. Novartis is willing to conduct stability studies with secondary packaging at 40°C/75% RH for up to 3 months followed with updated data. Novartis questioned, how much secondary protective packaging data would be required, and whether these data could be submitted post-approval, but the product approved for marketing with the secondary protective packaging.

The Agency stated that the issue of secondary protective packaging was discussed with Novartis on several occasions over many years. Three months of stability data at 40°C/75% RH will not give enough information about the long-term impact of the secondary protective packaging on the product. Comparative data, using the same batch of the drug product, should be generated with and without secondary protective packaging. If the secondary protective packaging does not provide any improvement, the current submission does not eliminate particle size distribution, emitted dose and degradation issues that have been raised before, and does not support a reasonable expiration dating period. The Agency can not agree on the proposed particles size distribution specifications.

Conclusion:

- The Agency will analyze the 5⁰C stability data for parameters such as assay, emitted dose, degradation and fine particles distribution, to determine if it is feasible to recommend refrigerated storage condition for this product.
- Novartis will provide the 9-month stability data (_____ packaging site) for the Agency's review.
- Novartis will study secondary protective packaging for this product and will further discuss with the Agency appropriate stability studies, with and without secondary protective packaging.
- At this time, the Agency can not establish appropriate expiration dating period and storage conditions of sufficient duration to allowing marketing.

/S/

Parinda Jani
Project Manager

CC:

ORIG NDA 20-831
DIV FILE/HFD-570
HFD-570/JANI
HFD-570/BERTHA/4-27-00
HFD-570/POOCHIKIAN/4-27-00
HFD-570/MEYER/4-28-00
HFD-570/WILSON
HFD-570/ANTHRACITE
HFD-570/GUO
HFD-570/PEI
HFD-570/UPPOOR

**APPEARS THIS WAY
ON ORIGINAL**

Meeting Minutes

Meeting Date: March 4, 1999

Time: 9:00-11:00 AM

Location: Conference Room "M"

IMTS #: 3814

Applicant: Novartis Pharmaceuticals Corporation

NDA: 20-831

Product: Foradil Aerolizer (formoterol fumarate powder for inhalation)

Type of Meeting: Post Action CMC

FDA Attendees:

James Bilstad, M.D.	Office Director, ODE II
Craig Bertha, Ph.D.	Chemistry Reviewer
John Gibbs, Ph.D.	Supervisory Chemist, ONDC II
Parinda Jani	Project Manager
John K. Jenkins, M.D.	Division Director
Steve Koepke, Ph.D.	Supervisory Chemist, ONDC II
John Leak, Ph.D.	Consultant, Chemistry Reviewer
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Brian Rogers, Ph.D.	Chemistry Reviewer
Cathie Schumaker	Chief, Project Management Staff
Steve Wilson, Ph.D.	Statistician, Team Leader
Tracey Zoetis, M.S.	Pharmacology Reviewer

Novartis Attendees:

Stephanie Barba	Executive Director, DRA, Global Therapeutic Area Head
Kathleen Creedon, Ph.D.	Assistant Director, DRA, Therapeutic Area
Trudi Haemmerli, Ph.D.	Director, DRA-CMC
Yatindra Joshi, Ph.D.	Vice President, US Analytical Research and Development
Thomas Koestler	Global Head, DRA and CS&E

Background: The original NDA for Foradil Aerolizer was submitted June 26, 1997. An "Information Request" letter was sent to the applicant on March 25, 1998. A meeting was scheduled on April 30, 1998, which was canceled at applicant's request, as no clarification was necessary of the issues in the IR letter. The Agency sent an "approvable" (AE) letter on June 26, 1998. The applicant submitted their response to the AE letter on October 19, 1998. The Agency considered this response incomplete and a FAX was sent on November 3, 1998, stating the reasons. A meeting was held with the applicant on December 14, 1998, to discuss the specific issues related to the incomplete response. Also, another "Information Request" letter was sent on January 21, 1999. This meeting was scheduled to clarify the content of that letter, and data required to restart the review clock. For additional information, refer to the minutes of the December 14, 1998, meeting, and the applicant's package dated February 25, 1999.

At the applicant's request the stability issues were discussed prior to clarifying the contents of the January 21, 1999, letter.

Novartis stated the objectives of the meeting as follows:

- Analysis of stability data to reach scientific agreement on applicable storage conditions and expiration dating
- Clarify and understand comments of the January 21, 1999, Agency letter
- Agree on requirements for a complete response to restart the review clock

Applicant's presentation:

- Novartis presented the _____ analysis for the stability data submitted in the NDA for the U.S. packaging.
- Novartis stated that the _____ blister packaging (PVC _____ is moisture permeable. Significant loss of drug is seen at higher humidity. Data were collected at only 2 time points for high humidity and at 3 time points for low humidity. These data are not yet submitted to the Agency.
- Novartis claimed to have conducted stability studies of up to 2 years for European packaging (aluminum blister) at 25°C, 30°C, and 40°C/ ambient RH (40-50%) and at 25°C/75% RH and 30°C/80% RH.
- The _____ degradation observed for aluminum blister packaging was similar at high and low humidity.
- The aluminum blister package is moisture impermeable and protects the product from environmental moisture.
- Novartis presented assay data for the aluminum blister package. Data from other attributes were not presented.
- Novartis is projecting shelf life of _____ months based on _____ analysis at _____ limits.
- Novartis stated that the chemical stability of the product is temperature, humidity and time dependent and _____ analysis can predict chemical degradation of the product.
- Novartis presented _____ data for the three NDA batches.
- Novartis believes that the U.S. product stability data are within Novartis specifications.
- Novartis is proposing storage at 20°C -25°C with shelf life of _____ months, based on the assumption that the warehouses and wholesalers maintain such storage conditions routinely and assuming retailers have similar storage conditions.
- Novartis believes that time and conditions during shipping can be monitored. Novartis will evaluate if the product can be shipped refrigerated based on the new stability data.
- Novartis questioned whether the Agency will be able to make scientific evaluation of new stability data of 3 months plus existing data to restart the review clock.

The Agency stated the following:

- Only assay data for the aluminum blister package are presented. It is critical to have data from other attributes. The assumption of linearity regression should be supported by data.
- The Agency noted that the _____ data for _____ for batch _____ had almost 50% difference between the highest and the lowest deposition. Such a difference is considered significant.

- The stability data for the batches presented in the NDA are not generated systematically. The Agency had clarified its position at the December 14, 1998, meeting, and also in the March 25 and June 26, 1998, and January 21, 1999 letters. The Agency has consistently requested such data from all other applicants.
- Systematic stability studies of 12 months at different temperature/humidity levels for three batches are required. Minimum of 12 months data are needed to help evaluate degradation profiles and changes in particle size distribution, emitted dose etc.
- Since the specifications are not finalized, as there are no data generated in systematic manner to set the specifications, Novartis' claim of NDA batches "meets the specification" is not meaningful.
- The mean ——— temperatures in U.S. is higher than in Europe.
- The Agency will accept the storage temperature range of 20°C -- 25°C if the stability data at 30°C/ 60% RH up to 12 months, and 25°C/ 75%RH for one-third of proposed expiration dating period or 6 months, are adequate to support it. In absence of such data, it is not feasible to recommend an expiration-dating period.
- The Agency has consistently requested systematic stability data at various temperature/humidity conditions long before the draft Guidance for Industry: MDI and DPI Drug Products was published by the Agency on November 13, 1998.
- All the applicants of approved MDI and DPI products have generated such stability data in systematic manner to support their applications.
- Novartis has made numerous assumptions regarding the stability data in their presentation, which may not be correct.
- As stated in the meeting dated December 14, 1998, six months of stability data at 40°C/ 75%RH are required. Novartis should generate systematic stability data at various temperature/humidity conditions to understand the effect of temperature and/or humidity on the product.
- Currently, it is not yet established the factors; temperature, time, packaging or humidity conditions, that are contributing to the product failure.
- Novartis presented data of only two parameters, assay and particle size distribution. Novartis did not conduct tests for any other parameters (such as dose delivery) and stopped the studies at 3 months for the 40°C/ 75%RH condition. Since there are no continuous data to compare, a scientific evaluation can not be made.
- At least 6 months of systematic stability data at various temperature/humidity conditions for 3 lots of the drug product packaged in the final to-be-marketed packaging will be required to reinitiate review of the NDA. The approval of the NDA will depend on the acceptability of the data, and the expiration dating period will depend on adequate available data before approval.

Following is the clarification provided by the Agency for the January 21, 1999, Agency letter.

1. Micronized drug substance particle size specification

In their submission dated February 25, 1999, Novartis has committed to tighten the specification for micronized drug substance particle size except for the particles oversize value at ———. The Agency is proposing ———. Novartis is proposing ———.

The Agency stated that its recommendation of _____ for the particles oversize value at _____ is based on the data that are submitted to the NDA for 28 lots. Of the data reported for 28 lots, only 2 lots have more than 3% particles larger than _____

Novartis has data from additional lots which will be submitted for Agency's review with their complete response. The proposed limit of _____ will be a review issue.

2. Impurities and degradation products of the drug substance

In their submission dated February 25, 1999, Novartis has committed to tighten the specification with the exception of _____
Novartis will monitor the impurity _____ in the future batches and tighten the specification based on additional data. For impurity _____ Novartis is proposing _____ based on the limit of quantitation for this impurity.

The Agency stated that its recommendation of _____ in the drug substance is based on the data submitted in the NDA. The Agency does not set the specifications based on the outliers. This will be a review issue.

3. Updated specification sheet

In their submission dated February 25, 1999, Novartis has committed to update the specification sheet that would include all the proposed specification changes and will submit with the complete response.

4. System suitability resolution factor

In their submission dated February 25, 1999, Novartis has committed to upgrade the system suitability resolution factor to reflect the actual results of the methods and will incorporate it into the affected methods _____. The revised methods and specification sheets will be submitted with the complete response.

5. Stability Protocol

In their submission dated February 25, 1999, Novartis has committed to submit the stability report for the drug substance that would include total of related substances, with the complete response.

The Agency stated that it would like Novartis to follow an adequate stability protocol that is agreed upon, one for the drug substance and one for the drug product. Any changes that might be made to the stability protocol post-approval will require a "prior-approval" supplement.

6. Method of integration of the peak

Novartis will amend the methods to include _____ integration.

7 & 8. Need for analytical data on several batches of lactose in order to establish adequate specifications and acceptance tests, and additional specifications for lactose

The Agency stated that Novartis should establish specifications based on reasonably consistent database, not based on outliers. As discussed at the meeting on December 14, 1998, the supplier of lactose may establish a DMF and provide all the required control results to the Agency. Novartis will be responsible for confirming the adequacy of the supplier's tests and repeating tests at regular intervals to confirm supplier's data. The proposed method for determining amorphous content of lactose is not sensitive enough. The proposed specification for amorphous lactose is an order of magnitude higher than the other approved inhalation powder products.

Novartis stated that it would revise the specification for level of quantitation for amorphous lactose. Novartis questioned if _____ is proposed for level of quantitation for amorphous lactose, the Agency would consider it. Novartis will submit the test methods and propose specifications with the complete response.

9. Additional acceptance criteria for lactose

The Agency stated that based on information in the NDA, there are three different mesh sizes of lactose available (100, 150 and 200) from the given source. The mesh sizes 150 and 200 can not be distinguished based on the proposed particle size distribution specifications. For the control of the incoming material, the method should be adequate enough to distinguish between the different mesh sizes of lactose.

Novartis stated that it would provide adequate information, data and specifications to distinguish the desired mesh size lactose from other available grades. Moreover, Novartis indicated that _____ mesh size lactose would not be used. Novartis will clarify in the complete response.

10. Contract packagers of the drug product

In their submission dated February 25, 1999, Novartis has stated that it plans to submit the batch records from _____ for the original stability batches, and batch records from _____ for product currently on stability.

The Agency stated that both of the DMFs are Type 1 DMFs. Both packagers should have information to describe the packaging part of the manufacture of the drug product, e.g., raw material controls (packaging materials and bulk drug), laminating conditions, in-process controls, release controls, storage conditions for raw materials and final products, and list of SOPs that apply to Foradil.

11. Controls on the packaged drug product

The Agency stated that Novartis should perform controls on the packaged drug product to ensure that no adverse changes due to temperature, humidity and time elapsed have occurred from release of bulk capsules until packaged capsules are ready for release for shipment.

12. Controls for the drug product

Mass Balance: The Agency stated that Novartis should provide data in detail, not just summary, of all testing done to determine product decomposition. The data should include mass loss, and impurities of lots used for the preclinical and clinical studies.

Validation of assay method: The Agency stated that the data submitted to justify a resolution requirement in the assay procedure between formoterol and GCP 47086A only shows resolution between formoterol and — 2570. Novartis should provide information for resolution between formoterol and — 2567 (GCP 47086A) in the system suitability test.

Longer retention time for formoterol: The Agency stated that there are two scans that show different retention times in the assay procedure for formoterol. The retention time has changed from 12 minutes to 6.5 minutes. If the retention time is cut in half, it will be difficult to differentiate between two — Novartis should identify the methods used, including assay and — data, for each scan.

Validation of related substances: In their submission dated February 25, 1999, Novartis is proposing resolution requirement of at least — for — 2567 Vs formoterol, at least — for — 2567 Vs — and a resolution requirement of at least — for the validation of related substances method.

The Agency stated that it would like to see supporting data to substantiate the proposed numbers. If the method has been shown to possess a resolution between — 2570 and formoterol of approximately 18-20, a resolution requirement for this pair of 11.0 is too low.

Single document for the specification sheet: Novartis stated that it uses 2 sets of documents for quality control of the product, one for the tests that are common to all countries where the product is approved, and one for the additional tests required in U.S.

As previously stated, the Agency would like Novartis to combine these two in a single document for the U.S. application.

13. Device specifications

The Agency stated that appropriate specifications for dimensional measurements, extractables of critical components, and flow resistance of the device should be established to ensure batch-to-batch consistency of the device.

14. Materials and their composition used to manufacture the laminates

The Agency stated that Novartis or the DMF holder should provide specific references and page numbers in the DMF where the information can be found for the material that will be used for Foradil. These references should include material to be used for the foil laminate, its manufacturer, brand, composition, extractables including plastics, adhesives, and aluminum etc.

15-19, 21 and 23. Stability

The Agency stated that at least 6 months of stability data at requested temperature and humidity conditions of 40°C/75% RH, 30°C/60% RH, 25°C/75% RH and 25°C/60% RH will be required at the time of the submission of the complete response to establish storage conditions, expiration dating, and whether the product will need a secondary packaging (See comments above).

20. DMFs _____

[REDACTED]

22. DMF _____

[REDACTED]

The concept of using European packaging for U.S. marketing was discussed. Novartis acknowledged that data for certain tests and time points are not available for this packaging.

The Agency stated that the stability protocol, the testing parameters and time points are not known and not reviewed by the Agency. It is up to Novartis to make the decision which packaging (U.S. vs European) to use for U.S. marketing. There are no guarantees that additional deficiencies will not be identified upon review of these data and associated DMFs. The Agency would like Novartis to review their data, determine whether the European protocol and data will address all the stability concerns the Agency has raised, and make that decision. Novartis must make sure that all other issues besides stability are addressed adequately for the Agency to start the review clock.

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL