Meeting Date: December 14, 1998 **Time:** 9:30-11:00 AM
Location: Conference Room "M" **IMTS #:** 3430
Sponsor: Novartis Pharmaceuticals Corporation
NDA: 20-831
Product: Foradil Aerolizer (formoterol fumurate powder for inhalation)
Type of Meeting: Post Action

FDA Attendees:

Raymond Anthracite, M.D.	Medical Reviewer
Craig Bertha, Ph.D.	Chemistry Reviewer
Albert Chen, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Keary Dunn	Project Manager
Ted Guo, Ph.D.	Statistical Reviewer
Peter Honig, M.D.	Medical Team Leader
Ladan Jafari	Project Manager
Parinda Jani	Project Manager
John K. Jenkins, M.D.	Division Director
John Leak, Ph.D.	Chemistry Reviewer
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Ramana Uppoor, Ph.D.	Clinical Pharmacology and Biopharmaceutics, Team Leader
Steve Wilson, Ph.D.	Statistician, Team Leader
Tracey Zoetis, M.S.	Pharmacology Reviewer

Novartis Attendees:

Stephanie Barba	Executive Director, Global Therapeutic Area Head
Robert Clark	Associate Director, Drug Regulatory Affairs, Parenteral Drugs
Kathleen Creedon, Ph.D.	Assistant Director, Therapeutic Area
David Danville	Packaging Development
Giovanni DellaCioppa, M.D.	Respiratory Therapeutic Area Head, Clinical Research
Susan Irwin, Ph.D.	Associate Director, Toxicology
Martin Keck, Ph.D.	Head of Quality Assurance Excipients
Peter Kiechle, Ph.D.	Head of Analytical Research and Development, Basel
Dan Lettrich	Assistant Director, Chemistry, Manufacturing and Controls
Sharon Olmstead	Assistant Director, Regulatory Liaison, Washington D.C.
Glen Thompson, Ph.D.	Pharmaceutical Analytical Development
Dr. Robert Walters	Consultant
Dr. Yegen	

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. A meeting was scheduled with the sponsor on April 30, 1998, and was canceled at sponsor's request as the sponsor did not require any clarification of the issues in the IR letter. The Agency sent an "approvable" letter to the sponsor On June 26, 1998. The sponsor submitted their response to the AE letter on October 19, 1998. The Agency considered this response incomplete and a FAX was

sent to the sponsor on November 3, 1998, stating the reasons. Sponsor submitted their response to the FAX on November 10, 1998, and requested a meeting. This meeting was scheduled to discuss the specific issues related to the incomplete response.

Lactose and Protein Testing:
Novartis described the manufacturing process for lactose testing used by the supplier and proposed not to include the tests for —— as the supplier's manufacturing process for lactose is

The Division stated the following.

- Since there is —— there is no way to verify the changes that may take place in the manufacturing process.
- Novartis must perform all the testing recommended in the letter for lactose, including testing for —— and protein, that will be used to manufacture Foradil. For additional guidance Novartis may refer to the draft Guidance for Industry: MDI and DPI Drug Products, published by the Agency on November 13, 1998.
- It is possible to reach an agreement with the Division to conduct the testing at a specific frequency for some attributes, once the reliability of the methods, and consistency of several lactose batches from a given source are established. The Agency will make the decision based on the production rate, batch size of the lactose, and how many batches Novartis receives per year.
- Similarly, the protein testing should be retained. The USP and the proposed testing for protein is acceptable, but instead of the USP values for protein content in lactose, Novartis should adopt actual values reflective of the data submitted in the NDA. The frequency of the protein testing should be discussed and pre-agreed with the Agency.
- Some of the proposed specifications for lactose are in terms of limits rather than actual numerical values. 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 should provide numerical values for any tests which presently states "non detected" and provide LOQ and LOD for it.
- Specifications should be established for the content of alpha and beta crystalline form of the lactose for consistency purposes.

Stability:
The issues of proposed expiration dating period of —months with storage recommendation below 25°C, and packaging material were discussed. The current Type 1 DMFs for packaging materials do not have adequate information on packaging.

The Division stated the following.

- The proposed expiration dating period is not justified with adequate supportive —— comprehensive stability data.
- Novartis should have followed a set stability study protocol as proposed in the FDA letters dated March 25, and June 26, 1998.

- Novartis stopped the stability studies for the 40°C/75%RH condition at 3 months because of the failure, which is unacceptable.
- Six months stability data at 40°C/75%RH are required, regardless of failure.
- The stability data submitted for the primary U.S. batches at 30°C have different humidity levels at 6, 9 and 12 months time points making analysis of the data impossible.
- Acceptable 12-month comprehensive stability data for 30°C/60%RH condition are required for the product, when it fails at 40°C/75%RH condition at 6 months.
- The stability studies should be conducted sequentially as recommended in the FDA letters dated March 25, and June 26, 1998. Such data are needed to assess the effect of humidity and temperature, and to determine whether secondary packaging is needed. Moreover, it appears temperature also has some adverse effect on the quality of the drug product.
- The dry powder inhalation drug products are very sensitive to higher humidity. Since the 40°C/75%RH condition stability studies were dropped, it is not known whether the failure is because of the humidity or temperature or both. If the failure is because of the moisture ingress, secondary packaging will be required.
- Submitted limited stability data demonstrate adverse effect of humidity on the quality of the drug product. In order for the Agency to make a decision whether a protective packaging will be required, adequate and comprehensive primary stability data should be submitted, incorporating various stability conditions indicated in the FDA letters dated March 25, and June 26, 1998.
- Availability of comprehensive stability data is very critical for the review clock to start.
- The Agency recommends that Novartis initiate new long-term and accelerated stability studies.
- At least 6 months of new stability data for different temperature/humidity conditions will be required for the product to be approved with a limited expiration-dating period.
- Novartis should include 95% confidence interval for the statistical evaluation of the stability data.
- If a product is labeled to be stored below 25°C, it indicates storage under refrigeration and there are no data to support such storage. Additional temperature studies will be required for such storage recommendation.
- As Novartis has _____ the Agency has primary stability data for only one batch. Primary stability data for 3 batches, reflective of the U.S. marketing conditions, are required for the approval of the NDA.
- The DMF holders may wish to follow the draft packaging guidelines.
- Novartis uses different packaging materials for the European batches than for the U.S. batches. Novartis was advised to use the packaging material for the stability studies that will be used for to-be-marketed product in the U.S.
- The DMF holder for the blister component _____
- The Type 1 DMF holders should provide more detailed information.

Mass Balance:

Novartis presented the background of mass balance deficit investigation. Novartis believes there are two potential reasons of mass balance deficit; potential migration of the drug substance into the capsule shell and chemical/physical interaction of the drug substance with lactose.

The Agency asked Novartis to provide a summary of all the analytical work conducted, a tabulation of all the preclinical and clinical batches, their ages and their impurity profiles, and detail justification of the effect of mass balance deficit on the safety of the drug product.

The Agency is currently reviewing the June 1, 1998 submission. Additional comments will be forwarded to Novartis based on the review of this submission, and if possible, October 19 and November 10, 1998, submission.

Conclusion:

- Novartis agreed to conduct additional testing for lactose as proposed in the draft Guidance for Industry: MDI and DPI Drug Products, published by the Agency on November 13, 1998.
- Novartis will propose the frequency for the lactose and protein testing. Once the reliability of the methods and consistency of several batches are established, the Agency will make the decision based on the production rate, batch size of the lactose, and how many batches Novartis receives per year.
- Novartis may [redacted]
- Novartis will initiate new stability studies, accelerated and long-term. The protocol should include intermediate conditions both 30^0C/60%RH and 25^0C or 30^0C at 75%RH. Novartis may submit the protocol for the Agency's comments.
- A minimum of 6-months of new stability data, long-term accelerated and intermediate if warranted, will be required for the product to be approved with limited expiration dating period.
- The review clock will not start until complete response is submitted for all the outstanding issues. All the required stability data must be submitted for the response to be considered complete.
- The Agency will forward additional comments, once the review of the June 1, 1998, submission is completed.

/S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: December 6, 2000 TIME OF CALL: 11:15 AM

APPLICATION NUMBER: NDA 20-831, Foradil (formoterol fumarate) 12 mcg capsules

BETWEEN:

Name: Tricia Chen, Director, Quality Assurance
Yatindra Joshi, Ph.D., Vice President, Pharmaceutical Development
Sheryl LeRoy, Assistant Director, Regulatory Affairs
Phone: 973-781-2225
Representing: Novartis Pharmaceuticals

AND

Name: Craig Ostroff, Pharm.D., Project Manager (for P. Jani)
Guirag Poochikian, Ph.D., Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT:
Sponsor's Inquiry on Stability Protocol

BACKGROUND:
A minor chemistry submission, dated December 1, 2000, was submitted to NDA 20-831. On December 4, 2000, a teleconference was held with the sponsor in order to address some concerns about the proposed stability protocol. The sponsor requested another teleconference to further clarify those issues prior to providing a formal submission.

DISCUSSION:

The following annual stability program outline was agreed upon:

Year 1: First three production batches plus two more during the year.
Year 2: 5% of total number of batches; max of three
Year 3 and Beyond: Continue on with Year 2 plan; Plan will be revised through discussion with the review division, with based upon results of stability data from first two years plus other factors (e.g. marketing demand, etc>) ; Any change of the stability protocol would require the submission of a supplement.

Year 1: Predict will make about —batches
Year 2: Predict will make about —batches
Batch size: ——— capsules

The Division asked that the stability submission be as clear as possible in listing, as appropriate, the packaging site, configuration and number of batches in the stability protocol.

Packaging Comments

The sponsor will test batches from ——— the sites, although ——— site will be used for launch.

Craig Ostroff, Pharm.D.
Project Manager

Concur:

Guirag Poochikian, Ph.D.
Chemistry Team Leader

APPEARS THIS WAY
ON ORIGINAL

MINUTES OF TELECONFERENCE

NDA: 20-831
Sponsor: Novartis Pharmaceuticals Corporation
Product: Foradil (formoterol Fumarate inhalation powder)

Date: December 4, 2000

Novartis Attendees: Leroy
FDA Attendees: Jani, Poochikian

The following issues were discussed.

- The proposal to test first three production batches and than 5% of batches, including maximum of three batches per year for the first year, two batches per year for the second year and one batch per year for the third year, is not acceptable. The Agency would like Novartis to propose as to how many batches would be tested per year. The current proposal may be acceptable for some of the parameters, but additional batches must be tested for some of the potential problematic parameters.

- Novartis ——— packaging sites – the stability testing protocol should address each site separately. Appropriate section of the stability protocol should be updated to reflect the changes.

- Novartis should clearly define the number of batches to be tested from each site.

- The stability testing protocol should clearly define the expiration-dating period for this product.

Novartis will verify the type of packaging, i.e., ——————— and provide clarification in the next submission.

Parinda Jani
Project Manager

Cc;
Orig NDA/20-831
Div File/HFD-570
HFD-570/Poochikian

APPEARS THIS WAY
ON ORIGINAL

MINUTES OF TELECONFERENCE

NDA: 20-831 **Date:** November 6, 2000
Sponsor: Novartis Pharmaceuticals Corporation
Product: Foradil (formoterol Fumarate inhalation powder)

Novartis Attendees: Barba, Creedon, Joshi, Leroy, Thomson
FDA Attendees: Jani, Poochikian

The following issues were discussed.

- Because of the variability seen with the data at various time points, The Agency would like Novartis to reduce the "out of refrigeration expiration dating period" to — months, until additional data are available.

  Novartis would like the Division to consider 4 months out of refrigeration expiration dating period because of the marketing purposes.

  The Agency stated that with adequate supportive post-marketing data, the out of refrigeration expiration dating period could be extended via a prior approval supplement. At this point, the Agency would require additional time to reanalyze the data to support the 4 months period.

- Novartis has proposed a limit of ——— for loss of mass. The Agency would like Novartis to change this specification to a limit of ———

  Novartis agreed to change the specification for loss of mass to ———

- The Agency would like Novartis to submit updated Methods Validation package, updated stability protocol and specification sheet.

- Novartis may be able to provide 6-month overwrapped product stability data during the first week of December 2000.

- The proposed refrigeration period of 18 months is acceptable.

/S/

Parinda Jani
Project Manager

MINUTES OF TELECONFERENCE

NDA: 20-831
Sponsor: Novartis Pharmaceuticals Corporation
Product: Foradil (formoterol Fumarate powder for inhalation)

Date: July 21, 2000
IMTS # 6022

Novartis Attendees: Barba, Creedon, DellaCioppa, Hassan, Kottakis, Thomson. Till, Zeihmer
FDA Attendees: Anthracite, Jani, Sullivan

Background: See the Agency's "approvable" letter dated May 24, 2000, minutes of the meeting dated June 9, 2000, the applicant's correspondence dated June 15, 2000, and the facsimile transmission dated July 20, 2000.

The following issues were discussed and agreed upon.

- Citations from the original NDA submission and a summary document to support the nocturnal asthma indication will be provided with the complete response.

- Belgium is the only country that has recently approved and launched Foradil. Approved labeling for Foradil in Belgium will be provided with the complete response (rest of the approved foreign labeling already provided to the Agency).

- Case report forms (CRFs) for deaths and discontinuations because of adverse events from all the trials will be submitted. CRFs for the asthma trials will be resubmitted as paper copies [redacted] and for the [redacted] trials will be submitted per the electronic submissions guidance document.

- There will be two integrated summaries of safety (ISS) submitted to the [redacted] ISS for the [redacted] patients, and ISS for all the patients.

- Novartis will provide the commitment for the submission date for ISS for all the patients in the cover letter of the [redacted] (no later than the 120-day safety update. Refer to the June 9, 2000, meeting minutes).

/S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

MINUTES OF TELECONFERENCE

NDA: 20-831
Sponsor: Novartis Pharmaceuticals Corporation
Product: Foradil (formoterol Fumarate powder for inhalation)

Date: July 6, 2000
IMTS # 6021

Novartis Attendees: Creedon, Este, Haeberlin, Joshi, LeRoy
FDA Attendees: Jani, Poochikian

Background: Novartis requested this teleconference to clarify comment # 5 (mass balance) of the May 24, 2000, approvable letter. See the applicant's correspondence dated June 15, 2000.

Novartis stated that the unaccounted loss of drug substance assay upon storage is attributed to the reaction between formoterol fumurate and lactose (Maillard reaction). There are multiple degradation products formed in the amounts below the limit of quantitation, which Novartis has not been able to identify with the existing analytical methodology. Novartis is willing to set a specification for the entire mass balance deficit.

The Agency stated that it is very clear that the mass balance issue is temperature related. The degradation is significantly higher at 40°C, almost up to 30%. Novartis may be able to provide information for the ——— that are observed compared to the parent compound with the ——— method.

Novartis stated that for the storage conditions, it is reconsidering combination of refrigeration and room temperature, i.e., the product will be refrigerated up to the patient dispensing stage of the distribution, and upon dispensing, patients can store it at room temperature. Novartis also stated that it is not feasible to develop commercial secondary protective packaging and put the batches on stability (Novartis will have 1-month accelerated (40°C/75%RH) secondary packaging data for the product by end of the month). If the secondary packaging indeed have a significant impact on the stability of the drug product after adequate stability data, Novartis will consider marketing the product with a secondary packaging, but would prefer to do so post-approval. Novartis is willing to make a commitment for the timing of submitting a supplement for marketing the product with secondary packaging.

The Agency stated that such approach would be considered in the next review cycle, but it will depend on the review of the available data.

/S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

MINUTES OF TELECONFERENCE

NDA: 20-831
Sponsor: Novartis Pharmaceuticals Corporation
Product: Foradil (formoterol Fumarate powder for inhalation)

Date: February 24, 1999

Novartis Attendees: Clark, Creedon, Joshi, Thompson
FDA Attendees: Jani, Poochikian

Background: A meeting was held with Novartis on December 14, 1998. At this meeting the Agency pointed out specific problems with the stability data submitted in the original NDA. Novartis agreed to submit a revised stability protocol and the Agency agreed to provide comments in a timely manner. The revised stability protocol was submitted on February 9, 1999. Following comments were provided to Novartis at this teleconference.

Novartis plans to conduct the stability studies on the final commercial packaging to-be-marketed in the U.S. Novartis does not plan to have a secondary protective packaging.

- The Agency stated that the proposed stability studies must provide information whether the stability problems were due to temperature or due to humidity. The burden to prove that a secondary protective packaging is not needed is upon Novartis.

Novartis plans to conduct the studies in two parts; 1) Capsules will be manufactured in Switzerland and shipped to the U.S., and packaged immediately. The stability studies will start immediately after packaging. 2) Bulk capsules will be stored at 2-8^{0}C for three months prior to packaging, to simulate cool transport conditions prior to blister packaging. Stability studies will start immediately after packaging. The batches to be tested will be the brand new batches.

- The Agency stated that the storage conditions statement in the labeling will be for controlled room temperature and not for storage under refrigeration.
- Novartis should document and provide information for the time period between manufacturing and packaging.

The samples of the capsules (approximately ——, will be taken from the middle of the production run for each stability test.

- The Agency questioned the purpose of taking the samples from the middle of the production run. There is no specific objection to this approach but it may be more informative if the samples were taken from the beginning, middle and end of the production run, to determine the effect of humidity during the capsulation time. Novartis should validate the process, control the filling environmental conditions, and demonstrate that there is no difference between the capsules filled at the beginning, middle, and end.

  Novartis has already packaged the capsules for the stability studies, but agreed to reevaluate the data. The Agency stated that the burden is on Novartis to prove that the filling conditions do not have any adverse effects on the capsules. A statement reflecting the production run time, environmental conditions during the filling etc. should be submitted with the complete response.

The Agency has no comments for the proposed stability program at this time. The proposed test parameters are acceptable. The particle size distribution (PSD) report should have data from each stage and other accessories. Selection of several groupings and combination of the stages could be determined for post-approval batches upon review of data generated. The Agency can not comment on acceptance criteria at this time pending the review of data.

/S/

Parinda Jani
Project Manager

CC:
ORIN NDA 20-837
DIV FILE/HFD-570
HFD-570/POOCHIKIAN/3-3-99
HFD-570/JANI/3-3-99

APPEARS THIS WAY
ON ORIGINAL

MINUTES OF TELECONFERENCE

NDA: 20-831
Sponsor: Novartis Pharmaceuticals Corporation
Product: Foradil (formoterol Fumarate powder for inhalation)

Date: July 21, 1998
IMTS # 3050

Novartis Attendees: Della Cioppa, Creedon, Lloyd, McAlary, Till, Yegen,
FDA Attendees: Anthracite, Gillespie, Guo, Honig, Jani, Wilson

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Background: On June 26, 1998, an approvable letter was sent for NDA 20-831. Novartis requested this telecon seeking clarification of the following issues.

1. **Case Report Form and ISS clarification (Item B3)**

   Novartis has submitted the CRFs for all patients who died or discontinued participation in the study prematurely due to adverse events. The CRFs for the patients who had serious adverse events but continued participation in the study were not submitted.

   Because of the difficulties in locating the CRFs in the NDA submission, this comment was provided as a deficiency. A complete index to locate the CRFs must be provided to facilitate the review. CRFs for all the clinical trials of other formulations are not required,

2. **Additional gender analyses for Protocol 54 (Item B12a)**

   Oral clearance (Dose/AUC) data stratified by weight and gender should be submitted.

3. **Pediatric Asthma indication (Item B1)**

   Novartis has submitted protocol 049, a double-blind, placebo-controlled study, to the IND. 25% of the patients enrolled are under 8 years of age. Novartis is in the process of completing the 3-month ITT analysis. The data will be submitted with the complete response to the approvable letter.

   The Division had reviewed protocol 049 when submitted and comments were given to Novartis. Whether the data, and the safety information are adequate to support the pediatric indication or not, will be a review issue.

4. **Pediatric EIB indication (Item B2)**

   Novartis proposes to support existing pediatric EIB studies with data extrapolated from other adult and pediatric clinical and pharmacodynamic studies. Novartis believes that it will be consistent with the Agency's Pediatric Use guidelines (i.e., "Pediatric Final Rule").

   This proposal is not acceptable. A pediatric EIB study would be required.

5. **Geriatric Use (FR vol 62 #166, August 27, 1997)**

   Novartis should submit the gender analysis by age range. The product will be labeled accordingly.

6. **Section D of the AE letter**

Novartis needed clarification as to whether the comments in this section are binding requests/requirements, and/or suggestions for the line extension and additional indications.

The Agency clarified that even though Novartis is not required to submit complete response to these comments for the approvability of the Foradil, they should have a discussion of them in the response to the AE letter, as the Agency may request Novartis to conduct such studies as Phase 4 commitments.

Action Items:

1. Novartis plans to submit the complete response to the AE letter in September 1998.

2. The issue of pediatric exclusivity will be discussed internally and the Agency will discuss the outcome with Novartis at a later date.

/S/

Parinda Jani
Project Manager

CC:
ORIG NDA 20-831
DIV FILE/HFD-570
HFD-570/JANI
HFD-570/SCHUMAKER/7-28-98
HFD-570/ANTHRACITE/7-28-98
HFD-570/HONIG/7-28-98
HFD-570/GILLEPSIE/7-28-98

APPEARS THIS WAY
ON ORIGINAL

NOVARTIS

Assistant Director
Drug Regulatory
Affairs

Tel (908) 277-3245
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Internet: kathleen.creedon
@pharma.novartis.com

Telephone Number (301) 827-1272

Attention Ms. Parinda Jani
Consumer Safety Officer
Division of Pulmonary Drug Products

Date July 17, 1998

Dear Parinda:

Attached is the final agenda for the telephone conference to be held Tuesday July 12, 1998 at 8:30 am to discuss clarification requests on the clinical, statistical and pharmacology sections of NDA 2-831 for Foradil Aerolizer™ (formoterol fumarate powder for inhalation).

Please note that due to some clarifications which have occurred in our earlier conversations and due to the time constraints, some of the items we originally planned to discuss have been omitted. In addition, there is a new clarification that has come up as we have begun to formulate our reply, it is the first item on the Agenda I will call on Monday to confirm that you have received this facsimile Otherwise, I will call you Tuesday morning at: (301) 827-1049.

Best regards,

Kathy

APPEARS THIS WAY
ON ORIGINAL

NDA 20-831 Foradil Aerolizer™

(formoterol fumarate powder for inhalation)

Agenda for FDA teleconference July 21, 1998

8:30 am -9:30 am (US time)

Attendees:

Novartis Pharmaceuticals Corporation:

Giovanni Della Cioppa, MD (Therapeutic Area Head, Clinical Research)

Umit Yegen, MD (Associate Director, Clinical Research)

Peter Lloyd, PhD (Head of Clinical Pharmacokinetics, Europe)

Denise Till (International Clinical Statistician)

Margaret McAlary (Sr. Biostatistician, Biostatistics)

Kathleen Creedon, PhD (Associate Director, Drug Regulatory Affairs)

Division of Pulmonary Drug Products (FDA):

Peter Honig, MD (Medical Officer, Team Leader)

Raymond Anthracite, MD (Reviewing Medical Officer)

Brad Gillespie, PhD (Clinical Pharmacology Reviewer)

Steve Wilson, PhD (Statistician, Team Leader)

Ted Guo, PhD (Statistical Reviewer)

Parinda Jani (Consumer Safety Officer, Project Management)

Agenda:

Case Report Form and ISS clarification (Action Letter Item B3):

FDA requested case report forms (CRFs) to complete the ISS.

Novartis seeks clarification on the details of this request. Novartis submitted case report forms for all patients who died or prematurely discontinued participation in clinical trials due to adverse events in the both the original application [21 (CFR 314.50(f)(2)], and in the safety information update [21 (CFR 314.50(d)(5)(*vi*)(*b*)], as required by the cited regulations, but not for patients who had serious adverse events but continued to participate in a clinical trial.

Novartis will provide FDA with a complete accounting and index of CRFs provided in the original NDA, the October 24, 1997 amendment and those that will be in the resubmission response to the June 26, 1998 action letter. However Novartis seeks further clarification regarding FDA's request for "CRFs for patients who suffered serious adverse events in clinical trials involving formoterol".

Additional Gender Analyses for protocol 54(Action Letter Item B12a):

FDA requested additional gender analyses for protocol 54.

Novartis seeks additional clarification on which additional data is being sought. The original application provided gender analysis for protocol 54 in volume1.71, page 23.

Pediatric Asthma Indication (Action Letter Item B1):

FDA requested an additional study in pediatric ROAD patients.

Novartis is completing the 3 month ITT analysis of protocol 49 (IND [redacted]

- double-blind, placebo controlled, 12 month trial
- efficacy and safety of 12 ug and 24 ug formoterol fumarate vs placebo
- 518 children, aged 5-12 (mean 9 years)
- outcome measures: 12 hour spirometry; PEFR; asthma symptoms

Pediatric Exercise-Induced Bronchoconstriction Indication (Action Letter Item B2):

FDA requested an additional study in pediatric EIB patients.

Novartis proposes to support existing pediatric EIB studies with data extrapolated from other adult and pediatric clinical and pharmacodynamic studies consistent with FDA "pediatric use" guidelines

Marketing Exclusivity Extension for Pediatric Indications:

Novartis seeks guidance on the appropriate method for which to pursue extended marketing exclusivity in accordance with FDA guideline "Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug and Cosmetic Act"

(Due to time limitations, this issue may need to be discussed separately.)

Additional clarification:

FDA reference to final rule for "geriatric use" (Federal Register volume 62 number 166. August 27, 1997)

Novartis seeks clarification on the impact of this rule, published after submission but prior to approval, and how to best implement "geriatric use" labeling for this product.

RECORD OF TELEPHONE CONVERSATION

NDA NUMBER: #20-831 DATE: 21 & 24 March, 2000

INITIATED BY: __APPLICANT __XX__FDA

FIRM NAME: Novartis

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Kathleen Creedon

TELEPHONE NUMBER: (973)781-3666

I initiated the phone call to address certain questions that arose during the NDA review of the 11/23/99 submission and pediatric trial 049. Replies are in the smaller typeface.

1. The entire age distribution appeared to under-represent the younger ages. Only 25% of the enrollees were 5-8 years old and 75% were 8-12 years old. A more detailed breakdown of ages was requested. Later FAXed and incorporated into the review.

2. Some of the early discontinuation categories were hard to interpret; e.g., "non-compliance" and "unsatisfactory treatment effect." Compliance was explicitly not measured, at least for medication use, and inefficacious treatment might well be considered as an AE. Were these categories better defined? Categories are undefined and left up to the interpretation of the individual CI's.

3. The primary efficacy variable was the $FEV_{1.0}$ AUC measured after three months of treatment. It was "standardized" for the number of hours actually measured to allow for data collection from those who required rescue medication during these 12-hour serial spirograms, therefore prematurely terminating them. I was unable to find the count of patients and their group identity who prematurely terminated this 12-hour study period at the third month. Reported to me over the phone and later FAXed and incorporated into the review.

4. On the days that 12-hour spirograms were performed, visits 2, 5 and 14, these vital signs were also measured pre-dose and at 30 minutes, 60 minutes, 2 hours and at 2-hourly intervals through 12 hours and the completion of the spirograms. If these were reported, where are they to be found? Appendix 7, Volume 29, Section 7.1, Tables 22.1 (pulse), 22.2 (systolic BP) and 22.3 (diastolic BP) and Volume 30, Exel spreadsheet on the Patient Data Locator disk.

She offered to find the answers to these questions for me.

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-831
HFD-570/Division File
HFD-570/Team Leader/Chowdhury
HFD-570/Medical Reviewer/Anthracite
HFD-570/PM/Jani

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

NDA NUMBER: #20-831 DATE: 16 March 2000

INITIATED BY: __APPLICANT __XX__FDA

FIRM NAME: Novartis

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Kathleen Creedon

TELEPHONE NUMBER: (973)781-3666

I called to ask how the $FEV_{1.0}$-AUC values could be on the same order of magnitude and have the same units (Liters) as the $FEV_{1.0}$ values at individual time points. A statistician answered that the $FEV_{1.0}$-AUC's had been normalized to allow for patients who had truncated the 12-hour test because of beta agonist use or other reasons. The normalization process involved dividing the $FEV_{1.0}$-AUC's by the number of hours over which they were obtained, in essence giving a mean for each patient at each visit. Truncated studies would have a mean comprised of the best portion of the post-dosing curve and this mean would be compared on an equal basis with the means of patients who had completed the entire 12 hours. One interpretation of this method of data handling is that it produces the best outcome for patients with truncated studies, but also gives more weight to these presumably more ill patients.

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-831
HFD-570/Division File
HFD-570/Team Leader/Chowdhury
HFD-570/Medical Reviewer/Anthracite
HFD-570/PM/Jani

RECORD OF TELEPHONE CONVERSATION

NDA NUMBER: #20-831 DATE: 24 February, 1999

INITIATED BY: _X_APPLICANT __FDA

FIRM NAME: Novartis

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:
Dr. Umit Yegen called 2/23/99 and left voice mail message

TELEPHONE NUMBER: (973)781-3517

Dr. Yegen asked two questions to help her design studies to answer some of the comments addressed in our 6/26/98 approvable letter.

First, she wanted to know if the post-dose testing in a pediatric single-dose exercise-challenge trial could be limited to ten hours instead of twelve. This was to limit the inconvenience of these young patients. I suggested that the interval between dose and challenge would establish the duration of action for this indication and that the experimental conditions and the data would drive labeling and marketing claims.

Second, she asked how long chronic dosing should be carried out in a multiple-dose trial to study tachyphylaxis to an exercise challenge in adults. We identified comment D.2. as the origin of her question. I clarified that we were concerned about the efficacy of formoterol, used for EIB prophylaxis, when the drug was also being administered chronically for the control of asthma. Study DP/SP2, a crossover trial with two-week treatment periods, had shown loss of protection against a methacholine challenge by the end of the treatment period. Study FO/UK2 suggested a mechanism for this, showing decreased beta-receptor density and affinity after 4-6 weeks of formoterol treatment. Dr. Yegen suggested a crossover trial design with two-week treatment periods and I thought her plan was reasonable.

/S/
Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-831
HFD-570/Division File
HFD-570/Division Director/Jenkins
HFD-570/Medical Reviewer/Anthracite
HFD-570/CSO/Jani

Memorandum

Date May 17, 2000

From Steven R. Koepke, /S/
Deputy Director, Division of New Drug Chemistry II,
Office of New Drug Chemistry

Subject NDA 20-831
Floradil (formoterol fumarate powder for inhalation)
Novartis

There are serious CMC deficiencies related to particle size and degradation products in the stability data submitted in this application. Up to 30% of the drug substance is unaccounted for in mass balance in the accelerated stability studies. In addition, there are significant changes in particle size and emitted dose over time. The sponsor has submitted limited refrigerated stability data to attempt to address some of these issues, but it is unclear that there is any significant improvement in this data. It is recommended that the sponsor be reminded that the Agency has recommended protective overwraps or other protective packaging be investigate to address these issues.

Overall CMC recommendation: There are remaining serious CMC deficiencies as of CMC review #6 . We concur with the overall recommendation of Approvable.

Environmental assessment: Categorical exclusion was claimed (see CMC review #1) – adequate.

Facility Inspections: Acceptable 12-May-2000

Tradename: Acceptable 16-Jul-1997 from LNC. Has this been reexamined by OPDRA?

Labeling: Acceptable from CMC

MEMORANDUM
May 10, 2000

TO: John K. Jenkins, M.D.
Leah Ripper
FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 20-831 (Formoterol fumarate inhalation powder)

I have reviewed the information to support the approvability of this NDA and concur with the recommendations of the Pharmacology/Toxicology Reviewers. The carcinogenicity, mutagenicity, impairment of fertility, and pregnancy category sections of the physician labelling, as written by the sponsor, are unacceptable. These sections should be re-written to conform with the label content suggested by Dr. Luqi Pei (contained in the review, stamp dated April 25, 2000, of subsequent submissions dated 10/19/98 and 11/23/99). Specifically, carcinogenicity study systemic exposure comparisons, as written by Dr. Pei, more accurately reflect the data and current practice in CDER concerning writing style. In addition, Dr. Pei includes information on the actual mutagenicity/genotoxicity studies that were conducted, as well as specific effects observed in nonclinical reproductive toxicity studies. These details are essential for the label to be considered accurate.

/S/

Kenneth L. Hastings, Dr.P.H.
Acting Associate Director for Pharmacology/Toxicology

FOOD AND DRUG ADMINISTRATION

TO (Division/Office):			FROM:	
Peter Cooney/ HFD 160			Parinda Jani/HFD 570 /S/ 11-3-98	
3-98	IND NO.	NDA NO. 20-831 20-831/S/	TYPE OF DOCUMENT CMC Amendment	DATE OF DOCUMENT June 1 and October 19, 1998
NAME OF DRUG Foradil Aerolizer	PRIORITY CONSIDERATION S		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 12-3-98

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- X RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW): To: J. Srinivasa /S/ 11/17/98	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY 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 RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

An Action letter was sent to the sponsor June 26, 1998. This is the response to the micro deficiencies.

Please call Parinda Jani at 7-1064 or Cathie Schumaker at 7-1050 for additional information.

Thanks

cc:
orig nda 20-831/div file HFD-570/ HFD-570 Schumaker, Poochikian, Leak , Jani

SIGNATURE OF REQUESTER /S/ 11-3-98	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER /S/	SIGNATURE OF DELIVERER /S/

24 PAGE(S) REDACTED