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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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

FACSIMILE TRANSMITTAL SHEET

Date: November 17, 2004

To: Ann Shea Associate Director, Regulatory Affairs	**From:** Akilah Green Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Drug Products
Fax number: 973-781-3966	**Fax number:** 301-827-1271
Phone number: 862-778-4567	**Phone number:** 301-827-5585

Subject: NDA 21-592 Information Request

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES X NO

NDA 21-592

We have completed our review of your submission dated October 4, 2004, to NDA 21-592, Foradil Certihaler (formoterol fumarate) Inhalation Powder, and we have the following comment. We need your response no later than December 1, 2004.

Tighten the surface area requirement for the Mg stearate excipient to reflect the

b(4)

If you have any questions, please contact, Ms. Akilah Green, Regulatory Project Manager, at 301-827-5585.

Akilah Green, Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

cc:

HFD-570/Green
HFD-570/Barnes
HFD-570/Bertha
HFD-570/Lostritto

Drafted by: Green/November 17, 2004
Initialed: Barnes/November 17, 2004
Bertha/November 17, 2004
Lostritto/November 17, 2004
Finalized: Green/November 17, 2004

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/s/

Akilah Green
11/17/04 04:20:29 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

Date: November 10, 2004

To: Ann Shea Associate Director, Regulatory Affairs	**From:** Akilah Green Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary and Allergy Drug Products
Fax number: 973-781-3966	**Fax number:** 301-827-1271
Phone number: 862-778-4567	**Phone number:** 301-827-5585

Subject: NDA 21-592 Labeling comments

Total no. of pages including cover: 5

Comments:

Document to be mailed: X YES NO

NDA 21-592

Your submission dated June 24, 2004, to NDA 21-592, is currently under review and we have the following comments.

Revise the following sections of your Package Insert to read as follows:

b(4)

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

b(4)

If you have any questions, please contact, Ms. Akilah Green, Regulatory Project Manager, at 301-827-5585.

_____

Akilah Green, Regulatory Project Manager

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ON ORIGINAL

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/s/

Akilah Green
11/10/04 10:01:31 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Ann Shea
Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

We acknowledge receipt on June 25, 2004, of your June 24, 2004, resubmission to your new drug application for Foradil Certihaler (formoterol fumarate) Inhalation Powder.

We consider this a complete, class 2 response to our October 17, 2003, action letter. Therefore, the user fee goal date is December 25, 2004.

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 waiver granted on February 16, 2001, for the pediatric study requirement for this application for the maintenance and treatment of asthma for children up to 5 months of age and for exercise-induced bronchospasm for children up to 3 years of age. In addition, we reference the deferral granted on December 31, 2001, for the pediatric study requirement for this application the maintenance and treatment of asthma for children 6 months to 5 years of age.

If you have any question, call Akilah Green, Regulatory Project Manager, at (301) 827-5585.

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/

Akilah Green
10/5/04 11:48:27 AM
Signed for Sandy Barnes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

DISCIPLINE REVIEW LETTER

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your December 17, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil Certihaler (formoterol fumarate inhaltion powder).

We also refer to your submissions dated August 29, July 15, and December 1, 2003, and June 24, 2004.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

References included in the comments refer to the June 24, 2004, amendment unless otherwise noted.

1. The following comments pertain to the lactose excipient control and relationship to the product performance in terms of the Aerodynamic Particle Size Distribution (APSD).

   a.

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   b.

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_____ § 552(b)(5) Deliberative Process

If you have any questions, call Akilah Green, Regulatory Project Manager, at 301-827-5585.

Sincerely,

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/

Richard Lostritto
8/24/04 05:41:22 PM

NOVARTIS

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Ann Shea, Senior Associate Director
Tel: 862-778-4567
Fax: 973-781-3966
Internet:ann.shea@pharma.novartis.com

June 24, 2004

Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
5901-B Ammendale Road
Beltsville, Maryland 20705-1266
Attn: Badrul Chowdhury, MD, PhD
Division of Pulmonary and Allergy
Drug Products/HFD-570

NDA No. 21-592

Foradil® Certihaler® (formoterol fumarate inhalation powder)

Complete Response to Approvable Letter dated 17-Oct-03

Dear Dr. Chowdhury:

Reference is made to NDA 21-592 for Foradil® Certihaler® (formoterol fumarate inhalation powder) for long-term, twice-daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older and the Approvable Letter dated October 17, 2003. Please find enclosed a complete response to the items outlined in the Approvable Letter.

Format and Content of the Complete Response

This complete response is presented in a Question and Answer format in the main document, "Complete Response to the 17-Oct-2003 Approvable Letter", followed by attachments. Please note that, except where indicated, this complete response is inclusive of Novartis' NDA amendments dated July 15, 2003 and August 29, 2003. Therefore, this response supersedes these two amendments to this NDA.

Please note that the response to Question 7.g also proposes a revision to the drug product specifications for aerodynamic particle size distribution, based on our current data and analytical methodology.

Two clinical study reports (Studies 2304 and 2306) are also included as Attachments 57 and 58 to Question 1a.

Electronic Sections

This submission is being provided in accordance with the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). The relevant technical details of the electronic portions of this submission are as follows:

- **Submission size:** approximately 18.8 MB
- **Electronic media:** one compact disc
- **Virus scan:** Network Associates Incorporated VirusScan© version 4.5.1 (formerly known as the McAfee VirusScan). The submission is virus free.

This submission includes the following components in electronic form only, and is contained on one CD-ROM that is located in Volume E1.

Proposed Labeling Text

Case Report Forms (Studies F2304 and F2306)

Case Report Tabulations (Studies F2304 and F2306)

If you have any general or clinical questions concerning this submission, please do not hesitate to contact me at 862-778-4567. For CMC-related issues, please contact Orin Tempkin, Ph.D., the Global Regulatory CMC representative, at 862-778-6949.

Sincerely,

Ann Shea
Senior Associate Director
Drug Regulatory Affairs

Attachments:
9 volumes
E1 volume (1 CD-ROM)

cc: Mr. Michael C. Rogers, Division of Emergency and Investigational Operations, FDA (cover letter only)

Foradil Certihaler
NDA Complete Response
Table of Contents

3 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

Memorandum of Telephone Facsimile Correspondence

Date: January 13, 2004

To: Ann Shea
Associate Director, Regulatory Affairs

Fax: 973-781-3966

From: Akilah Green
Regulatory Project Manager

Subject: NDA 21-592/ Foradil Certihaler (formoterol fumarate) Inhalation Powder
December 19, 2003

Reference is made to the meeting held between representatives of your company and this Division on December 19, 2003. 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) 827-5585.

Thank you.

APPEARS THIS WAY
ON ORIGINAL

Memorandum of Teleconference

Date: December 19, 2003 1:00-2:00pm

Application Number: NDA 21-592/Foradil Certihaler (formoterol fumarate inhalation powder)

Between:

Name: Ms. Ann Shea, Drug Regulatory Affairs
Colin Reisner, M.D., Clinical Research
Chad Orevillo, Clinical Research
Denise Till, Biostatistics
Orin Tempkin, Ph.D., Global Regulatory CMC
Barbara Haeberlin, Ph.D., Technical R&D-Inhalation & Device Development

Phone: 1-862-778-4567

Representing: Novartis Pharmaceuticals Corporation

AND:

Name: Badrul Chowdhury, M.D., Ph.D., Division Director
Eugene Sullivan, M.D., Deputy Director
Richard Nicklas, M.D., Clinical Reviewer
Craig Bertha, Ph.D., Acting Chemistry Team Leader
Lori Garcia, Regulatory Project Manager
Akilah Green, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: To discuss Novartis' submission dated December 1, 2003, regarding their proposed protocol entitled, "A 3-week open-label, uncontrolled, multi-center study evaluating the functionality of the Foradil Certihaler device in patients with asthma" as discussed in the November 19, 2003, teleconference.

Discussion:

The Division noted that the patient diary in the proposed protocol does not include directed questions related to the specific device problems that have been noted with this device previously. Novartis should include questions in the patient diary such as, "did the dose counter work?", "did you receive the dose?", and "did you have difficulty getting the dose?" The diary should also include an open-ended question regarding any other perceived problems. The questions do not need to be validated prior to their use in the study. Questions such as these will help Novartis specifically address two aspects of the device performance that have been raised as potential problems, the dose counter, and the actuation flow rate. Novartis verified that they will be testing all devices at the end of patient use (except those that may have been returned and tested earlier and they will be linking this information to patient reports of functional problems with the device recorded in the patient diary. Novartis stated that they are concerned about asking leading

questions in a non-validated setting and asked whether a guide would be sufficient to assist patients in completing the diary, i.e., a separate guide that would direct the patient to comment in the diary if the counter doesn't decrease by one. The Division stated that it is better to ask direct questions in the diary. The Division noted that if patients perceive that it is harder to trigger the device but subsequent in-vitro testing does not indicate any problems, then it will be concluded that, despite the patient's perception, the device functioned properly. However, the Division also noted that if the patient does not notice any problems but the device does not pass the in-vitro assessment, this has to be considered a non-functioning device.

Novartis stated that they are concerned that patients may not be able to perceive that they have received the dose because of the small volume of drug product emitted. However, there is a clicking sound when the dose is delivered and this may improve the patients' ability to perceive a dose. The Division noted that if patients don't perceive receiving the dose, but they received it that is acceptable. However, if this is the case, it would be important to state this in the label so that physicians and patients know what to expect when using the device.

Novartis is proposing an actuation flow rate of > — L/min as representing potential device failure for this study. However, CMC has indicated that > —L/min is beyond the Actuation Flow Rate (AFR) specifications for this particular device. Until the study results are obtained and analyzed, the Division can not agree that AFRs only > — L/min should be considered a "failure." At this time our default position would consider those AFRs above —L/min as being a potential problem. We will also consider that a device has failed if it does not pass the in-vitro testing criteria that have been established. Novartis may wish to report the number of device failures using both criteria. We want the data analyzed to see if it rises above the specified flow rate. Novartis noted that in simulated use (within unit), there is an increase in actuation flow rate in the range of about 5 L/min. Thus, if the initial AFR to trigger the device is —L/min, at the end the AFR would increase to approximately —L/min. Therefore, a large number of devices would be considered to have failing AFR readings. In 90-100 devices, there was an increase above —L/min and Novartis expects similar numbers in this study. The Division noted that identifying the problem does not increase the device failure range. Novartis needs to note the numbers of failures and provide an explanation. It is still a problem, but not a large problem. Novartis stated that they do not test routinely for the drug product. The Division recommended that Novartis do an actuation flow rate test at the beginning-of-life for filled devices the device and questioned if there was a difference between the actuation flow rate for an empty device versus a device that had drug in it but had not been used yet. We know the actuation flow rate get worse over the life of the device. Novartis stated that they do not know. They have to look at the data and compare it; they looked at the devices and noted that they increased 5 L/min through the device life when it was mechanically stressed. Novartis will report the data they collect in the technical assessment, and they plan to have a cut-off threshold. The Division recommended that Novartis analyze the data with different levels of failure (i.e., AFRs of 40, 45, 50, 55 L/min, etc.). In addition, Novartis should clarify what will be considered to be a device failure.

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The Division asked why Novartis is planning to exclude patients who are unable to generate a peak inspiratory flow rate of at least 100 liters per minute. The Division stated that patients should not be excluded based on inspiratory flow rate. Novartis stated that they will measure the peak inspiratory flow rate on entry into the study, but that patients will not be excluded based on the results.

The Division recommended that Novartis include an assessment of the locking mechanism after the last dose.

Novartis is proposing an actuation flow rate of > L/min as representing potential device failure for this study. However, CMC has indicated that > L/min is beyond the Actuation Flow Rate (AFR) specifications for this particular device. Until the study results are obtained and analyzed, the Division can not agree that AFRs only > L/min should be considered a "failure." At this time our default position would consider those AFRs above /min as being a potential problem. We will also consider that a device has failed if it does not pass the in-vitro testing criteria that have been established. Novartis may wish to report the number of device failures using both criteria. We want the data analyzed to see if it rises above the specified flow rate. Novartis noted that in simulated use (within unit), there is an increase in actuation flow rate in the range of about 5 L/min. Thus, if the initial AFR to trigger the device is L/min, at the end the AFR would increase to approximately L/min. Therefore, a large number of devices would be considered to have failing AFR readings. In 90-100 devices, there was an increase above L/min and Novartis expects similar numbers in this study. The Division noted that identifying the problem does not increase the device failure range. Novartis needs to note the numbers of failures and provide an explanation. It is still a problem, but not a large problem. Novartis stated that they do not test routinely for the drug product. The Division recommended that Novartis do an actuation flow rate test at the beginning-of-life for filled devices the device and questioned if there was a difference between the actuation flow rate for an empty device versus a device that had drug in it but had not been used yet. We know the actuation flow rate get worse over the life of the device. Novartis stated that they do not know. They have to look at the data and compare it; they looked at the devices and noted that they increased 5 L/min through the device life when it was mechanically stressed. Novartis will report the data they collect in the technical assessment, and they plan to have a cut-off threshold. The Division recommended that Novartis analyze the data with different levels of failure (i.e., AFRs of 40, 45, 50, 55 L/min, etc.). In addition, Novartis should clarify what will be considered to be a device failure.

b(4)

The Division indicated that we are aware that Novartis is shipping the devices out of the country for in-vitro evaluation, and noted that Novartis is taking a risk that damage may occur during the shipment. Should in vitro testing identify a problem with a device, there will be no way to convincingly establish that the problem developed during the shipping process.

On page 17 of Novartis' submission there is mention of patients being required to contact Novartis immediately if they notice a problem with the device. However, it is unclear

what the next step will be. The Division asked if the devices will be tested at that time using the same criteria that will be used at the end of three weeks of treatment. Novartis stated that it is their intent to first see if the patients do not understand how to use the device and determine whether or not they need to be trained. If the problem does not appear to be related to lack of understanding regarding the proper use of the device, the device will be returned for testing.

The Division recommended that Novartis compare the counter number on returned devices with data from the patient and identify any discrepancies between the number of doses reported by the patient and the number of doses indicated by the dose counter.

The Division noted that Novartis is planning a small study. Patient drop out should be kept to a minimum, and all of the devices should be accounted for. Otherwise, missing devices will be an issue.

The Division indicated that it is acceptable that the data from this study not be integrated into a safety update but cross referenced to the study report that will be part of the complete response.

Akilah Green
Regulatory Project Manager

cc:

HFD-570/Division Files
HFD-570/Bertha
HFD-570/Sullivan
HFD-570/Nicklas
HFD-570/Chowdhury

Drafted by: A. Green/December 24, 2003
Initialed: Nicklas/December 31, 2003
Sullivan/January 6, 2004
Bertha/January 7, 2004
Chowdhury/January 13, 2004
Finalized: A. Green/January 13, 2004

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/s/

Akilah Green
1/13/04 02:25:10 PM

Memorandum of Telephone Facsimile Correspondence

Date: December 4, 2003

To: Orin Tempkin, Ph.D.
Associate Director, Global Regulatory CMC

Fax: 973-781-3320

From: Akilah Green
Regulatory Project Manager

Subject: NDA 21-592/ Foradil Certihaler (formoterol fumarate inhalation powder)
November 19, 2003, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on November 19, 2003. 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) 827-5585.

Thank you.

Memorandum of Teleconference

Date: November 19, 2003 11:00-12:00pm

Application Number: NDA 21-592/Foradil Certihaler (formoterol fumarate inhalation powder)

Between:

Name: Dr. Orin Tempkin, Regulatory CMC-US
Dr. Barbara Haeberlin, Technical Project Leader, Technical R&D, Inhalation & Device Development
Ms. Ann Shea, Drug Regulatory Affairs, Therapeutic Area
Dr. Andre Van As, Clinical Development
Phone: 1-862-778-4315
Representing: Novartis Pharmaceuticals Corporation

AND:

Name: Badrul Chowdhury, M.D., Ph.D., Division Director
Richard Nicklas, M.D., Clinical Reviewer
Eugenia Nashed, Ph.D., Chemistry Reviewer
Craig Bertha, Ph.D., Acting Chemistry Team Leader
Akilah Green, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: In a letter dated October 23, 2003, Novartis requested a meeting with the Division to obtain agreement on their strategy for addressing several of the CMC items listed in the October 17, 2003, Approvable Letter. In addition, Novartis is seeking clarification on items 13 and 14 in the Approvable Letter and the requirement for a safety update.

The Division addressed the following questions, in bold italics, posed in Novartis' meeting package dated November 7, 2003.

Question 3.1

Please refer to question 1a in the Approvable letter. Is the strategy outlined below acceptable to the Agency for approval of the NDA?

The Division summarized concerns about the malfunctioning devices and data supporting a change from devices manufactured with [redacted] (used in Phase III studies) to [redacted] devices that will be used for marketing. The Division pointed out that the rate of counter failure for [redacted] devices (75 inhalers studied in simulated conditions) seems to be far greater (5.3%, 4 out of 75 devices) as compared to [redacted] devices (1.5%). Also, an increase (*ca* 5 L/min) in the actuation flow rate during the life of the device due to the powder deposition was noticed. Overall, a preliminary review of the studies submitted in the August 29, 2003, amendment suggests

b(4)

that in vitro data alone, even with a larger sample size, may be insufficient to address the concerns of device performance.

The Division would like Novartis to provide an explanation of the device lock-out in relation to the counter reading. In addition, the Division would like a comparison of the functionality failures (broken down by type of failure) for the [redacted] devices, and Novartis' plan for addressing the outstanding issue of increase in actuation flow rate for the devices. b(4)

The Division further noted that from a clinical standpoint, we are concerned with the original data Novartis submitted. There was an increase in actuation flow rate and some counters did not function properly. We are also concerned with the simulated use study. There were failures with the device and in increase in actuation flow rate by 5L/min that was necessary to trigger the device. The Division believes that the *in* vitro in-use study does not simulate actual clinical use. The Division recommended that Novartis perform an actual patient use study to ensure proper functioning of the device in patient's hands in actual clinical use. The Division also recommended that the devices used in the clinical study be tested in vitro. *In vitro* data are needed to evaluate devices near the end of the device life after actual use by patients (100-200 devices). Also, *in vitro* data are needed to evaluate devices that failed out of those studied. Normally a number of such devices (100-200) would be returned for routine *in vitro* evaluation from the Phase III clinical studies. Novartis needs to conduct a real-life in-use study where they give the drug to patients to use, have patients record problems with the device in response to a questionnaire, and then Novartis should check the devices (*in vitro* testing) when they are returned. Novartis should compare the determined *in vitro* actuation flow rates for any devices for which there are complaints with the flow rates achieved by patients in the Phase III clinical studies. Obtaining these data as a Phase IV commitment is not acceptable.

Novartis stated that a calculation of 1.5% failures ([redacted] devices used in phase III clinical trials) was done in a different way and can not be compared to the 5.3% counter failure rate observed for the limited *in vitro* "in-use" study. They indicated that several improvements were made to the device, i.e., [redacted] process that provides a better seal of the mouth piece. Also, the observed actuation flow increase brings the total actuation to about 45 L/min which is still well within the average flow actuation measured in patients, i.e., 50-70 L/min. b(4)

In regard to the mechanism of the lock out Novartis stated that when 0 appears in the window, the patient opens the device, uses it, closes it, and the window will show 999, so the window is integrated with the lock. When the window shows zero, the next dose locks the device.

Novartis proposed that they submit a detailed explanation of ongoing *in vitro* data (200 and 500 devices) in December and submit the patient performance data post-approval or during the next review cycle.

The Division noted that it is not acceptable for Novartis to submit data vital for approval during the review cycle. The necessary information must be included at the time of submission. Novartis may propose a plan for the Division to review prior to submission of the complete response. The scope of the study should be adequate to capture problems and the questionnaire should have directed questions. The issues to be addressed should be the problems Novartis is currently experiencing with the device. If Novartis wants to address other aspects of device performance, that will be their choice. If Novartis demonstrates that patient complaints are not associated with device failure, this will be in Novartis' favor. There should be 100-200 patients in the clinical trial and *in vitro* testing of the used devices should be carried afterwords.

Question 3.2

Is the strategy outlined below regarding lactose monohydrate acceptable to the Agency for approval of the NDA? (please also see question in section 3.2.5 at conclusion of this section)

b(4)

Question 3.3

Please refer to question 7b (i) & (ii) and 8d in the Approvable Letter. Is the proposed method (submitted in the 29-Aug-2003 Amendment) acceptable to the Agency?

b(4)

The Division stated that we have not had a chance to review the August amendment, therefore, we are unable to respond to this question.

Question 3.4
Does the Agency agree with Novartis' proposal regarding foreign particulate testing on formoterol fumarate drug substance?

Again, the August amendment has not been reviewed.

b(4)

However, we can give a final answer only after reviewing the data.

Question 3.5
Please refer to question 7d in the Approvable Letter. Is the sampling plan testing inhalers both at the beginning and end of device life proposed by the Agency intended to replace the current DCU and DCU through container life tests?

b(4)

Question 3.6
Please clarify the type of database being referred to in Question 13 of the Approvable letter.

The Division informed Novartis that a more extensive database for adolescent and elderly patients would help to define the expected response to this drug product in adolescents and the elderly in terms of efficacy and safety. The number of patients should be based on an assessment of the number of patients in these age groups that are required to demonstrate efficacy and safety. These studies can be done as a Phase IV commitment. The sponsor asked if would be acceptable to study adolescents 13-18 years of age, and patients older than 65 years of age, and the Division indicated that this would be acceptable. The sponsor asked if the duration of exposure should be 3 months and the

Division indicated that this was acceptable. The sponsor indicated that they are planning to do COPD studies in the future. The Division responded that if Novartis does a COPD study it will probably evaluate a sufficient number of patients in the elderly age group to provide a more extensive database in elderly patients. Therefore, Novartis should focus on developing a plan of study for the adolescent group and provide such a plan in their complete response.

Question 3.7
Please clarify the nature of the Agency's concerns expressed in Question 14 of the Approvable letter?

The Division indicated that our request for plans for educational activities is intended to minimize confusion in regard to Foradil Aerolizer and Foradil Certihaler. It is based on the assumption that practicing physicians will consider in their prescribing habits that the Certihaler is interchangeable with the Aerolizer. The Division of Drug Marketing, Advertising, and Communications will review the promotional materials. Novartis should submit the patient and physician education packet as part of the complete response, the Office of Drug Safety will review it.

Question 3.8
Does the Agency agree that a safety update is not required?

Novartis should submit a safety update and state that there is no data to report so that it is documented for the record.

Akilah Green
Regulatory Project Manager

cc:

HFD-570/Division Files
HFD-570/Bertha
HFD-570/Nashed
HFD-570/Nicklas
HFD-570/Chowdhury

Drafted by:	A. Green/November 20, 2003
Initialed:	Nicklas/November 21, 2003
	Bertha/November 24, 2003
	Chowdhury/December 3, 2003
Finalized:	A. Green/December 4, 2003

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/s/

Akilah Green
12/4/03 09:23:20 AM

Memorandum of Telephone Facsimile Correspondence

Date: July 22, 2003

To: Orin Tempkin, Ph.D.
Associate Director, Global Regulatory CMC

Fax: 973-781-3320

From: Akilah Green
Regulatory Project Manager

Subject: NDA 21-592
July 2, 2003, meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on July 2, 2003. 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) 827-5580.

Thank you.

Memorandum of Telecon

Date: July 2, 2003 12:30-1:30pm

Application Number: NDA 21-592/Foradil Certihaler (formoterol fumarate inhalation powder)

Between:

Name: Dr. Orin Tempkin, Regulatory CMC-US
Dr. Barbara Haeberlin, Technical Project Leader, Technical R&D, Inhalation & Device Development
Dr. Glenn Thompson, Analytical Development, Technical R&D, Inhalation & Device Development
Ms. Ann Shea, Drug Regulatory Affairs, Therapeutic Area
Phone: 1-877-805-0964
Representing: Novartis Pharmaceuticals Corporation

AND:

Name: Guirag Poochikian, Ph.D., Chemistry Team Leader
Craig Bertha, Ph.D., Chemistry Reviewer
Akilah Green, Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: To discuss Novartis's strategy for addressing and clarifying some of the items listed in the May 7, 2003, Discipline Review letter.

The Division addressed the following questions, in bold italics, posed in Novartis's meeting package.

Question 1

Novartis plans to submit a response to the Discipline Review (DR) Letter in mid-July 2003 (corresponding to 3 months prior to NDA action date). Would the Agency be able to accept and review an additional submission with further information and data by the end of August? If so, how much information?

The Division informed Novartis that we are not in control of our workload and have to review applications as they arrive. Therefore, we cannot commit to review any response to our DR letter before the action date for the application.

Question 2

Please refer to question 6b in the Discipline Review Letter. Is the strategy outlined below acceptable to the Agency for approval of the NDA?

The Division stated that the acceptability depends on the adequacy of their findings and approach to addressing the assay variability and [redacted] b(4)

4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

cc:

HFD-570/Division Files
HFD-570/Bertha
HFD-570/Poochikian

Drafted by: A. Green/July 8, 2003
Initialed: Bertha/July 14, 2003
Poochikian/July 14, 2003
Finalized: A. Green/July 22, 2003

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

/s/

Akilah Green
7/22/03 03:39:09 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

DISCIPLINE REVIEW LETTER

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your December 17, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil Certihaler (formoterol fumarate) Inhalation Powder, 10 mcg.

Our review of the Chemistry, Manufacturing and controls section of your submission is complete, and we have identified the following deficiencies:

1) The following comments pertain to the production of the drug product with devices manufactured with the ——— tooling and incorporating other changes. b(4)

b(4)

2)

11 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Guiragos Poochikian
5/7/03 01:27:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

APPLICATION FILING REVIEW ISSUES IDENTIFIED

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your December 17, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil Certihaler (formoterol fumarate) Inhalation Powder, 10 mcg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on February 16, 2003, in accordance with 21 CFR 314.101(a).

We request that you submit the following information:

1. Submit annotated versions of your proposed Foradil Certihaler labeling that clearly identify your proposed labeling revisions from those portions of the approved Foradil Aerolizer labeling.

2. You are reminded of our January 30, 2003, facsimile correspondence, which requested further statistical information. Additionally, we request that you provide SAS programs that generate both descriptive and inferential statistics as part of your response.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Dr. Craig Ostroff, Regulatory Management Officer, at 301-827-5585.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Badrul Chowdhury
2/28/03 02:43:29 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
DPADP - HFD-570

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2003

To: Ann Shea Associate Director Drug Regulatory Affairs	**From:** Craig Ostroff, Pharm.D. Regulatory Management Officer Division of Pulmonary and Allergy Drug Products
Company: Novartis	
Fax number: 973-781-3966	**Fax number:** 301-827-1271
Phone number: 862-778-4567	**Phone number:** 301-827-5585

Subject: NDA 21-592 Foradil Certihaler; Statistical Information Request

Total no. of pages including cover: 3

Comments:

See attached.

Document to be mailed: • YES ☑NO

We are currently reviewing the clinical statistics portion of your NDA submission and have the following request for information, in order to assist us with the review.

Please submit (or identify the location thereof) the following SAS programs for all studies contained in NDA 21-592:

1. SAS programs that created the derived data from the raw data (for example, SASDAT2.SAS).

2. SAS programs that generated the statistical results that support efficacy; include ISE.

3. SAS programs that generated the statistical results for safety; include ISS.

For each SAS program, submit documentation that explains the purpose of the program and identifies the input data and the output data (of tables).

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/s/

Craig Ostroff
1/30/03 04:38:06 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-592

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

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:	Foradil Certihaler (formoterol fumarate) Inhalation Powder, 10 mcg
Review Priority Classification:	Standard (S)
Date of Application:	December 17, 2002
Date of Receipt:	December 18, 2002
Our Reference Number:	NDA 21-592

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 February 16, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 18, 2003.

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:

US Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary & Allergy Drug Products, HFD-570
Attention: Document Room, 10B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Dr. Craig Ostroff, Regulatory Management Officer, at 301-827-5585.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Craig Ostroff
1/6/03 05:25:58 PM
Signed for Sandy Barnes

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Ann Shea, Associate Director
Tel: 862-778-4567
Fax: 973-781-3966
Internet:ann.shea@pharma.novartis.com

NOVARTIS

December 17, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

NDA No. 21-592

Foradil® Certihaler™ (formoterol fumarate inhalation powder)

New Drug Application

Dear Sir or Madam:

We are submitting a New Drug Application for Foradil® Certihaler™ (formoterol fumarate inhalation powder), NDA No. 21-592, for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children 5 years of age and older. Foradil Certihaler is a new multi-dose dry powder inhaler for the delivery of formoterol fumarate that can dispense sixty 10 µg metered (equivalent to 8.5 µg emitted) doses.

Format and Content of the Application

This NDA is presented as a Common Technical Document and was prepared in accordance with existing regulations, relevant guidelines and agreements reached at our pre-NDA meeting with the Division of Pulmonary and Allergy Drug Products on July 11, 2002. In addition, as outlined at the Pre-NDA meeting, only new data is presented in this application and reference is made to the approved NDA 20-831 for Foradil® Aerolizer® (formoterol fumarate inhalation powder) for data previously submitted.

Reference is also made to NDA 20-831 for information on the formoterol fumarate drug substance. As new Chemistry, Manufacturing and Controls information for the drug product is being submitted in this application, a Field Copy will be provided to Michael C. Rogers, Division of Emergency and Investigational Operations.

Electronic Sections

The overall size of the electronic files contained in Volume E1 is approximately 1.10 GB. The virus scanning software used for the submission is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

This submission includes the following CTD components in electronic form only, and is contained on one CD-ROM that is located in Volume E1.

Module 1, Tab 1.3.1.1 Proposed Labeling Text

Module 5, Tab 5.3.7 Case Report Forms

Module 5, Tab 5.3.7 Case Report Tabulations

Pediatric Deferral

A deferral of pediatric studies for patients 6 months to 5 years of age was requested and granted at the End of Phase 2 meeting on January 29, 2001.

User Fee

The FDA User Fee for this application (User Fee ID 4465) was submitted on November 20, 2002.

Novartis Pharmaceuticals Corporation considers the information contained within this application to be confidential, and its contents are not to be disclosed without express written consent.

If you have any questions concerning this submission, please contact me at 862-778-4567.

Sincerely,

Ann Shea
Associate Director
Drug Regulatory Affairs

Attachments:
69 volumes
E1 volume (2 CD-ROMs)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	December 17, 2002
TELEPHONE NO. (*Include Area Code*)	FACSIMILE (FAX) Number (*Include Area Code*)
(862) 778-4567	(973) 781-3966
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*):	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE
One Health Plaza East Hanover, New Jersey 07936-1080	

RECEIVED
JAN 17 2003
FDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (*If previously issued*) 21-592

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
formoterol fumarate inhalation powder	**Foradil® Certihaler™**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Multidose dry powder inhaler	**10 mcg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE:
Maintenance treatment of asthma

APPLICATION INFORMATION

APPLICATION TYPE (*check one*)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (*check one*) ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
New Multidose dry powder inhaler

PROPOSED MARKETING STATUS (*check one*) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 70 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-831

This application contains the following items: (*Check all that apply*)	
X	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
X	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
X	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
X	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
X	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (k)(3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Ann Shea	Ann Shea, Associate Director Drug Regulatory Affairs	**12/17/02**

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza East Hanover, New Jersey 07936-1080	(862) 778-4567

Public reporting burden for this collection of information is estimated to average 24 hours 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

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.

Establishment Information

Drug product sites of manufacturing, packaging and control

Site	CFN	Manufacturing	Quality control[1]	Stability	Packaging
SkyePharma Production SAS[2] Z.A. de Chesnes Ouest Rue du Montmurier 55, B.P. 45 F-38291 Saint Quentin-Fallavier cedex, France	9615709	X	X	X	X[3]
Novartis Pharma GmbH Oeflinger Strasse 44 D-79664 Wehr / Baden, Germany	9617734				X[4]
Novartis Pharmanalytica SA Via S. Balestra 31 Casella postale 447 CH-6601 Locarno, Switzerland	9614433		X[5]	X	
Novartis Pharma Stein AG Schaffhauserstrasse CH-4332 Stein, Switzerland	9692043		X[6]	X[6]	

CFN: Central File Number

1 The drug product will be tested according to the current Testing Monograph.

2 This site may be commonly referred to as "SkyePharma Lyon" due to proximity of Saint Quentin-Fallavier to Lyon.

3

4

5

6

b(4)

Contact persons

Contact persons for the above facilities are provided below. To facilitate contacting these individuals at the listed facilities, the Novartis contact in the USA is:

Michael Bruckheimer, Executive Director Global Quality Operations
Novartis Pharmaceuticals Corporation,
One Health Plaza
East Hanover, NJ 07936, USA
Tel number: (862) 778 7913
Fax: (973) 781 6052
e-mail: michael.bruckheimer@pharma.novartis.com

Novartis Wehr, Germany, Novartis Locarno and Stein, Switzerland

Dr. Stefan Bürki
Novartis Pharma GmbH,
Wehr, Germany
Tel number: +49 77 62822251
Fax: +49 77 62822307
e-mail: stefan.buerki@pharma.novartis.com

Dr. Bernd Stempfle
Novartis Pharmanalytica SA,
Locarno, Switzerland
Tel number: +41 91 7599102
Fax: +41 91 7599100
e-mail: bernd.stempfle@pharma.novartis.com

Dr. Andreas Brutsche
Novartis Pharma Stein AG,
Stein, Switzerland
Tel number: +41 62 8687050
Fax: +41 62 8686460
e-mail: andreas.brutsche@pharma.novartis.com

SkyePharma Saint Quentin-Fallavier, France

Christian Kalita, Head Quality Assurance
SkyePharma Europe,
Saint Quentin-Fallavier, France
Tel number: +33 474 952159
Fax: +33 474 952165
e-mail: ckalita@skyepharma.fr

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

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

Novartis Pharmaceuticals Corporation
One Health Net Plaza
East Hanover, New Jersey 07936

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 781-6940 - Vera Wolsch

3. PRODUCT NAME

Foradil ® Certihaler ™
(formoterol fumarate inhalation powder)

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

21-592

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).

6. USER FEE I.D. NUMBER

4465

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 A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) 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 COMMERCIALLY
(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

and

Food and Drug Administration
CDER, HFD-94
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	DATE
Vera Wolsch	Director, Drug Regulatory Affairs, Planning & Administration	11-20-02

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 10, 2002

IND: Foradil (formoterol fumarate) MDDPI

SPONSOR: Novartis

TYPE OF MEETING: In-person Meeting; IMTS 8471; PNDA

ATTENDEES:

Division of Pulmonary & Allergy Drug Products (DPADP, HFD-570)

Raymond Anthracite, M.D.	Medical Reviewer
Emmanuel Fadiran, Ph.D.	Clinical Pharmacology/Biopharmaceutics Team Leader
James Gebert, Ph.D.	Statistical Reviewer
Ted Guo, Ph.D.	Statistical Reviewer
Robin Huff, Ph.D.	Supervisory Pharmacologist
Mary Jane Kennedy, Pharm.D.	Clinical Pharmacology Fellow
Robert J. Meyer, M.D.	Director
Craig Ostroff, Pharm.D.	Project Manager
Timothy Robison, Ph.D.	Pharmacology/Toxicology Reviewer

Novartis:

Ann Shea	Associate Director, Drug Regulatory Affairs
Lisa Benison	Foradil Project Team Leader
Umit Yegen	Clinical Research Physician
Gunther Kaiser	Project Team Representative, PCS
Kim Andriano	Statistician
Jack Weet	Global Therapeutic Head, Drug Regulatory Affairs
Chin Koerner	FDA Liaison, Drug Regulatory Affairs
Jonah Smith	Statistician
Ann Horowitz	Assistant Director, Clinical Pharmacology
Ioannis Kottekis	Clinical Development, UK
James King	Regulatory Affairs, UK
Tim Overant	Clinical Research Scientist

BACKGROUND

Novartis submitted a PNDA meeting request dated March 1, 2002. The briefing book for this meeting was submitted on April 5, 2002. The goal of this meeting was to discuss the nonclinical, clinical and clinical pharmacology portions of the application. A separate CMC PNDA meeting was held on April 25, 2002.

MEETING DISCUSSION

[What follows is a summary of the meeting discussion beyond the information provided in the slides presented at the meeting, which are attached to the end of this document. Comments from the sponsor are in *italics*. Comments from the division are in regular typeface.]

The meeting began with personnel introductions and an overview of the meeting format. The applicant was afforded the opportunity to summarize the points discussed, at the close of the meeting, as they heard them. This summary allows the applicant and FDA the opportunity to clarify any points of discussion.

CLINICAL

Question 2
Does the Agency agree that the proposed inclusion of Study 603 in the 120-day update only is acceptable?

The division stated that the agreement to the shortened timelines for PDUFA assumes that the application will be complete at the time of NDA submission. If Study 603 were not a critical study for approval, then it would likely be acceptable to submit it with the 120-day safety update. Further, it does not appear to the division at this time, if the sponsor would ultimately need a one-year safety study for this drug, considering the similarities of this formulation to the approved formoterol formulation. This is a review issue. Until the NDA is submitted and reviewed, we cannot definitively know how critical Study 603 may then be. However, if Study 603 is submitted after NDA submission, it may or may not be reviewed as part of the first review cycle depending on review resources in the division.

Question 3
Does the Agency agree to revise the current package insert to include information on the MDDPI device? If Novartis prefers to have a separate label for the MDDPI formulation, would the Agency object?

The division stated that having the same package insert for both Aerolizer and MDDPI formulations is not encouraged because dissimilarities between the two formulations/devices (including doses) would make writing a unified label very difficult and confusing to read. Separate labels are acceptable and, in this case, we consider them to be desirable.

Question 6
Does the Agency agree with the proposed studies to be integrated for efficacy analyses?

The division stated that these may be analyzed in any number of ways that you may choose, but do analyze each study separately, which will be our primary interest.

Question 7
Does the Agency agree with the content of the proposed Summary of Clinical Efficacy as discussed and shown as post-text table shells?

The division stated that the presentation format described in Appendix 3 is acceptable. The post-text SCE tables also look acceptable.

Question 10
Does the Agency have any questions or need clarification about what was discussed concerning discontinuation of the electronic peak flow diary from MDDPI Study 603 and the ramifications thereof?

The electronic diaries have failed during the study. There is a problem with capturing rescue medication use. A number of patients entered the wrong information into the diary, subsequently mentioned this to the study investigators who noted these errors in the CRFs. The protocols capture any adverse events associated with asthma.

The sponsor is trying to make the best of an unfortunate setback with the electronic diary and the division will try to evaluate the data involved in this issue when it is submitted.

It appears that the definition of severe asthma exacerbation has now been changed to a consideration of asthma–related adverse events. Rescue medicine use, symptom scores and treatment compliance will all be effected to some degree.

Question 11
Does the Agency have any questions or need clarification about what was discussed concerning not using the daily PEFR data from the electronic peak flow diary as the primary efficacy endpoint for MDDPI Study 605?

The division was not clear about what was meant here.

The sponsor stated that this question referred to the change in endpoints.

The division responded that it mattered whether the choice was made blinded or unblinded (i.e., prior to the unblinding of the studies).

The division stated that we hoped that they had not broken the blind until after changing their endpoints.

The sponsor indicated that they did not break the blind until after they had already changed the endpoints. The division stated the sponsor should clearly state this in the application.

SAFETY ANALYSIS

The division stated that the sponsor should include all safety data in two major categories, controlled and uncontrolled studies. Any additional analyses are welcome.

INDEX

The division stated that the index for the original Foradil application was inaccurate and insufficient and whenever the sponsor refers to this original application in the MDDPI NDA, they will have to reliably identify the location of the information within the original submission. In addition, a

complete, accurate and detailed index to the Common Technical Document and the electronically submitted portions of it, is expected.

The sponsor stated that the new index will be complete and whenever they refer to information they agree to adequately refer to the location of the information.

STATISTICS

The division stated that pooling in the ISE is acceptable. We are interested in seeing the sponsor's own interpretation of the outcome. The sponsor does not need to adjust the data using the Hochberg method. It is unlikely that the Agency would give a claim for the symptom domain of the Quality of Life (QoL) instrument if the overall QoL score was not significant. It was mentioned that clinical significance of scores obtained from the QoL instrument is important, not just the statistical comparisons.

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

Question 4: Does the Agency agree with the content and format proposed for the following summaries: Nonclinical Overview (CTD Section 2.4)?

The division stated that the proposed format on page 17 of the package appears acceptable.

CLINICAL PHARMACOLOGY

The sponsor plans to submit full study reports of any new (previously non-reported) study.

The sponsor plans to submit the NDA approximately Dec 2002 or March 2003.

Novartis'
FORMOTEROL MDDPI
5/10/02 Pre-NDA Meeting

SPONSOR QUERIES
&
DIVISION RESPONSES

Raymond F. Anthracite, M.D.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

2. Does the Agency agree that the proposed inclusion of Study 603 in the 120-day update only is acceptable?

With the adoption of more stringent PDUFA review deadlines, we can no longer give assurance that late study reports will be reviewed within the first cycle.

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

3. Does the Agency agree to revise the current package insert to include information on the MDDPI device? If Novartis prefers to have a separate label for the MDDPI formulation, would the Agency object?

The same package insert for both Aerolizer and MDDPI formulations is not encouraged because dissimilarities between the two formulations/devices would make writing a unified label very difficult and confusing to read.

Separate labels are acceptable and, in this case, we consider them to be desirable.

4. Does the Agency agree with the content and format proposed for the following summaries:

- **Nonclinical Overview (CTD Section 2.4)**
  - Not described. This is an overview of pharmacology, pharmacokinetics, and toxicology that in general should not exceed 30 pages.
- **Nonclinical written and tabulated summaries (CTD Sections 2.6.2 to 2.6.7)**
  - The proposed format appears acceptable.

Module 4 Nonclinical Study Reports

- Provide full reports of the two referenced pharmacology and pharmacokinetic studies as well as the 4 toxicology studies with magnesium stearate and the 13-week bridging study in dogs.

4. Does the Agency agree with the content and format proposed for the following summaries:

- **Summary of Biopharmaceutic Studies and Associated Analytical Methods**
  - We Agree
- **Summary of Clinical Pharmacology Studies**
  - We Agree

5. Does the Agency agree with the following proposal for presentation of data from previous formoterol fumarate development programs?

- We agree, but provide full individual reports of the new studies.

6. Does the Agency agree with the proposed studies to be integrated for efficacy analyses?

These may be analyzed in any number of ways you wish but do analyze each study separately, which will be our primary interest.

7. Does the Agency agree with the content of the proposed Summary of Clinical Efficacy as discussed and shown as post-text table shells?

The presentation format described in Appendix 3 is acceptable. The post-text SCE tables also look acceptable.

8. Does the Agency agree with the proposed studies to be integrated in the safety analyses?

We are unclear about which studies you propose to integrate for safety.

Please integrate all MDDPI studies into two groups for safety analyses, all controlled studies and all uncontrolled studies.

9. Does the Agency agree that the proposed groupings of studies for the Clinical Summary of Safety are the most useful?

Please see the response to question #8.

10. Does the Agency have any questions or need clarification about what was discussed concerning discontinuation of the electronic peak flow diary from MDDPI Study 603 and the ramifications thereof?

We understand what was presented, but how these changes will effect the interpretation of this study will be a review issue.

The absence of PEFR data will mean that severe asthma exacerbations are undefined. What other effects on originally planned endpoints will the absent data have?

11. Does the Agency have any questions or need clarification about what was discussed concerning not using the daily PEFR data from the electronic peak flow diary as the primary efficacy endpoint for MDDPI Study 605?

Please see response to question #10. When the blind was broken relative to selection of the new primary endpoint will also bear on future regulatory decisions.

12. Does the Agency agree with the format and content of the efficacy SAS datasets for the MDDPI Studies 604, 2302 and 2303? Additionally, the sponsor will provide inferential efficacy programs for these efficacy datasets during review only upon request. Is this acceptable to the agency?

Yes. Yes.

13. Does the Agency agree with the proposal detailed for the inclusion of the defined CRFs, SAE narratives and publications?

We agree.

Additional Comments 1

We note that NDA 20831 was submitted and filed without a detailed index. During the course of reviews that led up to approving it, a complete index was never developed.

A complete, accurate and detailed index to the CTD, the electronically submitted portions of it and to referenced portions of NDA 20831 will be a prerequisite.

Additional Comments 2

- For your QOL analyses you only mention statistical significance. The Agency wants clinical significance.
- You perform a Hochberg adjustment for Total QOL and the Symptom Domain. It is unlikely that the Agency would approve a QOL claim only for the Symptom domain. All Domains should be analyzed.
- You must provide subgroup analyses for ethnic origin.
- Besides your analyses in special groups (age, gender, ethnic), provide some discussion whether there are differential effects in the various subgroups.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Craig Ostroff
5/31/02 06:22:37 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 25, 2002

IND: Foradil (formoterol fumarate) MDDPI

SPONSOR: Novartis

TYPE OF MEETING: In-person Meeting; IMTS 8407; PNDA-CMC

ATTENDEES:

Division of Pulmonary & Allergy Drug Products (DPADP, HFD-570)

Craig Bertha, Ph.D.	Chemistry Reviewer
Marianne Mann, M.D.	Deputy Division Director
Craig Ostroff, Pharm.D.	Project Manager
Guirag Poochikian, Ph.D.	Chemistry Team Leader

Novartis:

Lisa Benison	Foradil Project Team Leader
Barbara Haeberlin	Technical Project Leader, Pharma. & Analytical Development
Chin Koerner	FDA Liaison, Drug Regulatory Affairs
Michael Malone	Regulatory CMC
Ann Shea	Associate Director, Drug Regulatory Affairs
Orin Tempkin	Assistant Director, Drug Regulatory Affairs
Jack Weet	Global Therapeutic Head, Drug Regulatory Affairs

BACKGROUND

Novartis submitted a PNDA meeting request dated February 22, 2002. The briefing book for this meeting was submitted on March 27, 2002. The goal of this meeting was to discuss the chemistry portions of the application. A separate PNDA meeting regarding the remaining review disciplines was held on May 10, 2002.

MEETING DISCUSSION

[What follows is a summary of the meeting discussion beyond the information provided in the slides presented at the meeting, which are attached to the end of this document. Comments from the sponsor are in *italics*. Comments from the division are in regular typeface.]

The meeting began with personnel introductions and an overview of the meeting format. The applicant was afforded the opportunity to summarize the points discussed as they heard them, and at the close of the meeting. This summary allows the applicant and FDA the opportunity to clarify any points of discussion.

Question 1.
A short summary of the content and format of the CMC section of the NDA is described below. A table of contents can be found in Appendix I. Does the Agency agree with the following content and format proposals?

- The division stated that they agree with the proposals.

Question 2.
Does the Agency agree with the regulatory limits proposed for the content uniformity testing of the device (both "dose content uniformity" and "dose content uniformity through container life")? If not would the parametric or any other approach be acceptable?

- The division stated that they do not agree with the limits proposed. The division reminded the sponsor that both in the letter for the initial IND review and during the End of Phase 2 meeting we stated that they would need to tighten up their limits to be consistent with Agency expectations. It was agreed at the EOP2 meeting that the sponsor would have dose content uniformity (DCU) limits for the product that were wider than Agency standard (along the lines of the USP limits) with an eye toward tightening these up for the NDA.

- The division's current position is that of the Guidance. The USP DCU limits are not acceptable. The division is open to future discussion on this issue as long as the data is presented in a broken down format.

- In the summary provided by the sponsor there is no information on the points at the beginning-middle-end that is broken down under different conditions (i.e. Temperature/Humidity), formulation, container/closure, etc. In the absence of data it is premature to comment on this, but this data should be broken down in the NDA.

- The division pointed out that from the plots of preliminary data (see figure 7.2-1 on p. 16), it appears that there are quite a few "outliers" that might possibly be interpreted as product variability. This is not a filing issue, but a review issue.

Question 3.
Does the Agency agree to the proposed grouping of the ___ stage data? b(4)

- The division noted that it is premature to agree to certain groupings of ___ data in terms of acceptance criteria until the full body of stability data is evaluated for trends, or shifts in distribution.
- The sponsor should be looking for the data in terms of stage/accessory groupings that are most sensitive to changes. If certain groupings are proposed, the division may or may not agree at this time. The sponsor should look at the distribution data and look for shifts and trends during the analysis.

Question 4.
Does the Agency agree with the proposed limit for 'Foreign particulate matter in the reservoir by Microscopy (No. of particles > ___ µm): less than ___? b(4)

10 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Craig Ostroff
5/24/02 02:30:29 PM

Memorandum of Telephone Facsimile Correspondence

Date: March 9, 2001

To: Lynn Mellor
Regulatory Affairs

Fax: (973) 781-3590

From: Parinda Jani
Project Manager

Subject: IND 60,254/January 29, 2001 End of Phase 2 meeting minutes

Reference is made to the meeting held between representatives of your company and this Division on January 29, 2001. 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) 827-1064.

Thank you.

Meeting Date: January 29, 2001 **Time:** 1:00 PM - 2:30 PM
Location: Conf Rm "C" **IMTS #** 6299
IND: 60,254
Sponsor: Novartis Pharmaceuticals Corporation
Product: Formoterol fumarate multi-dose inhalation powder
Type of Meeting: End-of-Phase 2

FDA Attendees:

Ray Anthracite, M.D.	Medical Reviewer
Craig Bertha, Ph.D.	Chemistry Reviewer
Young Moon Choi, Ph.D.	Clinical Pharmacology and Biopharmaceutics Acting Team Leader
Ted Guo, Ph.D.	Biostatistics Reviewer
Robin Huff, Ph.D.	Pharmacology/Toxicology Team Leader
Parinda Jani	Project Manager
John Jenkins, M.D.	Office Director, ODE II
Marianne Mann, M.D.	Deputy Division Director
Robert Meyer, M.D.	Division Director
Craig Ostroff, Pharm.D.	Project Manager
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Tim Robison, Ph.D.	Pharmacology/Toxicology Reviewer
Monique Wakelkamp, M.D., Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer

Novartis Attendees:

Kim Andriano, Ph.D.	Biostatistics
Stephanie Barba	Drug Regulatory Affairs
Lisa Benison	Project Management
Philip Bentley, Ph.D.	Preclinical Safety
Giovanni DellaCioppa, M.D.	Therapeutic Head –Respiratory Clinical Development
Barbara Haeberlin, Ph.D.	Technical Research and Development
James King	Drug Regulatory Affairs
Ioannis Kottakis, M.D.	International Clinical Leader for Foradil-Respiratory Clinical Development
Sheryl LeRoy	Drug Regulatory Affairs - CMC
Michael Malone, Ph.D.	Technical Research and Development
Sharon Olmstad	Assistant Director, Regulatory Liaison, Washington D.C.
Nicki On, Ph.D.	Clinical Pharmacology/Pharmacokinetics
Umit Yegen, M.D.	Clinical Research Physician, Clinical Development

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Background: See the meeting request submissions dated October 10 and December 13, 2000.

The industry issues are listed in bold, followed by the responses from the Agency.

1. **We propose that the results of the Phase 2 dose finding studies including the PK data show that the new formoterol formulation is safe, well-tolerated and effective and supports the further evaluation in pivotal Phase 3 studies.**

   The Agency stated that decisions for "safety, tolerability and effectiveness" of a product are made during the NDA stage of the review process. The Agency agrees that this formulation is worthy of investigation and development, however, as expressed in a recent facsimile transmission dated January 23, 2001, there may be a more efficient way to develop this formulation. The Foradil Aerolizer (NDA 20-831) is likely to receive approval and, if so, this new MDDPI formulation might require as little as successful bridging and long-term safety studies in order to be approved for the same indications. Further, once Foradil Aerolizer is approved and marketed, it would be important for the prescribing physicians to have information regarding the comparability of the Aerolizer and the MDDPI. Therefore, comparability of the two products needs to be fully explored.

2. **Additionally Novartis proposes that the dose of Foradil 8.5 mcg emitted dose (10 mcg metered dose) in the MDDPI device is the appropriate dose for use in the Phase 3 program. Does the Agency agree?**

   The Agency stated that the 10 mcg metered dose in the MDDPI device appears to have a greater activity than the 12 mcg Aerolizer formulation dose. By most measures, the dose equivalent to the Aerolizer 12 mcg formulation dose appears to be about midway between the 5- and 10 mcg metered doses of the MDDPI. The Agency would like Novartis to identify the lowest efficacious dose, especially where on demand use is an additional proposed claim.

3. **The planned label claim would be:** [redacted] **Is this acceptable to the Agency?**

[redacted] b(4)

4. **The intended wording in the label would be:** [redacted] **is this acceptable to the Agency?**

[redacted] b(4)

found to be compelling enough to be included in the label, will be attributed to the tests that produced them. The instrument to be used for the quality of life assessments must be validated for the method, comparison and the sample under study.

5. **Novartis wishes to confirm the 3 month duration of the Foradil MDDPI pediatric study is acceptable, and that a placebo only controlled pediatric study is acceptable to the Agency. Does the Agency agree?**

The Agency stated that a placebo-controlled study of three months duration for the pediatric asthma study is acceptable.

6. **Acceptance that this program will provide, if the results are positive, sufficient evidence for a claim of efficacy in nocturnal asthma. Does the Agency agree?**

The Agency stated that nocturnal asthma is not exactly the same as nocturnal symptoms of asthma, and patients would have to be specifically sought for the former diagnosis. In addition to nocturnal symptoms, other endpoints that might bear on a claim will be night-time rescue medication use, awakenings and, possibly, morning PEFR. The acceptance of including these secondary endpoints in the label will be a review issue.

7. **Acceptance is sought that the studies being planned (603, 608, 2301), if positive, will support, the wording of the dosage and administration section of label for: relief of breakthrough bronchoconstriction and broncho-obstructive symptoms. Does the Agency agree?**

The on-demand use of inhaled long-acting $beta_2$- agonists is new and precedent-setting territory. It hinges on two main factors:

a. efficacy and onset of action that is comparable to the shorter acting inhaled beta-agonists (e.g., albuterol)

b. safety of the treatment as labeled and as it will likely be used.

The Foradil Aerolizer data suggests that the onset of action of formoterol is comparable to albuterol in non-emergent situations. However, a recent publication has described the onset of action of formoterol to be inferior to albuterol in the Emergency Room setting. These issues will have to be better studied. Trial 608 will address single-dose onset of action in a non-emergent setting. It will not shed light on onset of action under emergent conditions. It is also not clear if this study is to be done on patients under conditions of chronic beta-agonist use or after beta-agonist withdrawal. Given the differences in Foradil Aerolizer noted in the emergency room setting, FDA recommended this be further explored, perhaps by studying patients who are acutely bronchospastic (following methacholine or exercise challenge) and comparing efficacy of Foradil to a short-acting beta agonist in that setting.

- A further complication is that the higher dose of the Aerolizer that is undergoing NDA evaluation appears to be associated with more asthma SAE's . This opens the question of the wisdom of dose escalation by including prn use. As an aside, it has never been demonstrated that higher doses of formoterol may be helpful to patients who are inadequately treated with lower doses.

  Study 603 will address efficacy with regular and on-demand, albeit tightly controlled use. It is not clear if the efficacy of four inhalations/day, two of them taken on-demand will provide more information than an efficacy study of two inhalations taken twice daily. As such, the on-demand labeling may be superfluous and even dangerous if it encourages patients to overuse the drug by taking it whenever they need it. Higher doses are not necessarily more efficacious and may actually lead to worse outcomes.

- Study 2301 examines the efficacy of on-demand formoterol when added to anti-inflammatory medication in about 200 adolescent and adult patients. In light of the Aerolizer data, this is a trivial undertaking. A comparison of formoterol and albuterol for on-demand use would require four treatment arms. There is also a possible ethical problem in giving a placebo to patients in need of rescue treatment.

  If this drug is to be developed for on-demand use, a far more complete investigation of its benefits and risks would include establishing the maximum safe dose. In this way, the risks and benefits of on-demand prescribing could be assessed at the extremes of use.

Discussion: Novartis presented the design of the studies 603 and 2301. Novartis further stated that the intent of the on-demand use trials would be to pursue a claim of PRN use of Foradil within a boundary, i.e., use of 2 additional doses of Foradil per day for limited number of days per week, in stable mild-to-moderate asthmatic patients who have breakthrough symptoms. Novartis also questioned whether the PRN use studies could be conducted with Foradil Aerolizer.

The Agency stated that it is not clear how the patients would know whether their asthma is "stable" or not. One of the concern is that some patients may push the PRN use of the drug to the maximum limit. Novartis will have to identify the maximum tolerated dose for PRN use. The Agency further stated none of the $beta_2$-agonists, even shorter-acting beta-agonists are explicitly labeled for PRN use. The PRN use of a long-acting $beta_2$-agonist is therefore a unique claim and will require much discussion, possibly an Advisory Committee meeting for evaluation of trial results. The Agency strongly feels that a large controlled trial of a substantial number of patients would be required to support the PRN use claim due to safety concerns at this high level of drug exposure. Also, it was noted that a 60-dose device may not provide a typical one month supply for the PRN users, and the CMC expectations might be different. The studies could be conducted with Foradil Aerolizer.

8. **Novartis plans to concentrate collection of samples in the Phase 3 program for PK analysis in Study 2302. Does the Agency agree?**

The Agency stated that the proposed PK analysis plan (urine and plasma) for the Phase 3 study 2302 in adults and adolescents is acceptable. However, a similar PK sampling plan is requested for the pediatric population (study 604).

9. **We propose that the planned duration of treatment and the number of patients exposed to the MDDPI will be sufficient to support the indication in adults, adolescents and children aged 5-12 years. Does the Agency agree?**

The Agency stated that considering the approval of the Foradil Aerolizer NDA, 1155 additional patients exposed to the MDDPI and 400 exposed for one year would be sufficient.

10. **We request that pediatric studies in patients down to 6 months in age be incorporated into the clinical development program for the Foradil HFA pMDI device. Does the Agency agree?**

The Agency stated that the proposal is reasonable. However, a 13-week inhalation toxicity study with juvenile dogs (approximately 2-3 weeks of age at the start of the treatment) will be required before administering the new formulation to pediatric patients under the age of two years.

11. **Does the Agency agree with replacing a non-calculable 3 month AUC with the calculable AUC from the 1 month, 12-hour spirometry assessment?**

It is acceptable to estimate non-calculable 3-month AUC of FEV^1 values using those obtained from previous visits. The sponsor is advised to create a variable in the data set to indicate whether the AUC of FEV^1 value was calculated from the current visit or carried over from a previous visit.

12. **Would the Agency allow an AUC calculated from the 1 day, 12-hour spirometry assessment to be used as a replacement (for the primary analysis) for the 3 month AUC if both the 1 month and 3 month spirometry assessments are missing and/or have non-calculable AUC's?**

The Agency stated that the estimated data should be distinguishable from the original data. Novartis should include all the imputed data in the analysis.

13. **Does the Agency agree with the above definition of the ITTE?**

The proposed ITTE definition is acceptable.

14. **Does the Agency agree with using 231 patients per study for studies 2302 and 2303?**

The Agency stated that 231 patients per study might be adequate for the primary endpoint and to support the indication, however, the Agency does not agree with pooling the data from both studies to support any labeling claims.

15. **Does the Agency agree with the above pre-specified WIN criteria for the major (i.e., primary) labeling claim of maintenance therapy in patients at least 13 years of age who have at least moderate asthma, assuming, of course, an adequate safety and tolerability profile?**

The statistical comparisons among all treatment arms included in the study: formoterol fumarate MDDPI, albuterol and placebo should be made with adjustment for multiple comparisons.

16. **Does the Agency agree that a secondary labeling claim for superiority of formoterol via the MDDPI to albuterol via the pMDI on AUC can be obtained by pooling relevant data from studies 2302 and 2303? If so, does the Agency agree with the above pre-specified WIN criteria for this secondary labeling claim, assuming, of course, an adequate safety and tolerability profile?**

See the response to question 3.

17. **Does the Agency concur that failure to statistically obtain this secondary labeling claim does not negatively impact the WIN criteria for the primary labeling claim of maintenance therapy?**

The Agency stated that unless the secondary comparison is sequentially performed, based on the significance of a primary comparison ("protected"), the primary comparison should be corrected for multiple comparisons to avoid underestimation of a Type I Error.

18. **Does the Agency agree that a secondary labeling claim for the superiority of formoterol via the MDDPI to placebo on QOL can be obtained by pooling relevant data from Studies 2302 and 2303? If so, does the Agency agree with the above pre-specified WIN criteria for this secondary labeling claim, assuming, of course, an adequate safety and tolerability profile?**

See the response to question 4.

19. **Does the Agency concur that failure to statistically obtain this secondary labeling claim does not negatively impact the WIN criteria for the labeling claim of the maintenance therapy.**

See the response to question 17.

20. Does the Agency agree that the Sponsor may additional secondary labeling claims, if warranted, on these variables (especially nocturnal asthma)?

The Office of Medical Policy at FDA has suggested that the Agency would seriously limit the number of secondary claims unless they address truly different indications and are substantially supported.

21. Does the Agency agree that the above reflects an appropriate non-inferiority window for study 603 appropriate?

The Agency stated that it is not at all clear that a non-inferiority endpoint is acceptable, even if statistically significant and replicated in two independent studies. The 12 mcg twice daily dose of Foradil Aerolizer was superior to albuterol by several measures and the former has less of a PD effect than the 10 mcg MDDPI, which supports the feasibility of a superiority endpoint.

22. Does the agency agree with locking the 3-month Vitalograph database, switching patients to open-label on-demand use, using only 3 months of on-demand use data from study 603 to formally establish non-inferiority between formoterol via the MDDPI and albuterol via the pMDI?

The proposal of locking the data base at 3 months is acceptable. See response to question 21 about the acceptability of a non-inferiority endpoint.

23. Does the Agency agree that a secondary labeling claim of on-demand use of formoterol via the MDDPI can be obtained using data from studies 603 and 2301 (on a per study basis), assuming, of course, an adequate safety and tolerability profile?

See prior questions for establishing an on-demand claim from study 603. See response to question 7 for comments on study 2301.

24. Does the Agency concur that failure to statistically obtain this secondary labeling claim does not negatively impact the WIN criteria for the primary labeling claim of maintenance therapy for patients at least 13 years of age?

See the response to question 17.

25. Does the agency agree an *a priori* randomization scheme stratified by age group is not necessary for pediatric study 604?

The Agency stated that stratification by age is not necessary, but sufficient numbers of patients of throughout the entire range of ages (5-12 years) must be represented in order to gain approval for the proposed age range. At some point, we will want to see data on inspiratory air flow rates that 5-6 year old asthmatic children can generate.

26. Does the agency agree with the pre specified WIN criteria for a pediatric labeling claim of superiority to placebo on AUC, assuming, of course, an adequate safety and tolerability profile?

The Agency stated that it may be reasonable as a stand-alone comparison.

27. Does the Agency concur that failure to statistically obtain this pediatric labeling claim does not negatively impact the WIN criteria for the primary labeling claim of maintenance therapy in patients at least 13 years of age?

The Agency stated that the intent of this question is not clear.

Novartis responded that they simply wanted to have concurrence that if their pediatric trials fail, they would still obtain their claim in adults and adolescents 13 years of age and older. FDA responded that this is a review issue. If particularly serious concerns were raised, for example, in the pediatric trial--this might affect the approval of Foradil even in the adults and adolescents.

28. Does the agency concur with this definition of ITTS?

The Agency does not concur with the proposed definition of ITTS. The ITTS sample should include either all randomized patients or, if modified, all randomized patients who took at least one dose of any test treatment.

29. Does the agency agree that study 603 provides the requisite long-term safety data for adolescents and adults for maintenance as well as on-demand use? If so, does the Agency consider the analysis of the safety data in section 6 of statistical appendix 5 adequate?

The Agency stated that study 603 would provide 12 months of long-term safety information in 400 adults and adolescents, all exposed to some dose of formoterol MDDPI. It provides sufficient long-term safety information to support a regular maintenance dose of 10 mcg twice daily. The 24 mcg Aerolizer data will probably provide much of the necessary long-term safety information.

30. Does the Agency agree that study 604 provides the requisite safety data in children?

Backed up by the Aerolizer data, this 3-month study of 10 mcg twice daily will be sufficient.

31. Does the agency have any other statistical questions?

At some point in the development process, the life-of-the-device must be addressed. There were no additional issues, statistical or otherwise raised by Agency at this point.

32. Does the Division agree with the regulatory limits proposed for the content uniformity testing of the device (both "dose content uniformity" and "dose content uniformity through container life").

The Agency stated that the proposed specifications submitted in the package (——of doses within —— , of the label claim (LC) with all within —— % of the LC), are obviously wider than the Agency's standard, which have been conveyed to Novartis both through letters for the current application, and more widely in the draft CMC guidance for MDIs and DPIs.

Novartis asked if they could have wider specifications now for DCU at the IND stage and then move towards the Agency standard for the NDA. At present, with limited data Novartis is uncomfortable with tighter Agency limits of 90% within ±20% LC and 100% within ±25% LC.

The Agency stated that it would be a reasonable approach. Novartis should also determine the dose content uniformity of the product in terms of the *metered* dose so that the Agency can determine if the added variability comes in the process of "inhalation" by the *in vitro* testing apparatus or if it is the metering itself which includes the bulk of the variability in dosing.

33. Does the division agree with the testing proposed for the release of magnesium stearate before its use in the drug product?

The Agency stated that based on required controls for lactose, the controls for magnesium stearate as a DPI excipient need enhancement due to the following. These additional controls will help assure increased batch-to-batch reproducibility for this excipient and the resulting drug product formulation.

- For magnesium stearate there are two identified crystalline forms, a *trihydrate acicular* and a *dihydrate lamellar* form; The crystalline form needs to be controlled.

- If amorphous non-crystalline material is part of the magnesium stearate, this needs to be controlled as well;

- There should be a control on the moisture content of the magnesium stearate;

- The current PSD specification acceptance criteria proposed (i.e., min ——— ——————————————— , do not fully

control the size profile, e.g., if 90% of the material is less than 5 μm in size the material would still meet the acceptance criteria proposed; The distribution of the particle sizes needs to be control with acceptance criteria ranges to assure reproducibility.

- There should be a range for control of the magnesium stearate specific surface area.

- The compositional profile of the magnesium stearate should be well controlled to ensure the batch to batch reproducibility of this excipient and the resulting drug product. The ranges would be more appropriate than limit controls in terms of the compositional profile.

- Clarify the meaning of the "total" and "other" degradation product limits listed on p. 44 of the package for the magnesium stearate.

- Monitor for the presence of asbestos in the magnesium components used to prepare the exipient Magnesium Stearate.

Additional CMC Comments

Several comments were forwarded previously on various CMC aspects for the product. Following are additional comments based on the limited information in the package. These are not necessarily all inclusive.

Drug Product (DP) Characterization Studies: In general for guidance on DP characterization studies, refer to the draft *Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, Chemistry, Manufacturing and Controls Documentation.* For example, data should be included in the application characterizing the performance of the device in terms of DCU and aerodynamic PSD relative to the flow rate. Related to the flow rate generation by patients, data should also be included in the upcoming NDA on the flow resistance of the device as a whole and possibly the flow resistance of key components. The control of the flow resistance of the incoming devices (or possibly key components that contribute the most to the resistance) should be one of the acceptance tests.

Mass Balance Demonstration: In terms of the stability characterization for this product, and in light of the temperature related problems associated with the Foradil Aerolizer Inhalation Powder product, the mass balance of the DS in the DP should be characterized completely and accounted for during product shelf life.

Moisture Protective Packaging: The Agency has noted that Novartis did not propose to have an overwrap for the drug product. Novartis must convince the Agency that an overwrap is not necessary and have the data to support this as outlined in the MDI/DPI draft guidance. Along these lines, the stability protocol and testing should be in line with the decision tree as outlined in the draft MDI/DPI guidance. Novartis should test the product with the various stability

conditions as listed in the Scheme in the draft MDI/DPI guidance (i.e., 40°C/75%RH, 30°C/60%RH, 25°C/75%RH, and long term conditions of 25°C/60%RH).

DS Controls: On p. 68 it is noted that the DS can be yellowish in color. If this is the case then there should be a quantitative test and acceptance criterion for the color level.

Novartis said they have changed the description to "white."

Currently the DS monograph states that the formoterol is identified by HPLC and by TLC. There should also be an identification of the fumarate counterion

DP Controls: A test for the control of foreign particles in the DP formulation must be developed.

Novartis indicated that they were still having problems with this test due to the limited solubility of the Mg stearate and that they would welcome the Agency's input.

The Agency stated that with this new excipient for inhalation there certainly would be a learning curve both for Novartis and the Agency. Novartis should continue in their efforts to come up with a method for control of foreign particulates in the DP formulation.

Skypharma DMF : Novartis should work with Skypharma for the DMF submission for the device. It was emphasized that the device intended for marketing should be similar to that used in the clinical and primary stability studies to avoid unnecessary equivalency studies including design of the device, component composition, fabrication conditions, number of molds and design, etc. The DMF should also include the preclinical studies that Skypharma has conducted for magnesium stearate.

- A study was suggested to be done in 5-6 year old patients to assess their ability to generate the 40 L/min necessary to actuate the device.

- The life of the device (device performance) issue must be addressed in the NDA.

- In the clinical trials, the devices should not be replaced prematurely. In addition, the drug products used in the clinical trials should be returned at the end of their use to the applicant for full evaluation with regard to their performance characteristics and the ruggedness of the device.

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Project Manager

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X § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

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/s/

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