CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-592

APPROVABLE LETTER

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:

Please refer to your new drug application (NDA) dated December 17, 2002, received December 18, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Foradil Certihaler (formoterol fumarate) Inhalation Powder.

We acknowledge receipt of your submissions dated October 10, 2005, and March 1, and 30, 2006.

The October 10, 2005, submission constituted a complete response to our December 14, 2004, action letter.

We also acknowledge receipt of your submission dated March 29, 2006. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application(s), as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

1. The inadvertent overdosing of patients who used the Certihaler device marketed in Germany as outlined in your March 1, 2006, correspondence (e.g., scenarios 1 and 2) is a serious safety concern that needs to be resolved to support approval of the drug product. Simply revising the patient instructions will not be sufficient. To support approval, the device should be modified in such a way that any mishandling of the device will not result in an overdose. To ensure this beyond a reasonable doubt, the revised device will need to undergo extensive in vitro testing and may require clinical use studies. In addition, based on the impact the revisions of the device have on drug flow characteristics, additional clinical efficacy and safety studies may be required.

2. Submit revised draft labeling for Foradil Certihaler to address the recent heightened risk of severe asthma episodes and death in patients with asthma who use LABAs, including

formoterol. Include both a Boxed Warning and a Medication Guide. Your most recent labeling proposal dated March 30, 2006, remains deficient.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Ms. Akilah Green, Senior Regulatory Management Officer, at (301) 796-1219.

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
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Dear Ms. Shea:

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We acknowledge receipt of your submissions dated June 24, October 4, and November 22, and 23, 2004.

The June 24, 2004, submission constituted a complete response to our October 17, 2003, action letter.

We also acknowledge receipt of your submission dated December 7, and 9, 2004. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following deficiencies:

1. The data from the patient use studies indicate that a substantial number of patients are not able to operate this device successfully. This observation is of concern since participation in the clinical studies required that patients be able to understand and demonstrate the correct use of the device, after careful instruction. It is likely that difficulties using the device that were observed in the patient use studies would be more common in an unselected patient population. The fact that most of the devices that patients reported to be malfunctioning were found to function normally when tested *in vitro* likely indicates that the devices themselves are not malfunctioning. Rather, it would appear that the failure lies in the ability of patients to understand the directions for use, and implement them effectively. In order to support approval, you will need to develop improved mechanisms to instruct patients in the use of the device, and demonstrate in a patient use study that these improved mechanisms are effective.

Submit draft labeling revised as follows:

2.

3.

4.

5.

b(4)

6.

7.

8.

9.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Pulmonary and Allergy Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
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We acknowledge receipt of your submissions dated March 17, April 3, 14, and 30, July 15, and September 3 and 30, 2003. We also acknowledge receipt of your submissions dated July 15, 2003, and August 29, 2003, but these submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to 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)

   a. Provide a summary of the efforts that have been taken to assure that the drug product prepared with ——— tooled devices will have acceptable performance and will not display the same counter and actuation flow rate (or other) problems outlined in your included report in attachment 11 of section 3.2.P.2 and attachment 2 of this section in the March 17, 2003, amendment. Provide supporting data demonstrating the decrease in the percentage of complaints. A preliminary review of your response to the this comment suggests that in vitro data alone, even with a larger sample size, may be insufficient to address our concerns regarding device failures which may require the submission of additional clinical data. b(4)

   b. Provide batch release and any stability data as soon as available for the validation batches of drug product prepared with the devices fashioned from the ——— tools designed for commercial production. Refer to related comment 9.b.ii. b(4)

   c. Provide clarification of the type of ——— used in the mouthpiece locking device in the inhalers used in the clinical trials. Provide data supporting the improved ease of opening (e.g., force to open) associated with the switch to ——— and/or with b(4)

other improvements implemented through the change to [redacted] tools. Refer to related comment 8.c below. b(4)

2. Provide the details, including sampling plan, of how the reservoir fill weight in-process limits of [redacted] mg are applied during manufacturing.

3. Provide a description of the "primary" and "secondary" packaging that is applied by SkyePharma and Novartis, respectively, as indicated in the 3.2.P.3.1, p. 3.

4. The following comments pertain to the lactose excipient used in the drug product formulation.

   a. [redacted]

   b

   c.

   b(4)

   d.

   e.

   f.

   g.

   h.

8 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

19.

20.

21

22.

b(4)

23

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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Badrul A. Chowdhury, M.D., Ph.D.
Director
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/s/

Badrul Chowdhury
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