CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-512

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-512

Perrigo Company
515 Eastern Avenue
Allegan, Michigan 49010

Attention: Janette J. Meyer
ANDA Regulatory Affairs Project Manager

Dear Ms. Meyer,

Please refer to your new drug application (NDA) dated June 28, 2002, received July 1, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for loratadine 10mg tablets.

We also refer to your amendments dated: May 9, 12, and 23, June 18, 23 and 27, and July 1, 2003.

Your submission of May 9, 2002, received May 12, 2003, constituted a complete response to our May 1, 2003, action 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 adequately address the following deficiency:

The results of study 003214 cannot be considered valid in establishing the bioequivalence of the test loratadine tablets to the listed drug product because of the cross-well contamination of the subject samples during solid phase extraction as described in the Form 483 issued to [redacted] on July 9, 2003. You will need to reassay all the subject samples to demonstrate accuracy of the loratadine and descarboethoxyloratadine plasma concentrations in this study.

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 in 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Drug Products regarding the extent and format of your safety update prior to responding to this letter.

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, 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.

In addition to the above deficiency, as our accompanying letter explains, FDA is currently stayed from approving your application due to ongoing patent litigation. As you are also aware, a citizen petition submitted on behalf of Genpharm Inc. challenges, among other things, the appropriateness of approving your application under section 505(b)(2) of the act. We have not yet formally responded to that petition, but will notify you when we do.

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 Anthony Zeccola, Regulatory Management Officer, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Badrul Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy
Drug Products
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/

Charles Ganley
7/11/03 02:38:05 PM

Marianne Mann
7/11/03 02:41:37 PM
Dr. Mann (Acting Director) is signing for Dr. Chowdhury in his absence.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Attention: Janette J. Meyer

Dear Ms. Meyer,

Please refer to your new drug application (NDA) dated June 28, 2002, received July 1, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for loratadine 10mg tablets.

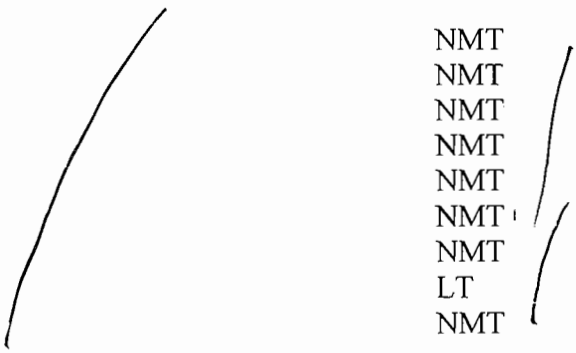
We also refer to your amendments dated December 18, 2002, January 22, February 18, March 4 (2 amendments), 5, 12, and 18, and April 11, 2003.

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 adequately address the following deficiencies.

1. The following comments pertain to the — drug substance specifications and test methods that were submitted in your application.

   a. ' — ' is vague. Describe the color in a quantitative way (e.g., APHA color index).

   b. Tighten the related substances specifications as follows:



   c. Provide structures and chemical names for the related substances on the specification sheet.

   d. Tighten the — acceptance criterion to NMT —

   e. Provide data and appropriate specification for —

2. The following comments pertain to the drug substance specifications from [redacted] that were submitted in your application.

   a. For "Description," see the comment 1(a) above.

   b. Provide structures and chemical names for the related substances on the specification sheet.

   c. [redacted]

   d. Tighten the acceptance criteria for residual solvents to reflect your production batch analysis data as follows:

[redacted]	NMT
	NMT
	NMT

   e. [redacted]

3. The following comments pertain to your drug substance specifications.

   a. For "Description," see the comment 1(a) above.

   b. Any unknown impurity should be limited to less than [redacted]

   c. For [redacted]' see the comment 2 (c) above.

   d. Comment 2 (d) is also applicable here.

4. The following comments pertain to the release specification of the drug product.

   a. Include "[redacted]' to the specification for drug product. You may indicate as a footnote that these tests are being performed as in-process controls.

   b. Provide test method and acceptance criteria for [redacted]

   c. Provide a secondary identity test.

   d. Modify the proposed impurity specifications as follows:

[redacted]	NMT
	NMT
Individual Unknown Impurities:	NMT
Total Impurities:	NMT

e. Modify the dissolution specification to be NLT(Q` —in 30 minutes.

f. Provide an updated specifications sheet which reflects the above changes.

5. The following comments pertain to the stability protocol for the drug product.

a. Update the stability protocol to include —

b. Provide test method and acceptance criteria for —

c. Modify the dissolution specification to NLT — in 30 minutes.

d. Modify the proposed impurity specifications as follows:

	NMT
	NMT
Individual Unknown Impurities:	NMT
Total Impurities:	NMT

e. Modify the Post-approval stability commitment D as follows: Perrigo will discuss the result, investigation, and conclusion with the reviewing Division (not the Office of Generic Drugs).

f. Simplify the table on page 185, vol. 1.4 as follows: The first three commercially marketed lots and proportional number of production lots (e.g., — of annual production lots) will be placed on stability.

g. Provide an updated stability protocol which reflects above comments.

6. The following comments pertain to the method validation package.

a. The information regarding samples provided on page 238, vol. 1.6 is not adequate. Provide adequate information on samples, e.g., sample number, sample type, batch number, quantity, and certificates of analysis. Include drug substance, reference standard, all impurity compounds, and drug product in the list of samples.

b. Provide updated specifications for drug substance.

c. Provide updated specifications for drug product.

d. Provide three copies of updated method validation packages.

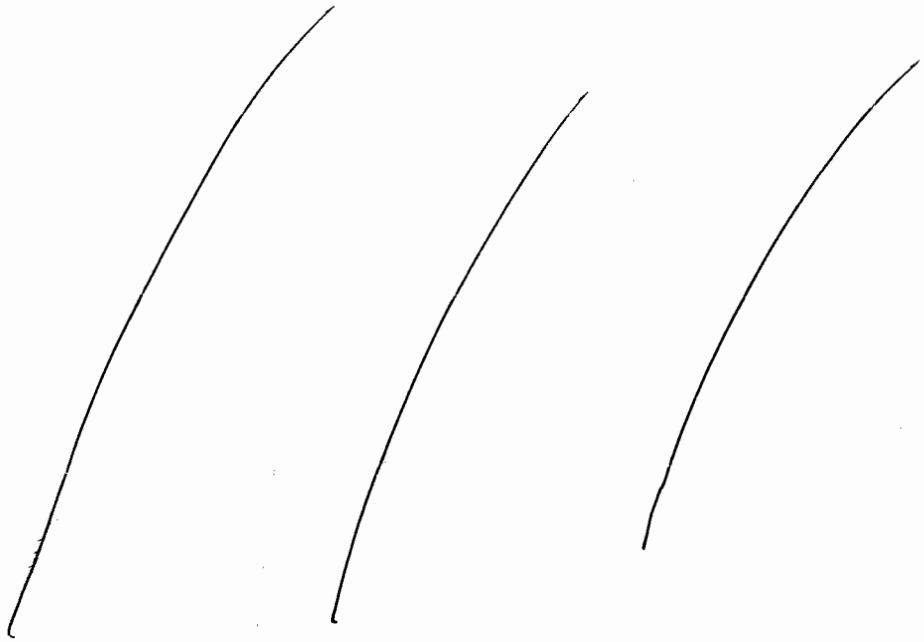
In addition, it will be necessary for you to submit draft labeling revised as follows:

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process



12. A satisfactory inspection of the _____ must be completed prior to approval of this application.

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.

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 Anthony Zeccola, Regulatory Management Officer, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Deputy Director
Division of Over-the-Counter Drug Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Badrul Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy
Drug Products
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
4/30/03 02:44:42 PM

Curtis Rosebraugh
5/1/03 09:03:56 AM