CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-512

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PERRIGO

PATENT CERTIFICATION

In accordance with Section 505(b)(2)(A) of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, Patent Certification is hereby provided for our New Drug Application for Loratadine Tablets, 10 mg.

In the opinion and to the best knowledge of L. Perrigo Company, there are three patents that claim the listed drug product referred to in this application, Claritin® Tablets, 10 mg, or that claim a use of the listed drug product.

PATENT CERTIFICATION PARAGRAPH III

The L. Perrigo Company hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent #4,282,233 assigned to Schering Corporation (Kenilworth, NJ) will expire on December 19, 2002. The L. Perrigo Company agrees not to market Loratadine Tablets 10 mg, which is the subject of this application, before the patent expiration on December 19, 2002.

PATENT CERTIFICATION PARAGRAPH IV

The L. Perrigo Company hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent #4,659,716 (expiring 10/21/2004) assigned to Schering Corporation (Madison, NJ) and U.S. Patent #4,863,931 (expiring 03/15/2009) assigned to Schering Corporation (Kenilworth, NJ) for listing with respect to Claritin® Tablets, 10 mg, are invalid, unenforceable and/or will not be infringed by the manufacture, use, or sale of L. Perrigo Company's Loratadine Tablets, 10 mg, for which this application is submitted.

STATEMENT CONCERNING NOTICE TO PATENT OWNER AND NDA HOLDER

As required by Section 505(b)(3)(A) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50(i)(1)(i)(A)(4) and 21 CFR 314.52, the L. Perrigo Company hereby states that the L. Perrigo Company, upon receiving from FDA an acknowledgement letter stating that this NDA is sufficiently complete to permit a substantive review, will give the notice required by Section 505(b)(3)(A) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.52 to Schering Corporation, the holder of the approved application for Claritin® Tablets, 10 mg, and the owner of U.S. Patents 4,659,716 and 4,863,931.

The notice to Schering Corporation will be sent via the US Postal Service as required by 21 CFR 314.52(a) and 21 CFR 314.52(c); and the contents of the notice will meet the requirements of these parts.

Concurrent with sending the notice to Schering Corporation, the L. Perrigo Company will, as required by 21 CFR 314.52(b), amended its NDA for Loratadine Tablets, 10 mg, to include a certification that the notice has been provided to each person identified under 21 CFR 314.52(a) and that the notice met the content requirements of 21CFR 314.52(c).

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

PERRIGO®

EXCLUSIVITY STATEMENT

There is no unexpired market exclusivity for Claritin® Tablets, 10 mg.

The Patent Certifications and Exclusivity Statement are supported by the attached information extracted from the electronic version of the 22nd Edition, Cumulative Supplement 2 (February 2002) of Approved Drug Products with Therapeutic Equivalence Evaluations.

Brian Schuster — 5-22-02

Brian R. Schuster — Date
Regulatory Affairs Manager

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

EXCLUSIVITY SUMMARY for NDA # 21-512 SUPPL #
Trade Name _____ Generic Name loratadine
Applicant Name Perrigo HFD- 570
Approval Date July 11, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /_X_/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      This is a 505(b)(2) application, only required bioavailability/bioequivalence studies (see Part III, 2(c) below).

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /___/

If the answer to (d) is "yes," how many ~~years of~~ exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /X/ NO /___/

If yes, NDA # list applicable Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 003214 BA/BE Study

Investigation #2, Study # 010177 BA/Food Effect Study

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PERRIGO

Item 16

FDA Form 356h Item 16: Debarment Certification

L Perrigo Company hereby certifies that it did not use and will not use the services of any person debarred pursuant to Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Brian R. Schuster
Manager, Regulatory Affairs

6-17-02
Date

515 Eastern Avenue
Allegan, Michigan 49010
(616) 673-8451

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-512	Efficacy Supplement Type SE-	Supplement Number	
Drug: loratadine tablets		Applicant: Perrigo	
RPM: Zeccola		HFD-570	Phone # 301-827-1058
Application Type: ( ) 505(b)(1) **(X)** 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N19-658	

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	**3**
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**May 1, 2003, July 12, 2003**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	**(X)** Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No
• This application is on the AIP	( ) Yes **(X)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	**(X)** Verified
❖ Patent	
• Information: Verify that patent information was submitted	( ) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II **(X)** III **(X)** IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	( ) AP (X) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**5/30/03**
• Most recent applicant-proposed labeling	**5/9/03**
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**4/15/03, 5/30/03**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	See AE Letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	4/15/03
❖ Clinical review(s) *(indicate date for each review)*	4/15/03 (DPADP and OTC)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	In Clinical Review 1/14/04 3rd cycle UP Jun
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A will do at time of AP
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	2/10/03, 4/27/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	Pending
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	4/14/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	4/14/03
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	4/16/03
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

OTC Drug Labeling Review

Division of Over-The-Counter Drug Products (HFD-560)

Center for Drug Evaluation and Research • Food and Drug Administration

Addendum Labeling Review

NDA # 21-512

Amendment Dates : 4/29/04
Review Date : 5/05/04

Applicant: Perrigo Company
515 Eastern Avenue
Allegan, MI 49010

Applicant's Representative: Janette J. Meyer
Regulatory Affairs Project Manager

Drug:
Loratadine Tablet, 10 mg

Pharmacological Category: Antihistamine

Submitted: COLOR MOCKUPS for the following:

Loratadine Tablets:

- 4- and 12-count blister *carton* labels
- 4- and 12-count non child-resistant push through *blister card* labels
- 10-, 30-, 300-count ***bottle carton*** label
- 10-, 30-, 300-count ***bottle label***
- Annotated Labeling: 4-count *blister carton label*

Background:
In response to the approvable letter dated June 28, 2002, for OTC Loratadine Tablets 10 mg OTC drug product (NDA 21-512), the sponsor has submitted color mockup draft labeling for the following:

- 4- and 12-count blister *carton* labels
- 4- and 12-count non child-resistant push through *blister card* labels
- 10-, 30-, 300-count ***bottle carton*** label
- 10-, 30-, 300-count ***bottle label***
- 4-count *blister carton label*: Annotated Labeling

Reviewer Comment:
An addendum labeling review of the sponsor's submission of 5/09/03 was completed on 5/30/03 and put into DFS as acceptable labeling. The color mockup draft labeling in this submission is the same as the May 9, 2003 labeling and is also acceptable.

RECOMMENDATIONS:
1. An approval letter can be issued to the sponsor requesting final printed labels for the following:
   - 4- and 12-count blister *carton* labels
   - 4- and 12-count non child-resistant push through *blister card* labels
   - 10-, 30-, 300-count ***bottle carton*** label

- 10-, 30-, 300-count ***bottle label***
- 4-count *blister carton label*: Annotated Labeling.

These final printed labels must be identical to the labels submitted on April 29, 2004.

2. Inform the sponsor that the word "NEW!" must be deleted from the PDP six months after introduction into the market place.

3. Note to file: It has been verified with the chemist (Dr. Kim) and the project manager (T. Zeccola) that CR package is not required for this application. Because the OTC switch of loratadine was accomplished prior to the effective date of the final rule for Child-Resistant Packaging for certain Over-the-Counter Drug Products, CR package is not required.

Cazemiro R. Martin
Regulatory Review Scientist/IDS

Concur: Marina Chang, R.Ph.
Team Leader

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

/s/

Cazemiro Martin
5/5/04 11:00:17 AM
INTERDISCIPLINARY

Marina Chang
5/5/04 11:06:32 AM
INTERDISCIPLINARY

PERRIGO®

May 4, 2004

Badrul Chowdhury, M.D., Ph.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
HFD-570, Document Room 10B45
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Anthony Zeccola

Via Facsimile and Federal Express

Re: Loratadine Tablets, 10 mg (OTC), NDA 21-512
GENERAL CORRESPONDENCE

Dear Dr. Chowdhury:

Please reference L. Perrigo Company NDA 21-512 for Loratadine Tablets, 10 mg (OTC) submitted June 28, 2002, pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Further reference is made to a request made by the Agency on April 27, 2004, that we agree to submit additional information in the quarterly periodic safety reports relating to reports of hypospadias as outlined below.

L. Perrigo Company hereby agrees to submit information in the quarterly periodic safety reports for the first three years following approval on reports from various sources of the occurrence of cases of hypospadias relating to loratadine. We will review the following sources for information relating to hypospadias: the clinical and non-clinical scientific literature, the FDA's Postmarketing Adverse Event Reporting System (N.T.I.S.) database, the World Health Organization (WHO) adverse event database and any relevant international regulatory actions, and all adverse drug experience information reported to L. Perrigo Company.

L. Perrigo Company certifies that a "field copy" which is a true copy of this correspondence is being submitted to the Detroit District Office.

Should you have any questions regarding this submission, please contact me by telephone at 269-673-9745, by FAX at 269-673-7655, or at the address upon this letterhead.

Sincerely,

Brian Schuster

Brian R. Schuster
Associate Director, Regulatory Affairs

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

MEMORANDUM

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

DATE: April 20, 2004

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 4/20/04
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering NDA 21-512
Loratadine — 10 mg tablets
Sponsored by Perrigo Company

TO: Badrul A. Chowdhury, M.D.
Director
Division of Pulmonary Drug Products (HFD-570)

At the request of HFD-570, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

> **Study 003214**: Comparative, Randomized, Single Dose, Four-Way Crossover, Fully-Replicated Bioavailability Study of Perrigo (— and Schering (Claritin®) 10 mg Loratadine Tablets in Healthy Adult Males Under Fasting Conditions Following a 40mg Dose.

The clinical and analytical portions of Study 003214 were conducted at ' —

History: The clinical and analytical portions of the study were audited at — between 7/7-9/03. — reported cross-well contamination in <1% of subject samples with highly anomalous values. — claimed that the contamination was limited to these samples without providing valid data to support their claim. Consequently, the study subjects' plasma concentrations are questionable because — failed to investigate the extent of contamination. Based on the failure to assure accuracy of study data, DSI recommended that the study **not** be accepted for Agency review.

In their subsequent response dated 10/2/03, [redacted] retracted their earlier inference of cross-well contamination in the automated assay. They provided results of a retrospective investigation using [redacted] to show that cross-well contamination was unlikely. Although [redacted] acknowledged that contamination might have occurred at numerous other places, they **maintained that the data from the study were "solid and valid" and proposed to reanalyze all study samples to support their conclusion.**

[redacted] reanalyzed all subject samples under [redacted] 003214-UJK. The data was submitted to the Agency on 12/22/04. Repeat analysis was performed following modification of the original automated [redacted] assay. The modifications included truncation of assay range from 20-50,000 pg/mL to 40-10,000 pg/mL and revising [redacted] parameters of the [redacted] Other modifications (i.e. plasma volume, internal standard volume and extraction wash steps) were unrelated to contamination and addressed clogging of extraction columns by study samples. Also, each analyst performed a successful test curve (i.e. included additional quality controls to mimic sample size of analytical runs) prior to study sample reanalysis.

DSI conducted a follow-up audit of the reanalyzed data at [redacted] [redacted] (2/9-13/04). Following the inspection, Form 483 was issued. The evaluation of the significant finding follows:

Follow-up Audit [redacted]

[redacted] did not systematically investigate the source of contamination in the original automated assay[1]. Instead, [redacted] made several attempts to reanalyze subject samples by making minor modifications to the original assay. All of the reanalyses, prior to [redacted] 003214-UJK, had to be aborted due to assay-related problems, although the assay used was validated prior to each analysis. The above findings demonstrate that [redacted] routine validation of the automated assay did not assure reliable assay performance during the study.

---

[1] [redacted] did have the source data to support the results of their retrospective investigation of the lack of cross-well contamination that was reported in their 10/2/03 response to the Agency.

The modified assay used in — 003214-UJK is the same as the original assay; i.e. automated LC/MS/MS with solid phase extraction. The modifications were minor and primarily addressed potential contamination from high concentration to low concentration samples. The minor modifications optimized assay performance in the repeat analysis, as suggested by the lack of QC failure in analytical runs and performance of the test curves. However, regarding the performance of the modified and original assays, — demonstrated in their response dated 3/5/04 that the performance of the modified assay was comparable to the original assay at high concentrations of loratadine. The original assay exhibited sporadic results only at low concentrations of loratadine. Since — established comparability of loratadine concentrations greater than 1200 pg/mL between the assays, DSI expects that the Cmax concentrations of loratadine between original and repeat analysis to be similar. However, **DSI's review of the data indicates that about 30% of the repeat Cmax concentrations for loratadine differ from the original value by more than 15%.** In addition, since — did not systematically investigate the source of contamination in the original — assay, the modifications to the original assay do not guarantee elimination of contamination.

Due to the lack of agreement between the original and repeat Cmax concentrations for loratadine, and the failure of — to systematically investigate the source of contamination, it is uncertain as to which data set accurately represents the actual concentration of loratadine.

Conclusion:

Since the firm has demonstrated that both assays were free of contamination issues at the high concentration range of loratadine, it is imperative for the loratadine Cmax values to be comparable between the original and repeat analysis. The fact that the Cmax values of loratadine differ significantly between the two analyses indicate that the original DSI findings of contamination issues associated with the assay procedures remain unresolved. Consequently, the data generated by — and submitted by Perrigo for this application is not valid. DSI recommends to HFD-570 against accepting this data.

After you have reviewed this memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

Final Classification:
OAI -

cc:
HFA-224
HFD-45/RF
HFD-48/Subramaniam(2)/Himaya/CF
HFD-870/Kim
HFD-570/Zeccola (Tony)
HFR-SW1575/MacInnes
Draft: SS 4/6/04
Edit: MKY 4/7/04, CTV 4/20/04
DSI:5461;O:\BE\EIRCOVER\21512per2.lor.doc
FACTS ID: 493042

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-512

Perrigo Company
515 Eastern Avenue
Allegan, MI 49010

Attention: Janette J. Meyer
ANDA Regulatory Affairs Project Manager

Re: New Drug Application (NDA) 21-512 (Loratadine Tablets, 10 mg)

Dear Ms. Meyer:

This letter concerns the approval status of the above-referenced NDA submitted by L. Perrigo Company (Perrigo) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act). By letter dated January 10, 2003, you advised the Food and Drug Administration (FDA) of Perrigo's belief that the December 2, 2002 complaint for patent infringement filed by Schering Corporation (Schering) against Perrigo in the U.S. District Court for the District of New Jersey should not delay approval of NDA 21-512 (Perrigo's NDA). As discussed below, however, after careful review, FDA has determined that the 30-month stay on approval of Perrigo's NDA resulting from Schering's initiation of patent infringement litigation has not been terminated. Accordingly, your NDA will not be eligible for approval until the 30-month stay either expires (on May 5, 2005) or is terminated by an appropriate court decision in the above-mentioned Schering-Perrigo litigation (Schering-Perrigo NDA litigation).

As your January 10, 2003 letter noted, Schering filed its December 2, 2002 complaint within 45 days of receiving notice of the Paragraph IV certification included in Perrigo's NDA. Under 21 U.S.C. 355(c)(3)(C) and 21 C.F.R. 314.107(b)(3), the filing of Schering's action obligates FDA to stay approval of Perrigo's NDA for a period of 30 months from the date Schering received notice of the Paragraph IV certification therein, unless certain specified conditions are met.

As you are aware, one condition that may terminate a 30-month stay is a court decision issued prior to the expiration of the stay finding the subject patent invalid, not infringed, or unenforceable. 21 U.S.C. 355(c)(3)(C)(i), 21 C.F.R. 314.107(b)(3)(ii). Contrary to the view expressed in your January 10, 2003 letter, however, to terminate the 30-month stay, the finding of invalidity, noninfringement, or unenforceability must be made by the court in the particular action for which the 30-month stay is in effect (i.e., in this case, the Schering-Perrigo NDA litigation). 21 U.S.C. 355(c)(3)(C)(i), 21 C.F.R. 314.107(b)(3)(ii).[1] Indeed, the purpose of the 30-month stay is to permit a certain length of time for

[1] 21 U.S.C. 505(c)(3)(C)(i) states in relevant part:

If the [section 505(b)(2)] applicant made a [Paragraph IV] certification, the approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided [regarding this certification to the patent owner and NDA holder] is

judicial resolution of the particular infringement action.[2] To date, there has been no court decision in the Schering-Perrigo NDA litigation.[3] Therefore, the 30-month stay on Perrigo's NDA remains in effect, and, accordingly, this NDA cannot be approved.

Your letter references the district court opinion in Schering Corp. v. Geneva Pharmaceuticals, Inc., 64 U.S.P.Q. 2d 1032 (D.N.J. 2002).[4] We understand that this decision involved the same patent at issue in the Schering-Perrigo NDA litigation; however, as explained above, the former does not serve to truncate the 30-month stay in the latter. While court decisions of patent invalidity or non-infringement in particular actions have been applied to parties not involved in those actions, this practice has been limited to the triggering of the 180-day marketing exclusivity period for abbreviated new drug applications (ANDAs) under section 505(j)(5)(B)(iv) of the Act (21 U.S.C. 355(j)(5)(B)(iv)) and 21 C.F.R. 314.107(b)(4). 180-day exclusivity for ANDAs is governed by statutory and regulatory provisions distinct from those that terminate the 30-month stays for NDAs like Perrigo's that are submitted under section 505(b)(2) of the Act (505(b)(2) NDAs). Neither FDA nor the courts have found that a judicial decision finding a patent invalid, not infringed, or unenforceable truncates the 30-month stay on approval of a 505(b)(2) NDA, or an ANDA, in an unrelated action.

The FDA guidance you reference entitled "Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act"

---

received. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice..., except that if before the expiration of such period the court decides that such patent is invalid or not infringed, the approval may be made effective on the date of the court decision.

Similarly, 21 C.F.R. 314.107(b)(3)(ii) states:

[If] the [505(b)(2)] applicant certifies...that the relevant patent is invalid, unenforceable, or will not be infringed, and the patent owner or its representative or the exclusive patent licensee brings suit for patent infringement within 45 days of receipt by the patent owner of the notice of certification from the applicant..., approval may be made effective 30 months after the date of the receipt of the notice of certification...unless...[i]f before the expiration of the 30-month period,...the court issues a final order that the patent is invalid, unenforceable, or not infringed, approval may be made effective on the date the court enters judgment[.]

[2] See, for example, the remarks of Rep. Henry Waxman during the House of Representatives' debate on the Hatch-Waxman Amendments to the Act:

Fourth, the period during which a generic drugmaker [sic] may not market pending the judicial resolution of a challenge to patent validity is expanded from the 18 months currently in the bill to 30 months. Some of the brand name drug companies felt this change increases the likelihood that such patent, [sic] litigation will be concluded before the generic drugmaker begins marketing.

130 Cong. Rec. H9114 (Sept. 6, 1984), reprinted in Fox & Bennett, The Legislative History of the Drug Price Competition and Patent Term Restoration Act of 1984, at 48 (FDLI 1987).

[3] We observe that the Schering-Perrigo NDA litigation is, in fact, currently stayed in accordance with the agreement of both parties. See Consent Order Staying Litigation (No. 02-CV-5718) (D.N.J. Jan. 21, 2003). Perrigo could have pursued a court decision declaring the patent at issue in this litigation invalid and/or not infringed based on the findings in the Schering Corp. v. Geneva Pharmaceuticals, Inc. decision noted later in this letter, as Perrigo did successfully in its separate litigation with Schering based on the Paragraph IV certification in Perrigo's ANDA for loratadine 10 mg tablets. Such a court decision would have ended the 30-month stay on approval of Perrigo's NDA. We note that the company elected instead to enter into the above-mentioned stay of action.

[4] Styled Geneva Corporation v. Teva Pharmaceuticals USA, Inc. in your January 10, 2003 letter.

(FDA's court decision guidance) is not to the contrary. This guidance addresses the modification of FDA's prior practice of approving ANDAs and triggering 180-day exclusivity based on court decisions from which no appeal can be or has been taken. The guidance does not describe the application of unrelated court decisions to terminate 30-month stays on approval of third parties' 505(b)(2) NDAs or ANDAs.

Significantly, as noted therein, FDA's court decision guidance is intended to reflect the D.C. District Court's opinion in Mylan Pharmaceuticals, Inc. v. Shalala, 81 F. Supp. 2d 30 (D.D.C. 2000). In contrast to 180-day exclusivity, which, as discussed above, may be triggered by a court decision in an action not involving the affected party, the Mylan opinion observes in part that, "If...an action [for patent infringement] is brought [following a patent holder's receipt of notice that a Paragraph IV certification has been filed in a pending application], the FDA cannot approve the [pending application] for 30 months" unless "the court hearing the infringement action rules before the expiration of the 30-month period that the patent at issue is invalid or not infringed...." Mylan, 81 F. Supp. 2d 30, 33 (emphasis added) (internal citations and quotations omitted). The pending application at issue in Mylan was an ANDA rather than a 505(b)(2) NDA; however, because the statutory provisions regarding the termination of 30-month stays for ANDAs and 505(b)(2) NDAs are virtually identical,[5] and the regulation governing 30-month stays is the same for both types of applications (21 C.F.R. 314.107(b)(3)), the D.C. District Court's observation is equally applicable to Perrigo's NDA.

In summary, because no court decision has issued in the Schering-Perrigo NDA litigation, the 30-month stay on approval of Perrigo's pending NDA 21-512 has not been terminated. Because this stay will not expire until May 5, 2005, Perrigo's NDA cannot be approved before this date, unless and until the court in the Schering-Perrigo NDA litigation issues a decision terminating the stay or otherwise modifies the stay in accordance with the Act.

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

[5] 21 U.S.C. 355(c)(3)(C)(i) (regarding the termination of a 30-month stay on approval of a 505(b)(2) NDA) states that approval of a stayed application "may be made effective" on the date of the court decision finding the patent at issue invalid or not infringed. 21 U.S.C. 355(j)(5)(B)(iii)(I) (regarding the termination of a 30-month stay on approval of an ANDA) is identical except that the above-quoted language reads "shall be made effective" instead of "may be made effective."

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 02:39:19 PM

Marianne Mann
7/11/03 02:44:33 PM
Dr. Mann (Acting Director) is signing in the absence of Dr. Chowdhury.

Zeccola, Anthony

From: Viswanathan, CT
Sent: Thursday, July 10, 2003 3:20 PM
To: Chowdhury, Badrul A; Zeccola, Anthony
Cc: Rhoads, Joanne L; Woodcock, Janet; Barnes, Sandy L (CDER); Fadiran, Emmanuel O
Subject: Re:Perrigo Inc.,- NDA 21-512 Loratadine Tablets 10 mg, OTC

In response to your inspection request on a bioequivalency study from the subject application, DSI has completed the audit yesterday in [redacted]. You may recall that earlier Mr. Edward John Allera, the attorney for Perrigo requested Dr.Woodcock to waive this foreign inspection. As promised, our staff have completed this inspection prior to tomorrow's PDUFA deadline date.

At the exit meeting a Form 483 was issued. Our staff have found significant contamination of the subject plasma samples, questioning the accuracy of the reported plasma drug concentrations. The firm's internal investigation and selective reassay of some of the samples fail to address the overall extent of contamination in the reported loratadine and descarboethoxyloratadine plasma concentrations. The extent of contamination could only be known if the firm reassayed all the samples. The firm's claim that the contamination is limited to the reassayed samples is unacceptable because the firm never reassayed other samples from the study. Consequently, there is no confidence in the accuracy of the reported plasma concentration data used in the subject bioequivalence study and it is recommended that the data not be accepted for your review.

21512per.lor1.
doc (30 KB)

Please see the attached memo for further details.

Vish

MEMORANDUM

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

DATE: July 10, 2003

FROM: Martin K. Yau, Ph.D.
Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering NDA 21-512
Loratadine — 10 mg tablets
Sponsored by Perrigo Company

TO: Badrul A. Chowdhury, M.D.
Director
Division of Pulmonary Drug Products (HFD-570)

At the request of HFD-570, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

> **Study 003214**: Comparative, Randomized, Single Dose, Four-Way Crossover, Fully-Replicated Bioavailability Study of Perrigo —, and Schering (Claritin®) 10 mg Loratadine Tablets in Healthy Adult Males Under Fasting Conditions Following a 40mg Dose.

The clinical and analytical portions of Study 003214 were conducted at —

History: The attorney for Perrigo Company (Edward John Allera) requested a waiver of this inspection. In his letter dated May 15, 2003 to Dr. Woodcock, Mr. Allera suggested that the inspection was unnecessary and that the facility was previously inspected. He further argued that such an inspection could delay the NDA approval. DSI evaluated Mr. Allera's concerns and concluded that the cited reasons are not relevant and do not merit the requested waiver. Study 003214 is the pivotal bioequivalence study for NDA 21-512. Although this facility has been inspected before, no loratadine bioequivalence study was

ever audited. Furthermore, this inspection is a directed data audit to confirm the accuracy of the reported plasma concentrations, which form the sole basis of the bioequivalence determination.

Following the inspection at [redacted] (7/7-9/03), Form 483 was issued. Although other minor deficiencies were noted and will be referenced in the EIR, this memo only evaluates the most significant inspectional finding which is as follows:

> **Failure to assure the accuracy of loratadine and descarboethoxyloratadine concentrations in study subject samples in that cross-well contamination during solid phase extraction using the [redacted] was not fully resolved. The exact number of subject samples affected by the cross-well contamination is unknown and have not been accurately determined. The contamination is not limited to the study subject samples identified in the analytical report (Project 00321/PMF, Tables T5.1 and T5.2).**

The firm's internal investigation of the cross-well contamination is summarized in Attachment 1. [redacted] selectively reassayed pre-dose and elimination phase subject samples that were in microtiter plate wells adjacent to subject samples with high analyte concentrations (Attachment 2, [redacted] Table T5.1 and T5.2). The original values were 2-fold to 133-fold greater than the reassay results, confirming that contamination from samples of high concentration to samples of low concentration occurred, in at least 11 analytical runs. We have determined that the firm's contention that "clinical samples at the pre-dose and elimination phase would most likely be affected" is only a speculation. The extent of contamination could only be known if the firm reassayed all the samples. The firm's claim that the contamination is limited to the reassayed samples (Attachment 2) is unacceptable because the firm never reassayed other samples from the study. We maintain that the firm should have reassayed all the subject samples to have demonstrated the accuracy of the loratadine and descarboethoxyloratadine plasma concentrations in this pivotal bioequivalence study.

Please note that the confirmed cross-well contamination raises the question whether other loratadine bioequivalence studies conducted by this firm deserve to be examined.

At the inspection closeout, ——— stated they would respond to the Form 483 observations.

Conclusion:

We are unable to verify the extent of contamination in the reported loratadine and descarboethoxyloratadine plasma concentrations in Study 003214. The firm's internal investigation and selective reassay of some samples fail to address the overall extent of contamination. DSI has no confidence in the accuracy of the reported plasma concentration data used in the subject bioequivalence study and recommends that the data **not** be accepted for Agency review.

After you have reviewed this memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

Martin K. Yau, Ph.D.

Final Classification:
OAI - ———

cc:
HFA-224
HFD-45/RF
HFD-48/Yau/Subramaniam/Himaya/CF
HFD-570/Zeccola
HFD-870/Kim
HFR-PA2535/Hall
Draft: SS 7/9/03
Edit: MKY/JAO/MFS 7/9,10/03
Edit: CTV 7/10/03
DSI:5461; O:\BE\EIRCOVER\21512per.lor.doc
FACTS ID: 399066

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-512

INFORMATION REQUEST LETTER

Perrigo
515 Eastern Avenue
Allegan, Michigan 49010

Attention: Janette J. Meyer
Regulatory Affairs Project Manager

Dear Ms. Meyer,

Please refer to your May 9, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for loratadine tablets 10mg.

We also refer to your submission dated May 12, 2003.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We are sending you preliminary CMC comments for your consideration. These comments are not all inclusive.

1. The following comments pertain to "description " of the drug substance [Responses 1(a) and 2(a)].

   a. Modify the acceptance criterion to '

   b. Demonstrate equivalency of the proposed different acceptance criteria between Drug Substances with data from multiple batches.

2. The following comment pertains to specifications for "

4. Provide an agreement to submit a prior approval supplement for any new propietary name in the future.

We may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Anthony Zeccola, Regulatory Management Officer, at 301-827-1058.

Sincerely,

Guirag Poochikian, Ph.D.
Chemistry Team Leader, DNDC II for the
Division of Pulmonary and Allergy Drug Products,
HFD-570
DNDC DNDC II, Office of New Drug Chemistry
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/

Guiragos Poochikian
6/10/03 11:25:38 AM

Division of Over-the-Counter Drug Products
Addendum Labeling Review

NDA # 21-512

Amendment Dates : 5/09/03
Review Date : 5/30/03

Applicant: Perrigo Company
515 Eastern Avenue
Allegan, MI 49010

Applicant's Representative: Janette J. Meyer
Regulatory Affairs Project Manager

Drug:
Loratadine Tablet, 10 mg

Pharmacological Category: Antihistamine

Submitted:

Loratadine Tablets:

- 4- and 12-count blister *carton* labels
- 4- and 12-count non child-resistant push through *blister card* labels
- 10-, 30-, 300-count ***bottle carton*** label
- 10-, 30-, 300-count ***bottle label***
- Annotated Labeling: 4-count *blister carton label*

Background:
In response to the approvable letter dated June 28, 2002, for OTC — Allergy drug product (NDA 21-512), the sponsor has agreed to withdraw the brand name — and has renamed its product "Loratadine Tablets, 10 mg". The sponsor has submitted revised draft labeling, including the new proposed product name, for the following:

- 4- and 12-count blister *carton* labels
- 4- and 12-count non child-resistant push through *blister card* labels
- 10-, 30-, 300-count ***bottle carton*** label
- 10-, 30-, 300-count ***bottle label***
- 4-count *blister carton label*: Annotated Labeling

Reviewer Comment:
The sponsor has incorporated all of the Agency's required and recommended labeling changes described in the approvable letter. The labeling is acceptable.

RECOMMENDATIONS:
1. An approval letter can be issued to the sponsor requesting final printed labels for the following:
   - 4- and 12-count blister *carton* labels
   - 4- and 12-count non child-resistant push through *blister card* labels
   - 10-, 30-, 300-count ***bottle carton*** label
   - 10-, 30-, 300-count ***bottle label***
   - 4-count *blister carton label*: Annotated Labeling.

   These final printed labels must be identical to the labels submitted on May 9, 2003.

2. Inform the sponsor that the word "NEW!" must be deleted from the PDP six months after introduction into the market place.

Cazemiro R. Martin
Regulatory Review Scientist/IDS

Concur: Marina Chang, R.Ph.
Team Leader

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

/s/

Cazemiro Martin
6/9/03 09:19:58 AM
INTERDISCIPLINARY

Marina Chang
6/9/03 09:28:45 AM
INTERDISCIPLINARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-512

Perrigo
515 Eastern Avenue
Allegan, Michigan 49010

Attention: Janette J. Meyer
Regulatory Affairs Project Manager

Dear Ms. Meyer,

We acknowledge receipt on May 12, 2003 of your May 9, 2003 resubmission to your new drug application for loratadine 10mg tablets.

We consider this a complete, class 1 response to our May 1, 2003 action letter. Therefore, the user fee goal date is July 12, 2003

If you have any question, call Anthony M. Zeccola, Regulatory Management Officer, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

Sandra L. Barnes
Chief, Project Management Staff
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/

Sandra Barnes
6/3/03 04:06:05 PM

Memorandum of Telephone Facsimile Correspondence

Date: 5/21/03

To: Janette Meyer
Project Manager, ANDA Regulatory Affairs

From: Chong Ho Kim, Ph.D.
CMC Reviewer

Through: Anthony Zeccola
Regulatory Management Officer

Subject: Request for Information – NDA 21-512

Total Pages: 3 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

{See appended electronic signature page}

Anthony M. Zeccola
Regulatory Management Officer
Division of Pulmonary Drug Products

Please provide the following information to assist in our review of NDA 21-512:

Provide data for the basis of your proposed specifications for Comments 1(a), 1(e), 2(a), 2(c), 3(a), 3(c), 4(a), 4(b), and 5(a), included in your May 9, 2003 response to our May 1, 2003 Approvable letter.

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

/s/

Anthony Zeccola
5/21/03 11:14:34 AM
CSO

Division of Over-the-Counter Drug Products
Addendum Labeling Review

NDA # 21-512

Amendment Dates : 3/04/03
Review Date : 4/15/03

Applicant: Perrigo Company
515 Eastern Avenue
Allegan, MI 49010

Applicant's Representative: Valerie Gallagher
Supervisor, Regulatory Affairs

Drug:

— - Loratadine Tablet, 10 mg

Pharmacological Category: Antihistamine

Submitted:

—

- 4- and 12-count blister *carton* labels
- 4- and 12-count non child-resistant push through *blister card* labels
- 10-, 30-, 300-count ***bottle carton*** label

- 10-, 30-, 300-count ***bottle*** (*submitted 12/18/02*)
- Annotated Labeling for — drug products (*submitted 12/18/02*)

Background:

The purpose of this amendment is to clarify and simplify the statement of all package configurations for which approval is being requested. Perrigo is requesting the withdraw of all labeling in either the original application or the Labeling Amendment dated December 18, 2002 for the following:

- labeling for the trade name —
- —
- — count blister cartons labeling

In this submission, the sponsor has submitted draft labeling for the following:

- 4- and 12-count blister carton and non child-resistant blister strip labeling
- revised labeling for the 10-, 30-, and 300-count bottle carton labeling that addresses the labeling comments provided by the Division of OTC Drug Products (HFD-560) during a teleconference call on February 12, 2003, and comments by HFD-570 (Dr. Kim) on February 24, 2003.

The sponsor's submission indicates that the draft labeling for the 10-, 30-, and 300-count bottle labeling remains the same as submitted on December 18, 2002. This submission does not mention withdraw of the annotated labeling for — products included in its 12/18/03 submission which identifies optional copy and position of various graphic features and promotional statements in the carton labeling.

A

6 Page(s) Withheld

_____ Trade Secret / Confidential

/ Draft Labeling

_____ Deliberative Process

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

/s/

Cazemiro Martin
4/15/03 10:19:10 AM
INTERDISCIPLINARY

Marina Chang
4/15/03 10:55:18 AM
INTERDISCIPLINARY

Regulatory Affairs Department
Fax: 269-673-7655

FACSIMILE TRANSMISSION

DATE: **February 5, 2003**

TO: **Elaine Abraham**

Fax 301-827-2315

COMPANY: **FDA, CDER**
Division of OTC Drug Products

FROM: **Janette Meyer**
Regulatory Affairs Project Manager

TEL. # **269-686-1978**

NUMBER OF PAGES (INCLUDING COVER PAGE) 3

MESSAGE:

L. Perrigo Company respectfully requests a telephone conference with FDA to discuss NDA 21-512 Loratadine Tablets, 10 mg. Please refer to the attached letter.

Please call Janette Meyer at (269) 686-1978 if there are transmission problems.

PERRIGO®

February 4, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
HFD-560
Attention: Elaine Abraham
5600 Fishers Lane
Rockville, Maryland 20857

Re: New Drug Application
Loratadine Tablets, 10 mg
NDA 21-512

Dear Ms. Abraham:

Please reference NDA 21-512 for Loratadine Tablets, 10 mg submitted June 28, 2002, under Section 505(b)(2)(A) of the Federal Food, Drug & Cosmetic Act.

L. Perrigo Company respectfully requests a telephone conference call with FDA to discuss the topics listed below.

1. As explained in the previous telephone conference, Perrigo

2. Perrigo understands that it may market loratadine tablets, 10 mg without a proprietary name, using only the established name of the drug product. The blister strips would be similarly labeled. Such labeling would be included in the Annual Report.

Compare To Statements

Perrigo commonly uses comparison statements relative to the approved reference listed drug (i.e. Compare to the Active Ingredient of Claritin®) with its OTC ANDA drug products. As a matter of fact, "compare to" statements are commonplace in store-brand marketing, used with both OTC monograph drug products and OTC ANDA drug products.

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

Comparison advertising is not only permissible but encouraged by the Federal Trade Commission as a source of important information to consumers, which assists them in making rational purchase decisions. It is for this reason that this type of advertising is commonplace in the retail field. The use of comparison statements assists the consumer in identifying alternative products on the shelf and serves as a communication to the consumer that the RLD and the generic version contain comparable active ingredient(s), the same doses, and the same strengths. For consumers, the comparison statement functions like the "Orange Book", which assists physicians and pharmacists in identifying therapeutic equivalents of prescription products. Perrigo has, in the past, received communications from the Division of Drug Labeling Compliance in which it has stated that "...we have not objected to claims such as "Compare to the active ingredients in Brand X", if the active ingredients are in fact the same...".

Although we understand that the regulations governing 505(b)(2) NDA's do not require that bioequivalence to a reference listed drug be demonstrated in all cases, for NDA 21-512 bioequivalence has been demonstrated to the stated reference listed drug, Claritin®. To our knowledge, the Rx and OTC versions of Claritin® are identical, and clearly the active ingredient of the Perrigo loratadine tablets and the Claritin® reference drug are comparable. Therefore, Perrigo requests confirmation that the labeling submitted in the amendment dated 12/18/02, which includes the statement "Compare to the active ingredient of Claritin®" will be acceptable for approval. It is important that Perrigo verify the acceptability of the labeling as soon as possible so that product launch plans may be finalized in anticipation of the NDA approval in May 2003.

I may be contacted directly by telephone at 269-686-1978 or by FAX at 269-673-7655.

Sincerely,

Janette J.Meyer
Regulatory Affairs Project Manager

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

/s/

Elaine Abraham
2/26/03 02:18:11 PM
CSO

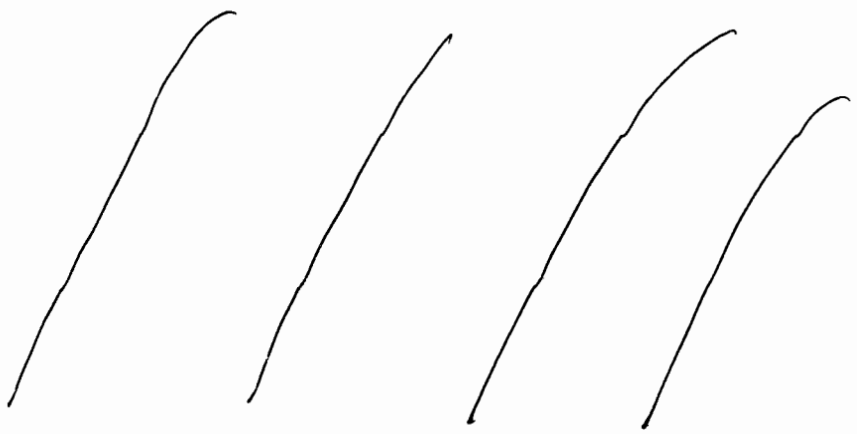
RECORD OF TELEPHONE CONVERSATION

Date:	February 12, 2003
Project Manager:	Elaine Abraham
Subject:	Discuss labeling questions
NDA:	21-512
Sponsor:	Perrigo
Product Name:	Loratadine tablets 10 mg
Phone No:	(269) 686-1978

FDA participants:	Marina Chang, R.Ph., Team Leader Cazemiro R. Martin, Regulatory Review Chemist/IDS Elaine Abraham, R.Ph., Project Manager
Perrigo participant:	Janette Meyer, Project Manager, Regulatory Affairs Brian Schuster, Associate Director, Regulatory Affairs Valerie Gallagher, Supervisor, Regulatory Affairs

Background: On February 5, 2003, Perrigo faxed FDA a request for a telephone conference call on labeling issues (attached). Perrigo's questions and FDA responses are listed below.

1) **As explained in the previous telephone conference,** _____



2) **Perrigo understands that it may market lorartadine tablets, 10 mg without a proprietary name, using only the established name of the drug product. The**

blister strips would be similarly labeled. Such labeling would be included in the Annual Report.

FDA response: Yes, if "loratadine" is used as the product name, "loratadine" should appear on the blister package labeling. If a proprietary name is used on the outside package, that name should also appear on the blister pack.

3) **Perrigo commonly uses comparison statements relative to the approved reference listed drug ...with its OTC ANDA drug products... Perrigo requests confirmation that the labeling submitted in the amendment dated 12/18/02, which includes the statement "Compare to the active ingredient of Claritin®" will be acceptable for approval.**

FDA response: We agree that the statement "Compare to the active ingredient of Claritin®" would be acceptable on the labeling. However, the labeling submitted in the 12/18/02 amendment did not include that specific language and is not acceptable. We would also recommend adding "tablets" to the comparative statement requested in your fax, so that an acceptable statement would be "Compare to the active ingredient of Claritin® tablets".

Draft by: HFD-560/Abraham/2-25-03
OK: HFD-560/Chang/2-26-03
OK: HFD-560/Martin/2-26-03

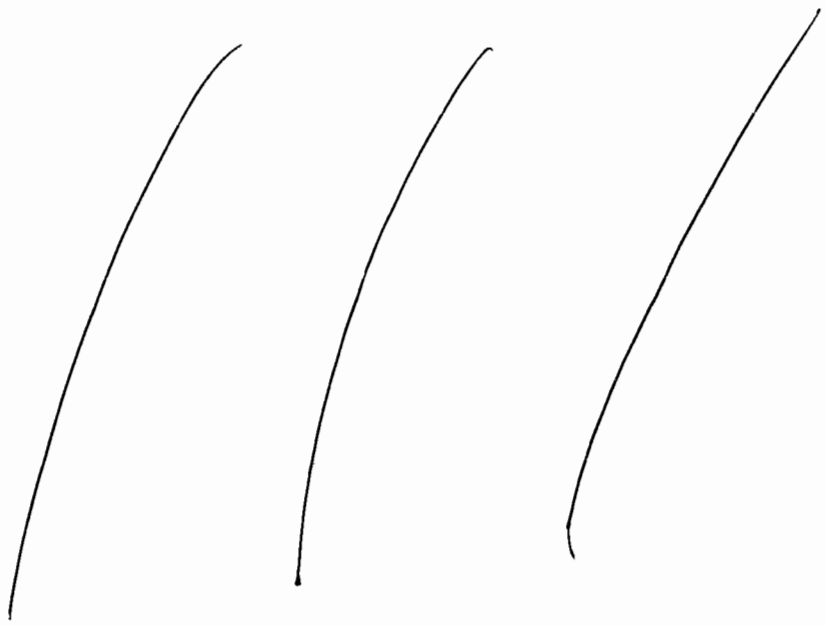
C:\word\N21-512 Labeling Tcon4.doc
IMTS #: 10007

RECORD OF TELEPHONE CONVERSATION

Date:	November 27, 2002
Project Manager:	Elaine Abraham
Subject:	Discuss labeling questions
NDA:	21-512
Sponsor:	Perrigo
Product Name:	Loratadine tablets 10 mg
Phone No:	(269) 686-1978

FDA participants:	Marina Chang, R.Ph., Team Leader Cazemiro Martin, IDS Reviewer Elaine Abraham, R.Ph., Project Manager
Perrigo participant:	Janette Meyer, Project Manager, Regulatory Affairs Brian Schuster, Associate Director, Regulatory Affairs Valerie Gallagher, Supervisor, Regulatory Affairs

Background: On November 15, 2002, Perrigo faxed FDA a request for a Tcon on labeling issues (attached). Perrigo's questions and FDA responses are listed below.



B

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Regulatory Affairs Department
Fax: 269-673-7655

FACSIMILE TRANSMISSION

DATE: **November 15, 2002**

TO: **Elaine Abraham**

Fax 301-827-2315

COMPANY: **FDA, CDER**
Division of OTC Drug Products

FROM: **Janette Meyer**
Project Manager, ANDA Regulatory Affairs

TEL. # **269-686-1978**

NUMBER OF PAGES (INCLUDING COVER PAGE) 3

MESSAGE:

L. Perrigo Company respectfully requests a telephone conference with FDA to discuss NDA 21-512 Loratadine Tablets, 10 mg. Please refer to the attached letter.

Please call Janette Meyer at (269) 686-1978 if there are transmission problems.

PERRIGO®

November 15, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
HFD-560
Attention: Elaine Abraham
5600 Fishers Lane
Rockville, Maryland 20857

Re: New Drug Application
Loratadine Tablets, 10 mg
NDA 21-512

Dear Ms. Abraham:

Please reference NDA 21-512 for Loratadine Tablets, 10 mg submitted June 28, 2002, under Section 505(b)(2)(A) of the Federal Food, Drug & Cosmetic Act.

L. Perrigo Company respectfully requests a telephone conference call with FDA to discuss the topics listed below.

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

C

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Elaine Abraham
1/15/03 03:34:44 PM

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, 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

APPLICANT INFORMATION

NAME OF APPLICANT
L. Perrigo Company

DATE OF SUBMISSION
1/10/03

TELEPHONE NO. (Include Area Code)
269- 673-8451

FACSIMILE (FAX) Number (Include Area Code)
269- 673-7655

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
515 Eastern Ave.
Allegan, MI 49010

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*: 21-512

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*: Loratadine Tablets

PROPRIETARY NAME *(trade name)* IF ANY: —

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: 4-(8-chloro-5,6-dihydro-11H-benzo [5,6] cyclohepta [1,2-b] pyridin-11-ylidene)-1-piperidinecarboxylic acid, ethyl ester

CODE NAME *(If any)*: 275

DOSAGE FORM: Tablet

STRENGTHS: 10 mg

ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE: For the temporary relief of symptoms of hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes and itching of the nose or throat

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: Claritin Holder of Approved Application: Schering Corporation

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 OR 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: Patent Amendment

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

NUMBER OF VOLUMES SUBMITTED:

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.

See section 3.2.P.3.1 of this NDA.

L. Perrigo Company CFN No.: 1611666.
All facilities are ready for inspection.

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

DMF's:

ANDA: 76301

This application contains the following items: *(Check all that apply)*

☒	1. Index	
☐	2. Labeling *(check one)*	☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))	
☐	4. Chemistry section	
☐	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)	
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
☐	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))	
☐	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)	
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
☐	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)	
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
☐	14. 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)	
☐	16. Debarment certification (FD&C Act 306(k)(1))	
☒	17. Field copy certification (21 CFR 314.50(k)(3))	
☐	18. User Fee Cover Sheet (Form FDA 3397)	
☐	19. Financial Information (21 CFR Part 54)	
☒	20. OTHER *(Specify)* Patent Amendment	

CERTIFICATION

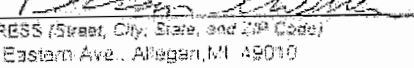
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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, 211or 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 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 review and, to the best of my knowledge 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
	Brian R. Schuster, Associate Director, ANDA Regulatory Affairs	1/10/03

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
575 Eastern Ave., Allegan,MI 49010	269-673-9367

PERRIGO

January 10, 2003

PATENT AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
HFD-570
Document Room 10B45
Attn: Anthony Zeccola, Regulatory Management
5600 Fishers Lane
Rockville, Maryland 20857

Re: Loratadine Tablets, 10 mg
NDA 21-512

Dear Mr. Zeccola:

The L. Perrigo Company is filing a patent amendment to NDA 21-512 for Loratadine Tablets, 10 mg, submitted June 28, 2002, under Section 505(b)(2)(A) of the Federal Food, Drug & Cosmetic Act.

This patent amendment is to notify the Agency that a complaint for patent infringement was filed by the patent and NDA holder, Schering Corporation, on December 2, 2002, within 45 days of receipt of the notice required under 21 CFR 314.52 and Section 505(b)(3)(B) of the Act.

The Paragraph IV certification contained in NDA 21-512 stated that U.S. Patent 4,659,716 and U.S. Patent 4,863,931 are invalid, unenforceable and will not be infringed by the manufacture, use or sale of L. Perrigo Company's Loratadine Tablets, 10 mg. The enclosed complaint (Section 2) cites only Patent 4,659,716.

Reference is made to the August 8, 2002, U.S. District Court Opinion and Order in *Schering Corporation v. Teva Pharmaceuticals USA, Inc.*, which declared that claims 1 and 3 of patent 4,659,716 were invalid and entered summary judgment for the defendants (Section 3). Claims 1 and 3 of patent 4,659,716 are the only claims asserted in the enclosed complaint as being infringed.

Further reference is made to the March 2000 FDA guidance document *Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, which defined "court decision" as the decision of a district court. In light of the August 2002 district court decision and the March 2000 guidance, Perrigo considers that the approval of its application should not be delayed by the December 2, 2002, Schering complaint of patent infringement.

In accordance with 21 CFR 314.50 (l)(3), the L. Perrigo Company certifies that a "field copy" which is a true copy of this patent amendment submitted to the FDA headquarters, has been submitted to the Detroit District Office.

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

Should you have any questions, please contact me by telephone at (269) 686-1978, by facsimile at (269) 673-7655, by email at jmeyer2@perrigo.com or at the address upon this letterhead.

Respectfully submitted,

Janette J. Meyer
ANDA Regulatory Affairs
Project Manager

TABLE OF CONTENTS

Patent Amendment
January 10, 2003

Loratadine Tablets, 10 mg
NDA 21-512

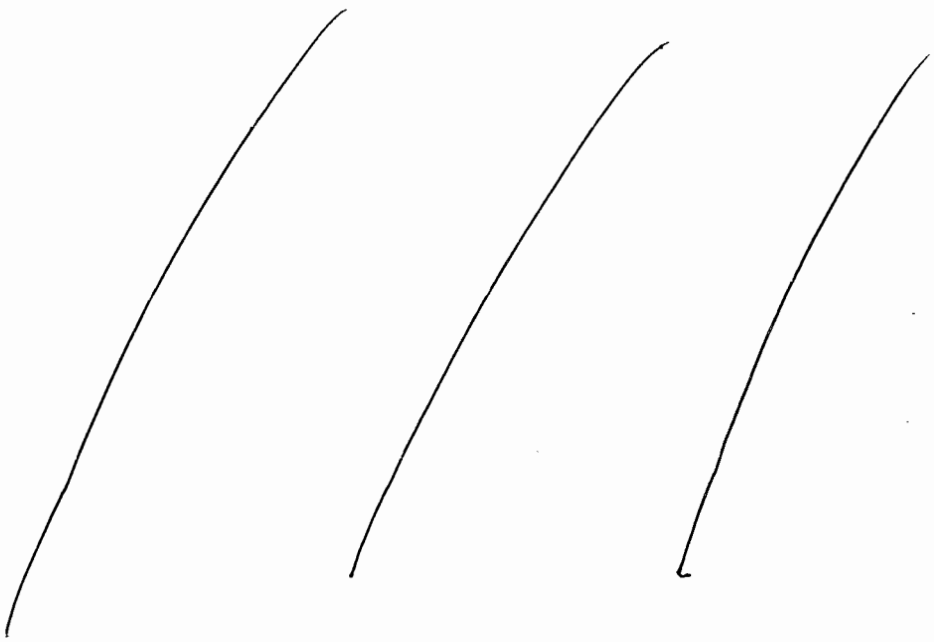
RECORD OF TELEPHONE CONVERSATION

Date: November 7, 2002
Project Manager: Elaine Abraham
Subject: Discuss labeling questions
NDA: 21-512
Sponsor: Perrigo
Product Name: Loratadine tablets 10 mg
Phone No: (269) 686-1978

FDA participant: Elaine Abraham, R.Ph., Project Manager

Perrigo participant: Janette Meyer, Regulatory Affairs

Perrigo called FDA on November 1, 2002, with the questions listed below. FDA responded on November 7.



Draft by: HFD-560/Abraham/1-8-03

C:\word\N21-512 Labeling Tcon2.doc

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

/s/

Elaine Abraham
1/9/03 08:28:43 AM
CSO

PERRIGO

November 15, 2002

PATENT AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
HFD-570
Attention: Document Room 10B45
5600 Fishers Lane
Rockville, Maryland 20857

Re: New Drug Application
Loratadine Tablets, 10 mg
NDA 21-512

Dear Mr. Buehler:

The L. Perrigo Company is filing an amendment to NDA 21-512 for Loratadine Tablets, 10 mg, submitted June 28, 2002, under Section 505(b)(2)(A) of the Federal Food, Drug & Cosmetic Act.

We hereby certify that, in accordance with 21 CFR 314.52 and Section 505(b)(3)(B) of the Act, a "Notice of Invalidity, Unenforceability, and/or Non-Infringement of a Patent" (here-in-after "Notice") has been provided to the person identified under 21 CFR 314.52(a) and that such Notice met the content requirements under CFR 314.52(c). Notice was sent to the name listed below via certified mail; return receipt requested:

Name:	Chief Legal Counsel
NDA Holder:	Schering Corporation, NDA 19-658
Patent No.:	4,659,716
Assignee:	Schering Corporation
Patent No.:	4,863,931
Assignee:	Schering Corporation
Date Post-Marked:	October 31, 2002
Date Received:	November 15, 2002

As required under 21 CFR 314.52(e), a copy of the "Domestic Return Receipt", PS Form 3811 (here-in-after "Receipt"), is attached (Section 2) and serves to document the receipt of Notice by the patent owner and holder of the approved New Drug Application 19-658 for the listed drug Claritin®, Schering Corporation. Documentation of the delivery of PS Form 3811 by the US Postal Service is included in Section 3.

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

In accordance with 21 CFR 314.50(k)(3), the L. Perrigo Company certifies that a "field copy" which is a true copy of this patent amendment submitted to the FDA headquarters, has been submitted to the Detroit District Office.

Respectfully submitted,

Janette J. Meyer
ANDA Regulatory Affairs
Project Manager

Enclosures

TABLE OF CONTENTS

Patent Amendment

Loratadine Tablets, 10 mg
NDA 21-512

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, 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

APPLICANT INFORMATION

NAME OF APPLICANT
Perrigo Company

DATE OF SUBMISSION
11/15/02

TELEPHONE NO. (Include Area Code)
616- 673-8451

FACSIMILE (FAX) Number (Include Area Code)
616- 673-7655

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
515 Eastern Ave.
Allegan, MI 49010

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-512

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Loratadine Tablets

PROPRIETARY NAME *(trade name)* IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* 4-(8-chloro-5,6-dihydro-11H-benzo [5,6] cyclohepta [1,2-b] pyridin-11-ylidene)-1-piperidinecarboxylic acid, ethyl ester

CODE NAME *(If any)* 275

DOSAGE FORM: Tablet

STRENGTHS: 10 mg

ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

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: Claritin Holder of Approved Application: Schering Corporation

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 OR 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: Patent Amendment

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

NUMBER OF VOLUMES SUBMITTED:

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.

See section 3.2.P.3.1 of this NDA.

L. Perrigo Company CFN No.: 1811886.
All facilities are ready for inspection.

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

DMF's:

ANDA: 75301

This application contains the following items: *(Check all that apply)*

☒	1.	Index
☐	2.	Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3.	Summary (21 CFR 314.50(c))
☐	4.	Chemistry section
☐		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)
☐	5.	Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	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))
☐	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)
☐	10.	Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11.	Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12.	Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
☐	13.	Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	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)
☐	16.	Debarment certification (FD&C Act 306(k)(1))
☒	17.	Field copy certification (21 CFR 314.50(k)(3))
☐	18.	User Fee Cover Sheet (Form FDA 3397)
☐	19.	Financial Information (21 CFR Part 54)
☒	20.	OTHER *(Specify)* Patent Amendment as required by 21 CFR 314.52

CERTIFICATION

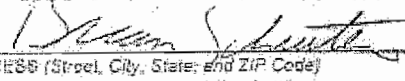
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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, 211or 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 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 review and, to the best of my knowledge 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
	Brian R. Schuster, Associate Director, ANDA Regulatory Affairs	11/15/02

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
515 Eastern Ave., Allegan,MI 49010	616-673-8367

RECORD OF TELEPHONE CONVERSATION

Date:	October 31, 2002
Project Manager:	Elaine Abraham
Subject:	Discuss labeling questions
NDA:	21-512
Sponsor:	Perrigo
Product Name:	Loratadine
Phone No:	(269) 686-1978

FDA participants: Marina Chang, R.Ph., Team Leader
Cazemiro Martin, IDS reviewer
Elaine Abraham, R.Ph., Project Manager

Perrigo participant: Jeanette Meyer, Regulatory Affairs

Background: FDA called Perrigo on October 30 and left a message requesting that they send the blister pack for the Alavert product which was not included in the original submission. The sponsor returned the call and stated that the submitted (—) blister pack will be used for all of their loratadine products.

Discussion: FDA informed the sponsor that the proprietary name is required to be on the blister pack according to 21 CFR 201.10(i). The sponsor agreed to submit the blister packs to the NDA as a minor labeling amendment.

Draft by: HFD-560/Abraham/10-31-02
OK: HFD-560/Chang/11-1-02

C:\word\N21-512 Labeling Tcon.doc

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

/s/

Elaine Abraham
11/1/02 09:27:47 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	—	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Brian R. Schuster	Regulatory Affairs Manager
FIRM/ORGANIZATION: Perrigo Company	
SIGNATURE: Brian Schuster	DATE: 06/28/02

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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

Perrigo Company
515 Eastern Avenue
Allegan, MI 49010

2. TELEPHONE NUMBER *(Include Area Code)*

(616) 673-8451

3. PRODUCT NAME

Loratadine Tablets, 10 mg

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

21-512

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

4344

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)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Brian Schantz	Manager, Regulatory Affairs	June 14, 2002