

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-350

APPROVABLE LETTER 2



NDA 21-350

Cato Research, agent for
RTP Pharma, Inc.
Attention: Lynda Sutton
Senior Vice President, Regulatory Affairs
200 Westpark Corporate Center
4364 South Alston Avenue
Durham, North Carolina 27713-2280

Dear Ms. Sutton:

Please refer to your new drug application (NDA) dated June 22, 2001, received June 25, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [REDACTED] (fenofibrate tablets; [REDACTED])

We acknowledge receipt of your submissions dated July 13, August 20, September 6 and 18, October 16 and 26, November 9, and December 28 (2), 2001, and January 7, February 14 and 25, March 1, 6, and 25, and April 10, 2002.

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

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

1. Final approval is contingent on the successful inspection of the clinical and analytical portions of the bioequivalence studies FEN100-C05 and FEN100-C06 conducted at [REDACTED]
2. The dissolution method and specifications should be modified as follows:

Dissolution Method:

Apparatus Type: USP apparatus 2
Speed of Rotation: 50 rpm
Medium: [REDACTED] sodium lauryl sulfate (SLS), 37°C
Volume: 900 mL

Dissolution specifications:

50 mg: not less than [REDACTED] (Q) in 30 minutes
160 mg: not less than [REDACTED] (Q) in 60 minutes

PACKAGE INSERT

3. The following revisions to the draft submitted March 25, 2002, are needed:

- a. In the **CLINICAL PHARMACOLOGY , Pharmacokinetics**, Absorption section, second paragraph change:

~~_____~~

to:

“Peak plasma levels of fenofibric acid occur an average of 3 hours after administration.”

- b. In the **CLINICAL PHARMACOLOGY , Pharmacokinetics**, Effect of Food on Absorption section, second paragraph change:

~~_____~~

to:

~~_____~~

- c. In the **DOSAGE and ADMINISTRATION** section, second and third paragraphs change:

~~_____~~

to:

~~_____~~

- d. Provide draft package insert reformatted to conform to 21 CFR 201.57.
- e. Revise all references to the drug product name in the package insert, immediate container and carton labels to include the proprietary name, [REDACTED]

CHEMISTRY, MANUFACTURING, AND CONTROLS

- 4. Because your product is inherently unstable, the expiry date will be determined based on real time (long term) stability data. Since data collected under accelerated conditions showed some failures, these data cannot be used for extrapolation of real time data. Accordingly provide the following stability data in order to determine the expiry of your product:
 - a. Additional data (beyond 3 months) from the one batch of your 50 mg tablets and additional data from the three batches of your 160 mg tablets made in [REDACTED]
 - b. Site specific stability data from your new manufacturing facility at SkyePharma Production SAS for at least two batches of the 50 mg tablets and one batch of the 160 mg tablets stored at 5°C.
 - c. Three months of data from a 6 month study (one batch of each strength of tablets made at SkyePharma Production SAS) of accelerated (25°C/60% RH) stability.

Provide a commitment indicating that failure of batches/lots to meet the stability acceptance criteria will be reported to the Agency, as required under 21 CFR 314.81 (b)(1)(ii).

- 5. With respect to the establishment of drug product specifications:
 - a. Provide acceptance criteria for total impurities as part of the drug product regulatory release and stability specifications.
 - b. Characterize the cause and extent of the [REDACTED] of the 50 mg tablets noted after storage. (Depending upon your response to these concerns, specifications may have to be established for [REDACTED] as appropriate).
 - c. Provide a description of test methods [REDACTED] for the particle size specification.
- 6. Regarding the manufacture of your drug product.
 - a. Provide a specific identification test (e.g., by [REDACTED]) for each lot of fenofibrate received as part of your acceptance criteria for the drug substance (fenofibrate).
 - b. Provide a re-calculation of the correction factor in the tablet size, [REDACTED] to account for the [REDACTED]. The submitted correction factor [REDACTED] appears to be wrong and should be [REDACTED] which equates with [REDACTED]
 - c. Provide a target range for the total tablet weight of the two tablet strengths.
 - d. Provide a description of in-process test methods: [REDACTED]
 - e. Provide a reprocessing procedure if applicable or, if not applicable, provide a statement indicating that no reprocessing will be carried out.
- 7. Provide USP<671> test results on the container closure system.

In addition, DMF # ~~_____~~ regarding the manufacture of fenofibrate drug substance was found to be inadequate to support this application. A letter listing the deficiencies was sent to the DMF holder on April 12, 2002.

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Mary Parks
4/24/02 08:08:15 AM
for Dr. Orloff