

The second method was a noncompartmental approach, whereby the known equality of the ratio of metabolite AUC to parent drug AUC after a single dose in the single dose, fasted study and during a steady-state interval in the multiple dose study, was extrapolated to the ratios of the maximum concentrations (C_{max}). Equality of the observed ratios from the single dose and multiple dose studies, is evidence that an accurate estimate of pentoxifylline maximum concentration was obtained in the multiple dose study.

The ratio of metabolite to parent drug C_{max} was calculated for each subject in the single dose, fasted study. Similarly, the ratio of metabolite to parent drug C_{max} was calculated for each subject during the steady state dosing interval of the multiple dose study. The mean ratios were compared by a t-test and were not statistically different for either metabolite I or metabolite V after the reference product and after the test product. This result indicates that the pentoxifylline C_{max} estimated from the sampling schedule used during the multiple dose, steady state dosing interval accurately characterizes the true steady-state maximum concentration of pentoxifylline. A more detailed summary can be found in Attachment # 3 with associated graphs and tables in Attachment # 4.

Both of the pharmacokinetic approaches result in a conclusion that, for pentoxifylline, a sampling protocol that starts 0.5 hours after a dose does provide an accurate estimate of the maximum concentration occurring at steady-state.

Based on published literature and the Summary Basis of Approval (SBA) for Trental®, Upsher-Smith agreed with the blood sampling plan prepared by the Division of Bioequivalence and published in the "Pentoxifylline Extended Release Tablets *in vivo* Bioequivalence and *in vitro* Dissolution Testing Guidance". This sampling plan begins with the first post-dose sample point at 0.5 hour for the multiple-dose, fasting study.

The SBA for Trental® (pentoxifylline) by Hoechst-Roussel, document #105086, reports the results of a multiple-dose bioavailability study (protocol 170) that included the innovator's 400 mg extended-release tablet. The subjects (n=15) receiving the 400 mg extended-release tablet were dosed twice a day for 5 days with pharmacokinetic parameters measured after the final dose on day 5. The mean t_{max} for this group of subjects was 2.4 hours (SD unavailable). On page 2 of the Pentoxifylline Extended Release Tablets *in vivo* Bioequivalence and *in vitro* Dissolution Testing Guidance the results of published literature regarding the multiple-dose pharmacokinetics of pentoxifylline are summarized. The mean t_{max} ranged from 0.9 to 2.0 hours.^{1,2,3}

¹Beerman B, Ings R, Mansby J, Chamberlain J, McDonald A. Kinetics of intravenous and oral pentoxifylline in healthy subjects. Clin Pharmacol Ther 1985;37:25-8.

²Mauro VF, Mauro LS, Hageman JH. Alteration of pentoxifylline pharmacokinetics by cimetidine. J Clin Pharmacol 1988; 28:649-54.

³Mauro VF, Mauro LS, Hageman JH. Comparison of pentoxifylline pharmacokinetics between smokers and nonsmokers. J Clin Pharmacol 1992; 32:1054-8.

Therefore, subjects # 1, 5, 6, 11, 12, 13, 14, 15, 22, and 23 should not be excluded from the statistical analysis. The pentoxifylline 90% confidence interval for the log-transformed C_{max} is 97.3 - 122. This demonstrates that the test product Pentoxil™ (pentoxifylline) is bioequivalent to the reference product Trental® (pentoxifylline).

- b. The report stated that there were no significant differences between concentrations at 48 hr and 72 hr time points, and thus steady-state was reached at the time when the measurement of AUC(0- τ) was started, 72 hours. The Division currently has no guidelines for determination of steady-state conditions in multiple dose studies. The REG procedure of SAS may be used to determine if slopes through the three C_{min} values are significantly different from zero.

The SAS output for use of REG procedure on trough levels has been completed for the multiple dose study, and the results are submitted as Attachment # 5. The SAS REG procedure was applied to all trough levels of pentoxifylline and its metabolites M-I and M-V (24 hr, 48 hr, and 72 hr time points) of both the TEST and REFERENCE formulations and did not find a slope different from zero for any of the analytes in either formulation.

P-VALUE FOR SLOPE		
ANALYTE	TEST	REFERENCE
Pentoxifylline	0.2168	0.1516
M-I	0.0874	0.1003
M-V	0.5937	0.1541

- c. The coefficients of variation for the amounts found for the QC analyses using the analytical method were greater than 20% for the middle concentrations (pentoxifylline, 20.9% for 100 ng/mL; MI, 28.1% for 200 ng/mL; MV, 28.4% for 500 ng/mL). Please explain these observations in light of the lower %CV's reported in the corresponding pre-study validation report and the corresponding QC data reported for the fasting and food studies.

The 1991 Conference Report entitled "Analytical Methods Validation: Bioavailability, Bioequivalence, and Pharmacokinetic Studies" states: "At least four of the six QC samples must be within 20% of their respective nominal values; two of the six QC samples (not both at the same concentration) may be outside the +/- 20% respective nominal value."

In all cases, the QC sample criteria were met. The %CV for the medium concentration samples were above 20% because of unusually low recoveries for three sample preps. The results for the three sets of data are clearly outliers. The analytical laboratory which processed these samples, has addressed this low recovery problem in a letter dated July 30, 1997 which is included here as Attachment # 6. In that letter it is noted that a possible extraction problem on the solid phase extraction discs might have contributed to the unusually low recoveries of the three analytes compared to the internal standard in these QC samples. If these data were not included, the %CVs would significantly lower to 11.0% for PTX at 100 ng/ml, 7.6% for B-OH at 200 ng/ml, and 8.3% for P-C4 at 500 ng/ml.

3. The dissolution testing has been found acceptable; no further data are required. Your proposed dissolution testing should be conducted in 900 mL of deionized water at 37° C using USP 23 apparatus 2 (paddle) at 75 rpm. Based on the data submitted, DBE agrees with the conditions of testing, however the following specifications are recommended:

DBE requests comparative dissolution data at 50 rpm if this information is available.

In the original ANDA, Upsher-Smith provided 12-tablet comparative dissolution data using the dissolution method provided in the Agency's guidance "Pentoxifylline Extended Release Tablets *In Vivo* Bioequivalence and *In Vitro* Dissolution Testing" dated December 22, 1995. Per the guidance method, comparative dissolution testing was generated using USP apparatus 2 (paddles) at 75 RPM. However, for purposes of finished product release and stability testing, Upsher-Smith proposed a different dissolution test method using USP apparatus 1 (baskets) at Upsher-Smith recognizes that per comment 3, the Agency is recommending that Upsher-Smith adopt the dissolution method outlined in the Agency's guidance for finished product and stability testing and reset the specifications around the data provided for Pentoxil™ bioequivalence study lot (lot #61037).

In evaluating the guidance method, Upsher-Smith has concluded that Pentoxil™ Tablets, as well as the innovator product, Trental®, show a tendency to adhere to the dissolution vessel walls. This adherence of the tablets causes uneven tablet agitation and thus less consistent release, which results in higher variability in the data. The high level of variability due to the paddle method could potentially mask variability produced from the manufacturing process.

For these reasons, Upsher-Smith proposes to conduct finished product and stability dissolution testing using apparatus 1 (baskets). In order to achieve a similar agitation rate of the tablets, it is typical to double the speed of the basket as compared to the established speed of the paddle method. Since the guidance method calls for paddles at 50 or 75 RPM, doubling the speed for a basket method results in a speed of 100 or 150 RPM. Upsher-Smith proposes that the method utilize 100 RPM with baskets, since these conditions ensure a discriminating method and are most typical of USP finished product dissolution test conditions.

Based on the comparative dissolution data submitted in the ANDA, the Agency recommended resetting the specifications as follows:

In switching from the guidance method of 75 RPM with paddles to the proposed method of 100 RPM with baskets, it is necessary to adjust the Agency's recommended specifications by shifting the specification ranges at the 8 and 12 hour time points up by 5%, as follows:

This shift is supported by the 12-tablet dissolution data for the Pentoxil™ biolot using the revised method, as well as dissolution data based on 6 tablets from each of seven different trial lots of Pentoxil™ Tablets. Graphs of the dissolution data for the Pentoxil™ biolot, as well as a graph of how the biolot compares to the seven trial lots, is included as Attachment #7. The frequency distribution of the dissolution data is provided with Attachment #7 as well.

Dr. Nicholas Fleischer
September 8, 1997
Page 8

Please note that in conducting dissolution testing of Pentoxil™ lot #61037 using the revised method, USP Chapter <724>, "Drug Release", Acceptance Table 1 was used. Data at 12 hours meet the criteria of level L₂ testing.

The revised finished product and stability dissolution test method as well as revised finished product analytical results form and revised stability data forms, are included with Attachment #8.

Upsher-Smith acknowledges DBE's request for comparative dissolution data at 50 rpm, if available, however, these data are not available at this time.

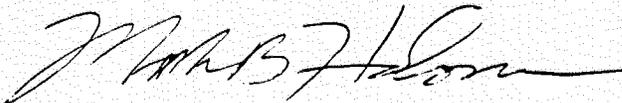
This Amendment #003 is being submitted in triplicate as a bioequivalence review copy, a chemistry review copy and an archival copy for incorporation into our file.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of this Amendment #003 has been submitted to the Minneapolis district FDA for their review as well.

Should you have any questions regarding the information contained herein, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612)449-7261.

Sincerely,

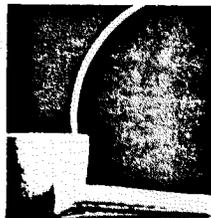
UPSHER-SMITH LABORATORIES, INC.



Mark B. Halvorsen, Pharm. D.
Manager
Clinical and Regulatory Affairs

enclosure

Labeling submitted
for approval - Marketing
review drafted 12/4/97
A. V. S.



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

12/4/97
FA noted
① To labeling reviewer,
then ② To Chem
reviewer for review
/S/

November 26, 1997

NEW CORRESP

NC

VIA FACSIMILIE: (301)827-4337

Frank O. Holcombe, Jr., Ph.D.
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Holcombe

**RE: ANDA 74-962; PENTOXIL™ (PENTOXIFYLLINE EXTENDED-RELEASE TABLETS, 400 MG)
FACSIMILE AMENDMENT #004 TO PROVIDE RESPONSE TO THE
OCTOBER 30, 1997 FACSIMILE DEFICIENCY LETTER**

Reference is made to Upsher-Smith Laboratories, Inc.'s pending ANDA 74-962 for the above referenced drug product.

Reference is also made to the Agency's October 30, 1997 minor deficiency letter received via facsimile.

In response to this deficiency letter, an amendment is submitted herewith to the above referenced ANDA. This amendment has been designated as a FACSIMILE AMENDMENT by the Agency. Each deficiency item enumerated in the Agency's letter is shown in bold print and has been addressed in the sequence that it was presented.

RECEIVED

NOV 28 1997

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX# 612-476-4026 Sales & Distribution 1-800-654-2209

GENERIC DRUGS

Chemistry Deficiency:

Labeling Deficiencies:

All labeling deficiencies enumerated by the reviewer have been incorporated into the Pentoxil™ package insert. To facilitate review of this amendment, and in accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the revised, proposed package insert (Rev. 1197) with the last submission (Rev 0497), is provided as Attachment #2. The final printed package insert is provided as Attachment #3. Twelve copies of the final printed package insert are included in Attachment #3 of the archival copy of this Amendment.

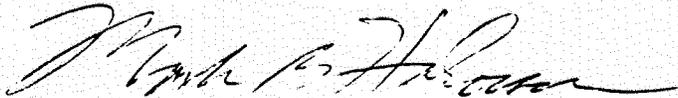
This Amendment #004 is being submitted via facsimile, as directed in the Agency's deficiency letter. A hard copy of this Amendment is also being submitted in duplicate for incorporation into our file.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of this correspondence has been submitted to the Minneapolis District FDA for their information as well.

Should you have any questions regarding the information contained herein, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612)449-7261.

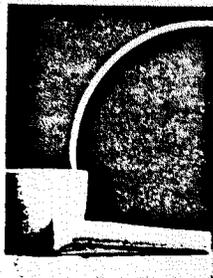
Sincerely,

UPSHER-SMITH LABORATORIES, INC.



Mark B. Halvorsen, Pharm.D.
Manager, Clinical and Regulatory Affairs

enclosures



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

January 15, 1999

FEDERAL EXPRESS

AM

Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
HFD-600
Rockville, MD 20855-2773

**RE: ANDA 74-962
Pentoxil™ (Pentoxifylline Extended-release Tablets, 400mg)
Response to the January 13, 1998 and April 3, 1998 deficiency letters and
January 7, 1999 telephone communications**

Dear Mr Sporn:

Reference is made to the Upsher-Smith Laboratories, Inc. pending Abbreviated New Drug Application, 74-962, for Pentoxil™ (Pentoxifylline Extended-release Tablets, 400mg).

Reference is also made to the January 6, 1999 telephone communication with Ms. Lizzie Sanchez, Assistant to the Director for the Division of Bioequivalence, eliminating the requirement for a new bioequivalence study.

Finally, reference is made to the January 6, 1999 telephone communication with Mr. Tim Ames, Project Manager, Division of Chemistry, recommending that Upsher-Smith request reclassification of the amendment from MAJOR to MINOR with a Priority Review Status.

RECEIVED

JAN 19 1999

GENERIC DRUGS

UPSHER-SMITH

Douglas L. Sporn
January 15, 1999
Page 2

In response to the deficiency letters, dated January 13, 1998 and April 3, 1998, an amendment is submitted herewith to the above referenced ANDA. The deficiency letters have been included for reference and may be found in Attachments 1 and 2.

Upsher-Smith agrees to, and has provided in this amendment, all the changes and information requested in the deficiency letters. The amendment also includes minor updates to the CMC section to remain consistent with compendial changes for two raw materials. In addition, an identification method was revised to incorporate a recommendation provided by the District FDA Office.

The following Attachments are included in this amendment:

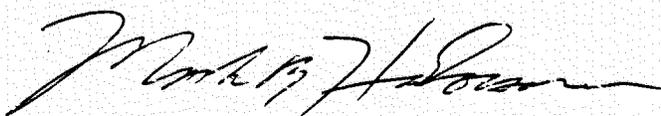
- Attachment 1:** Division of Bioequivalence deficiency letter dated January 13, 1998 and Upsher-Smith response.
- Attachment 2:** Division of Chemistry deficiency letter dated April 3, 1998 and Upsher-Smith response
- Attachment 3:** CMC Update

In addition, Upsher-Smith certifies that no substantive changes, other than those included in this amendment, have been made to the labeling or Chemistry, Manufacturing and Controls data or any other part of the application that would affect approval.

It is our understanding that this Amendment concludes the responses to all deficiency questions, therefore Upsher-Smith Laboratories, Inc. anticipates a timely approval.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of this Amendment (#005) has been submitted to the Minneapolis District FDA for their information. Should you have any questions regarding this Amendment or require additional information, please contact Cindy Farner, Sr. Regulatory Affairs Specialist at (612) 449-7267.

Sincerely,
UPSHER-SMITH LABORATORIES, INC.



Mark B. Halvorsen, Pharm D.
Manager, Clinical and Regulatory Affairs

Douglas L. Sporn
January 15, 1999
Page 3

enclosure

cc:

Tim Ames
Project Manager
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
HFD-617
Rockville, MD 20855-2773



DEPARTMENT OF HEALTH AND HUMAN SERVICE

Public Health Service

Food and Drug Administration
Detroit District Office
Central Region
1680 East Jefferson Avenue
Detroit, MI 48207-3178
Telephone: (313) 226-4260
FAX: (313) 226-3078

March 15, 1999

Luchia Tang HFD-647
Food and Drug Administration
ANDA Review Branch IV
Room 279, Bldg. MPN2
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855-2773

Dear Ms. Tang:

On February 8, 1999 the Detroit District of FDA received a FAX from Upsher-Smith addressing the concerns we had regarding ANDA 74-962 for Pentoxifylline Extended Release Tablets 400 mg/tab.

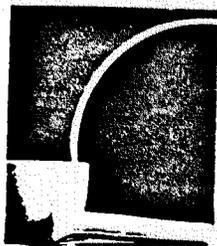
- A. In the method for the assay of the raw material, a stock standard was prepared with the standard in 500 mL of deionized water. Our analyst had difficulty dissolving the method and suggested using a more dilute stock standard. The firm agreed and has written, in the 15, directions to use 50 mg in 1000 mL of deionized water. We find this change acceptable.
- B. The determination for related substances by thickness of the The method did not specify the 11 has addressed this oversight and describes the This addition is acceptable.
- C. The method for the preparation of the sample solution heated the sample composite, in mobile phase, to minutes followed by the analyst found this not adequate for complete dissolution of the active ingredient. The firm has agreed to a modification of the method to heat the powdered sample, in mobile phase, for approximately followed by minutes and mechanically shaking for approximately to enhance sample dissolution. The method is acceptable.
- D. The Uniformity of Dosage method lacked details for volume and dilutions to be used. The firm modified the method to give the directions necessary to perform the analysis. The method is acceptable.

I have notified Upsher-Smith that I was sending this letter to you and that we feel that they have met the approval of the Detroit District.

Sincerely,

Shirley A.L. Li
ANDA Method Validations Team Leader

cc: Sharon Thoma NDA/ANDA Pre-Approval Mgr. Min. District HFR-CER
NDA/ANDA File



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

TELEFAX / FEDERAL EXPRESS

March 12, 1999

NDA ORIG AMENDMENT

N/A

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**RE: ANDA 74-962; Pentoxil™ (Pentoxifylline Extended-release Tablets, 400 mg)
Minor Amendment #006 to Provide Response to the FDA March 2, 1999 Deficiency
Letter Containing FDA District Laboratory Method Validation Comments**

Dear Mr. Sporn:

Reference is made to the Upsher-Smith Laboratories, Inc. pending ANDA 74-962 for the above referenced drug product.

Reference is also made to the Agency's deficiency letter dated March 2, 1999 containing FDA Detroit District Laboratory comments regarding the Upsher-Smith method validations.

Upsher-Smith provides the following responses to the concerns raised in the March 2, 1999 deficiency letter. Upsher-Smith satisfactorily resolved and obtained concurrence from the Detroit District Laboratory regarding the acceptability of the method revisions presented. This amendment has been designated as a **MINOR AMENDMENT** by the Agency. Each deficiency item reiterated below in bold type, followed by the Upsher-Smith response, is addressed in the sequence presented in the deficiency letter.

Drug Substance

- a. **Assay for Pentoxifylline and**

Dosage Form

a. Assay for Pentoxifylline: Method QS-254-04

The method calls for heating a portion of the sample composite in 180 mL of mobile phase at 60°C for 30 minutes followed by sonication for 15 minutes. The chemist found this treatment inadequate to completely disperse the powder and fully release the drug. Initially, by following the method as written, duplicate sample results differed by over 4%. A second pair of duplicate samples heated for approximately 75 minutes, sonicated approximately 45 minutes and shaken for 30 minutes gave results within 1%

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration
March 12, 1999
Page 3

agreement. Although the powder in these solutions was not totally dispersed, there was much less clumping of the sample material. The method needs to be modified to assure the initial sample solution contains little—or preferably, no—clumped sample material.

As evidenced by the acceptable results obtained during the original Upsher-Smith method validation, Upsher-Smith is persuaded that the current methodology, with more detailed instructions, is acceptable. However, to minimize the delay in obtaining FDA approval for this product, Upsher-Smith has decided to adopt the modifications suggested by the FDA District Laboratory.

Therefore, the sample preparation instructions have been modified to include heating the powdered sample in mobile phase for approximately _____ minutes, followed by _____ approximately _____ minutes and mechanically shaking for approximately _____ minutes to enhance sample dissolution, as specified in the FDA District Laboratory comments. In addition, greater detail is provided regarding the initial addition of the mobile phase to the powdered sample, to ensure consistency. A copy of the revised method, incorporating these sample preparation changes (in addition to the revisions discussed elsewhere) is attached. The method validation protocol and report addenda validating the sample preparation modifications are provided following the copy of test method _____ 05.

b. Uniformity of Dosage: Method

The cited method is a general content uniformity method and lacks details as to what volume or dilutions are to be used for pentoxifylline tablets. Two phone calls were needed to obtain the necessary information. This information should be incorporated into the method.

As noted above under “assay for Pentoxifylline”, special care was taken to ensure complete sample dissolution. It was observed that after the powdered samples were allowed to sit overnight, there was little or no clumping of the sample material and the shaking step mentioned above was omitted.

As indicated, method _____ 0 is a general content uniformity method. The method, which has been subsequently revised to delete references limiting the application to “Process Validation”, refers the analyst to the assay method listed on the specification form. The finished product release testing specification form (i.e., Pentoxil [Pentoxifylline Extended-release Tablets, 400mg] Analytical Results Form) lists both methods _____ and _____ for content uniformity testing. Therefore, Upsher-Smith has incorporated specific sample preparation instructions for the content uniformity testing in the assay method _____, to satisfy the concerns regarding insufficient instructions.

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration
March 12, 1999
Page 4

Due to anticipated time constraints for routine analytical testing during commercial production as well as the 24-hour stability limitation on standards and samples, Upsher-Smith chooses not to implement the overnight sample preparation suggested by the FDA District Laboratory. However, the same recommended sample preparation revisions provided for the finished dosage form assay have been incorporated for the content uniformity analysis. Copies of the revised methods, _____ and _____ incorporating these changes (in addition to the revisions discussed elsewhere) are attached.

Upsher-Smith is providing method revisions to accommodate each of the concerns identified by the FDA District Laboratory addressed in the March 2, 1999 deficiency letter. Upsher-Smith considers these method revisions to have adequately resolved the method validation observations and has obtained verbal concurrence from the FDA Detroit District Laboratory. Therefore, Upsher-Smith is submitting this amendment to update our ANDA with the revised test methods.

Upsher-Smith acknowledges the dissolution method parameters and specifications provided by the Division of Bioequivalence. Upsher-Smith has already incorporated the specified dissolution testing into our stability and quality control programs applicable to this product.

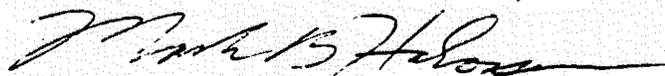
This Amendment #006 is being submitted in duplicate for incorporation into our file.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of this amendment has been submitted to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of this amendment.

It is our understanding that resolution of the methods validation issues is the only outstanding item delaying approval of this product, therefore, Upsher-Smith requests expeditious review of this amendment and prompt approval of our application. If there are any questions regarding this amendment or other aspects of our application, please contact Cindy Farnier, Senior Regulatory Affairs Specialist at (612) 449-7267.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.



Mark B. Halvorsen, Pharm.D.
Manager, Clinical and Regulatory Affairs

Enclosures