* The in each tablet consists of the following components, %W/W: D&C Red No. 27 Aluminum Lake, ; FD&C Blue No. 1 Aluminum Lake, C . Hydroxypropyl Methylcellulose, USP, Polyethylene Glycol, NF, Polysorbat NF, Titanium Dioxide, USP,

IN VITRO COMPARATIVE DISSOLUTION TESTING

The dissolution results for the test and reference products under different dissolution media using USP 23 apparatus 2 (Paddle) at indicated that the dissolution profiles for the test and reference products are comparable. The dissolution profiles of the test and reference drug were investigated using water, buffer (pH 1-1.5), e buffer (pH 4-4.5), buffer (pH 6-6.5), and : buffer (pH 7-7.5) and are shown in Tables 29-33. Water was selected as the dissolution media for routine testing.

OVERALL COMMENTS

1. The firm's single-dose bioequivalence study under fasting conditions demonstrated that the test product, Pentoxifylline 400 mg Extended Release Tablets and the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets are bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} are within of the acceptable range of 80-125% for Pentoxifylline, MI and MV.
2. In the single-dose bioequivalence study under fasting conditions the data for pentoxifylline showed that the C_{max} values for 14 out of 38 subjects (#'s 4, 6, 9, 12, 15, 17, 23, 25, 26, 30, 32, 36, 38, and 40) during test and/or reference treatment were the first nonzero concentrations. Therefore, data from these 14 subjects were deleted and the statistics were recalculated by the reviewer. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} remained within the acceptable range of 80-125%.
3. The firm's single-dose bioequivalence study under non-fasting conditions demonstrated that the test product, Pentoxifylline 400 mg Extended Release Tablets and the reference listed product, Hoechst-Roussel's Trental® 400 mg Extended Release Tablets are bioequivalent. The ratios of the test LSMEAN to the reference LSMEAN for AUC_{0-t}, AUC_{0-inf} and C_{max} are within the acceptable range of 0.8-1.2 for Pentoxifylline, MI and MV.
4. In the single-dose bioequivalence food study the data for pentoxifylline showed that the C_{max} values for 8 out of 24 subjects (#'s 1, 4, 11, 14, 16, 18, 19, and 24) in the fasting leg (test product treatment) were the first nonzero concentrations.
5. In the multiple-dose bioequivalence study the data for pentoxifylline showed that the C_{max} values for 10 out of 25 subjects (#'s 1, 5, 6, 11, 12, 13, 14, 15, 22, and 25) during test and/or reference treatment were the first nonzero concentrations. Therefore, data from these 10 subjects were deleted and the statistics were recalculated by the reviewer. The 90% confidence interval for the log-transformed C_{max} was 94.4-132.2%.
6. Also, in the multiple-dose bioequivalence study the data for MI showed that the C_{max} values for two out of 25 subjects (#'s 1 and 6) for the test treatment were the first nonzero

concentrations. Therefore, data from these two subjects were deleted and the statistics were recalculated by the reviewer. The 90% confidence intervals for the log-transformed $AUC_{0-\tau}$ and C_{max} remained within the acceptable range of 80-125%.

7. For the multiple-dose study the firm stated that there were no significant differences between concentrations at time 48 hr and 72 hr, and thus steady-state was reached at the time when the measurement of $AUC_{0-\tau}$ 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.

8. In the multiple-dose study 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). The firm should 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.

9. The dissolution testing conducted by Upsher-Smith Laboratories, Inc. on the test product, Pentoxifylline 400 mg Extended Release Tablets (Lot #61037) is acceptable.
The firm proposes that the dissolution testing should be conducted in 900 mL of deionized water at 37° C using USP 23 apparatus 2 (paddle) at nd that the test product should meet the following specifications:

Based on the data submitted, the Division of Bioequivalence recommends the following specifications:

The Division of Bioequivalence requests firm to submit comparative dissolution data at rpm if this information is available.

10. No long term stability data was submitted on the analytes stored in frozen plasma over the period of time corresponding to the time and temperature at which the frozen plasma samples were actually stored in the bioequivalence studies.

11. The test product used for the fasting, food and steady state studies, and the dissolution studies were from the same batch (#61037).

12. The pharmacokinetic parameters and statistics were calculated by the reviewer and were in satisfactory agreement with what the firm reported.

DEFICIENCIES

1. In the multiple-dose bioequivalence study the data for pentoxifylline showed that the C_{max} values for 10 out of 25 subjects (#'s 1, 5, 6, 11, 12, 13, 14, 15, 22, and 25) during test and/or reference treatment were the first nonzero concentrations. Therefore, data from these 10 subjects were deleted and the statistics were recalculated by the reviewer. The

90% confidence interval for the log-transformed C_{max} was 94.4-132.2. The Division of Bioequivalence considers these results to be unacceptable for use in bioequivalence determination. For future studies, the sponsor may consider a sampling time of 0.25 hour.

2. No long term stability data was submitted on the analytes stored in frozen plasma. Stability data should be submitted on the analytes (pentoxifylline, MI and MV) stored in frozen plasma over the period of time corresponding to the time and temperature at which the frozen samples were actually stored in the bioequivalence studies.

RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study, and the single-dose, fed/fasted bioequivalence study conducted by Upsher-Smith Laboratories, Inc. on its Pentoxifylline Extended Release 400 mg Tablet, lot #61037 comparing it to Hoechst-Roussel's Trental 400 mg tablet, lot #0780665 have been found incomplete due to deficiency number 2 by the Division of Bioequivalence.

2. The bioequivalence study (multiple dose, fasting conditions) conducted by Upsher-Smith Laboratories, Inc. on its Pentoxifylline Extended Release 400 mg Tablet, lot #61037, comparing it to Hoechst-Roussel's Trental 400 mg tablet, lot #0780665, has been found unacceptable by the Division of Bioequivalence due to deficiency #1.

3. The dissolution testing conducted by Upsher-Smith Laboratories, Inc. on its Pentoxifylline Extended Release 400 mg Tablet has been found acceptable. The firm's proposed dissolution testing should be incorporated into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deionized water at 37° C using USP 23 apparatus 2 (paddle) at The test product should meet the following tentative specifications:

The firm should be advised of comments 7-9, and the deficiencies and recommendations.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang /S/ 6/30/97
FT INITIALED YCHuang

Concur: /S/ Date: 6/30/97
Nicholas M. Fleischer, Ph.D.
Director, Division of Bioequivalence

cc:

JEC/060397/WP#74962sd.996

Table 29. In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline
Dose Strength: 400 mg
ANDA No.: 74-962
Firm: Upsher-Smith Labs
Submission Date: 9/17/96
File Name: 74962sd.996

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 75 No. Units Tested: 12
Medium: Deionized Water; Volume: 900 mL
Specifications:

Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 61037 Strength (mg) 400			Reference Product Lot # 0780665 Strength(mg) 400		
	Mean	Range	%CV	Mean %	Range	%CV
1	16.4		4.5	14.6		2.5
2	25.4		4.3	22.6		2.3
4	39.6		3.9	35.4		2.5
6	51.2		3.8	46.7		2.7
8	61.8		3.8	57.1		2.8
10	71.3		3.7	66.8		2.7
12	80.2		3.8	75.4		2.7
14	87.6		3.8	83.3		2.4
16	93.5		3.5	90.2		2.1
18	98.0		3.2	95.1		2.3
20	100.4		3.0	100.0		1.9
22	102.3		2.8	103.8		1.8

Table 30. In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline
Dose Strength: 400 mg
ANDA No.: 74-962
Firm: Upsher-Smith Labs
Submission Date: 9/17/96
File Name: 74962sd.996

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 75 No. Units Tested: 12
Medium: Potassium Chloride Buffer (pH 1-1.5); Volume: 900 mL
Specifications:

80%

Reference Drug: Hoechst-Roussel's Trental™ 400 mg Extended Release Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 61037 Strength (mg) 400			Reference Product Lot # 0780665 Strength(mg) 400		
	Mean	Range	%CV	Mean %	Range	%CV
1	15.8		3.0	14.4		3.2
2	24.6		2.9	22.6		3.4
4	38.6		3.2	36.1		3.5
6	50.3		3.2	48.2		2.7
8	61.0		3.2	59.3		3.3
10	70.5		3.4	69.7		3.3
12	78.9		3.1	78.9		3.1
14	86.5		2.9	87.1		2.9
16	92.6		2.6	94.1		2.8
18	96.9		1.9	98.7		3.6
20	100.5		2.2	102.9		1.8
22	102.6		2.1	105.5		1.3

Table 31. In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline
Dose Strength: 400 mg
ANDA No.: 74-962
Firm: Upsher-Smith Labs
Submission Date: 9/17/96
File Name: 74962sd.996

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 75 No. Units Tested: 12
Medium: Sodium Acetate Buffer (pH 4-4.5); Volume: 900 mL
Specifications:

Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Assay Methodology: HPLC with UV Detection

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 61037 Strength (mg) 400			Reference Product Lot # 0780665 Strength(mg) 400		
	Mean	Range	%CV	Mean %	Range	%CV
1	15.6		2.4	31.0		19.5
2	24.7		22.4	39.4		15.5
4	38.6		2.2	52.7		11.6
6	49.8		2.1	64.0		9.5
8	60.0		2.1	73.9		7.7
10	69.3		2.0	82.6		6.3
12	77.7		2.0	90.0		4.7
14	85.1		1.8	95.8		3.2
16	91.4		1.9	99.7		2.4
18	95.9		1.6	102.2		1.7
20	99.9		1.6	104.3		1.2
22	102.7		2.0	105.2		1.2

Table 32. In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline
Dose Strength: 400 mg
ANDA No.: 74-962
Firm: Upsher-Smith Labs
Submission Date: 9/17/96
File Name: 74962sd.996

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 75 No. Units Tested: 12
Medium: Phosphate Buffer (pH 6-6.5); Volume: 900 mL
Specifications:

Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 61037 Strength (mg) 400			Reference Product Lot # 0780665 Strength(mg) 400		
	Mean	Range	%CV	Mean %	Range	%CV
1	15.1		2.9	14.4		6.1
2	23.7		2.2	22.6		4.4
4	37.3		1.8	35.7		3.9
6	48.4		1.5	47.1		3.5
8	58.4		1.5	57.5		3.4
10	67.3		1.5	67.2		3.2
12	75.5		1.5	76.6		2.7
14	83.0		1.5	84.7		2.5
16	89.2		1.2	91.6		2.1
18	94.4		1.4	96.7		2.2
20	97.7		1.9	101.3		2.0
22	100.9		1.4	105.7		1.1

Table 33. In Vitro Dissolution Testing

Drug (Generic Name): Pentoxifylline
Dose Strength: 400 mg
ANDA No.: 74-962
Firm: Upsher-Smith Labs
Submission Date: 9/17/96
File Name: 74962sd.996

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 75 No. Units Tested: 12
Medium: Phosphate Buffer (pH 7-7.5): Volume: 900 mL
Specifications:

Reference Drug: Hoechst-Roussel's Trental® 400 mg Extended Release Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 61037 Strength (mg) 400			Reference Product Lot # 0780665 Strength(mg) 400		
	Mean	Range	%CV	Mean %	Range	%CV
1	15.5		3.3	13.6		2.8
2	24.2		3.0	21.5		2.9
4	37.6		2.9	34.1		3.8
6	48.3		2.7	45.1		4.3
8	58.1		2.6	55.4		4.3
10	66.9		2.4	64.8		4.3
12	75.0		2.4	73.7		4.3
14	82.0		2.3	81.8		4.2
16	87.9		2.2	88.9		3.9
18	93.1		2.3	94.7		3.7
20	97.1		2.1	100.1		3.0
22	99.7		2.0	104.0		2.3

Page(s) 10

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Table 1. Comparison of mean AUC_{0-t} values for pentoxifylline, MI, and MV and the corresponding 90% confidence intervals under fasting conditions obtained using the / assay and the combined method.

Parameter						
	Test	Reference	Test	Reference	Test	Reference
PENTOXIFYLLINE						
Arithmetic Mean	497.7	533.2	540.5	565.4	1.09	1.06
Arith Mean SD*	222.1	271.1	246.7	282.7	—	—
LSMeans	498.2	535.4	541.4	567.6	1.09	1.06
Geometric LSMean	450.9	476.7	487.8	506.7	1.08	1.06
90% Conf. Int.	84.6-105.8		87.4-106.0		—	—
MI						
Arithmetic Mean	2282.6	2354.4	2502.5	2512.6	1.10	1.07
Arith Mean SD*	918.9	1058.1	893.2	1046.2	—	—
LSMeans	2285.8	2362.7	2505.6	2522.2	1.10	1.07
Geometric LSMean	2117.8	2146.9	2358.9	2315.3	1.11	1.08
90% Conf. Int.	89.5-108.8		92.2-112.5		—	—
MV						
Arithmetic Mean	5715.7	5620.0	6208.2	6029.7	1.09	1.07
Arith Mean SD*	1362.0	1063.2	1312.6	934.10	—	—
LSMeans	5699.2	5610.8	6191.6	6021.0	1.09	1.07
Geometric LSMean	5546.0	5514.8	6059.2	5949.9	1.09	1.08
90% Conf. Int.	95.8-105.5		98.4-105.3		—	—

Table 2. Comparison of mean AUC_{0-t} values for pentoxifylline, MI, and MV and the corresponding 90% confidence intervals under fast/fed conditions obtained using the assay and the combined method

Parameter	Test Fed	Test Fast	Ref Fed	Test Fed	Test Fast	Ref Fed	Test Fed	Test Fast	Ref Fed
PENTOXIFYLLINE									
Arithmetic Mean	655.6	500.7	671.4	—	—	—	—	—	—
Arith Mean SD*	300.6	229.5	280.4	—	—	—	—	—	—
LSMeans	655.6	507.0	671.4	687.9	568.6	689.5	1.05	1.12	1.03
Geometric LSMean	599.6	466.0	624.2	633.9	524.4	642.6	1.06	1.12	1.03
MI									
Arithmetic Mean	2799.9	2512.7	2668.4	—	—	—	—	—	—
Arith Mean SD*	1078.1	925.6	888.5	—	—	—	—	—	—
LSMeans	2799.9	2512.7	2668.4	2853.7	2616.1	2780.0	1.02	1.04	1.04
Geometric LSMean	2602.9	2347.1	2512.7	2666.4	2451.1	2625.3	1.02	1.04	1.04
MV									
Arithmetic Mean	5282.0	5344.8	5144.9	—	—	—	—	—	—
Arith Mean SD*	1109.7	1134.4	1083.0				—	—	—
LSMeans	5282.0	5344.8	5144.9	5542.4	5782.6	5368.4	1.05	1.08	1.04
Geometric LSMean	5169.8	5224.0	5021.9	5437.1	5664.9	5257.9	1.05	1.08	1.05

ANDA 74-962

JUL 10 1997

Upsher-Smith Laboratories, Inc.
Attention: Mark S. Robbins
14905 23rd Avenue, North
Minneapolis, MN 55447-4709

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on September 17, 1996, for Pentoxifylline Extended Release Tablets, 400 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The single-dose fasting study, and the single-dose fed/fasted study have been found incomplete as no long term stability data was submitted on the analytes stored in frozen plasma. Stability data should be submitted on each analyte (pentoxifylline, MI and MV) stored in frozen plasma over a period of time equivalent to the longest time between first sample withdrawal, and final sample analysis, and at the temperature at which the frozen samples were actually stored in the bioequivalence studies.

2. The multiple dose, fasting study has been found unacceptable by the Division of Bioequivalence (DBE) for the following reasons:

   a. The data for pentoxifylline showed that the Cmax values for 10 out of 25 subjects (#'s 1, 5, 6, 11, 12, 13, 14, 15, 22, and 25) during test and/or reference treatment were the first non-zero concentrations. DBE has found that this particular situation results in undependable results; therefore, data from these 10 subjects were deleted and the statistics were recalculated by the reviewer. The 90% confidence interval for the log-transformed Cmax was 94.4-132.2. DBE considers these results to be unacceptable for use in bioequivalence determination. For future studies, consider adding a sampling time at 0.25 hour.

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 $AUC_{(0-\tau)}$ 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.

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.

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 Based on the data submitted, DBE agrees with the conditions of testing, however the following specifications are recommended:

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

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

/ \

cc:

File

Chez, CSI

BIO-LETTER INCOMPLETE

Endorsements:

J. Chaney
Y.C. Huang
L. Sanchez /S/

DRAFT LSG June 30, 1997 X:\WPFILE\BIO\74962BIO.DST
REVISED ALS 7/1/97 x:\WPFILE\BIO\FINAL\74962BIO.DST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-962

JUL 10 1997

Upsher-Smith Laboratories, Inc.
Attention: Mark S. Robbins
14905 23rd Avenue, North
Minneapolis, MN 55447-4709

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on September 17, 1996, for Pentoxifylline Extended Release Tablets, 400 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The single-dose fasting study, and the single-dose fed/fasted study have been found incomplete as no long term stability data was submitted on the analytes stored in frozen plasma. Stability data should be submitted on each analyte (pentoxifylline, MI and MV) stored in frozen plasma over a period of time equivalent to the longest time between first sample withdrawal, and final sample analysis, and at the temperature at which the frozen samples were actually stored in the bioequivalence studies.

2. The multiple dose, fasting study has been found unacceptable by the Division of Bioequivalence (DBE) for the following reasons:

   a. The data for pentoxifylline showed that the Cmax values for 10 out of 25 subjects (#'s 1, 5, 6, 11, 12, 13, 14, 15, 22, and 25) during test and/or reference treatment were the first non-zero concentrations. DBE has found that this particular situation results in undependable results; therefore, data from these 10 subjects were deleted and the statistics were recalculated by the reviewer. The 90% confidence interval for the log-transformed Cmax was 94.4-132.2. DBE considers these results to be unacceptable for use in bioequivalence determination. For future studies, consider adding a sampling time at 0.25 hour.

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 Cmin values are significantly different from zero.

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.

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 n. Based on the data submitted, DBE agrees with the conditions of testing, however the following specifications are recommended:

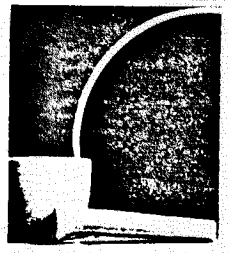
DBE requests comparative dissolution data at rpm if this information is available.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

July 18, 1997

NAI
Will Resm. (11
/S/
7/25/97

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence
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

NEW SUBMISSION

Dear Dr. Fleischer:

RE: ANDA 74-962
Pentoxil™ (Pentoxifylline Extended-release Tablets, 400 mg)
Intent to File Major Amendment

Reference is made to the Division of Bioequivalence's deficiency letter dated July 10, 1997 (see attached) which provides comments to the above referenced ANDA. Upsher-Smith Laboratories, Inc. wishes to avail ourselves of the opportunity per 21 CFR 314.120(a) of filing a major amendment to the application, addressing the items cited in the above-referenced letter.

This correspondence is being submitted in duplicate for incorporation into our file.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Dianne L. Gibbs

Dianne L. Gibbs, RAC
Regulatory Affairs Specialist

RECEIVED
JUL 23
GENERIC DRUGS

enclosure

Madeline
7-25-97