CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-337/S-013

Trade Name: Acetaminophen Uniserts Rectal Suppositories

Generic Name: acetaminophen

Sponsor: Upsher-Smith Laboratories Inc.

Approval Date: August 26, 1992

Purpose: Provides for a new 80 mg dosage strength

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-337/S-013

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-337/S-013

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-337/S013

AUG 26 1992

April 7, 1992
Submission was used as Base document. All earlier submissions were submitted to Generic Drugs ANDA (b) (4) (b) (5)

Upsher-Smith Laboratories Inc.
14905 23rd Avenue North
Minneapolis, Minnesota 55447

Attention: Harvey M. Arbit, Pharm. D.
Director of Scientific Affairs

Dear Dr. Arbit:

Please refer to your supplemental new drug application dated April 16, 1986 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acetaminophen Uniserts Rectal Suppositories. B. Friedman Sally Banne

Reference is also made to your submissions dated September 19, 1986, September 25, 1987, June 19, and September 13, 1991.

The supplement provides for a new 80 mg dosage strength.

We have completed our review of this supplemental application including the draft labeling which was submitted on June 19, 1991 (package insert) and April 7, 1992 (carton and wrapper labels) and it is approved effective as of the date of this letter.

Please submit twelve copies of the final printed version of the FPL as soon as possible. This submission should be designated for administrative purposes as "FPL for approved supplemental NDA 18-337/S013". Approval of this labeling is not required before the labeling is used.

We have also received your letter of September 13, 1991 agreeing to the following Phase IV commitment:

> To design and perform a characterization study in children to show bioavailability of acetaminophen administered by rectal suppository versus an oral solution.

We ask that you submit completed results from this study within one year of the date of this letter.

Please submit the original of all communicatins regarding the Phase IV study to this Division with a copy to the Division of Drug Information Resources, HFD-80, since that Division is responsible for tracking Phase IV studies.

We also have the following recommendation regarding the manufacturing and controls portion of your application:

> The production stability studies should be done at 27°C rather than at 22°C. The 22°C study may also be done as a "fall-back" temperature in case of failure as the higher temperature. Also 15 - 30°C is not an acceptable definition of ambient temperature for stability purposes.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Pilot Drug Evaluation Staff Review Team
Center for Drug Evaluation and Research

John G. Harter, M.D.
Director
8-26-92

Victoria G. Hale, Ph.D.
Pharmacokineticist

Charlotte A. Yaciw 8-26-92

Charlotte A. Yaciw
Chemist

cc:
Orig NDA 18-337/S013
HFD-007 Div File
HFD-83(labeling)
HFD-8PSavino
HFD-007Review Team
HFD-232/ (with labeling)
HFC-130/JAllen
HFD-007/SBarnes/8/24/92
R/D Init. by: DPease/8-25-92
VHale/8/26/92
CYaciw/8-25-92

Paul Hillery 8-26-92
VHale 8-26-92 / EM 8/26/92
CAY 8-26-92

F/T by: DWolfe/8-26-92

Doc AP18337S012

Supplemental Approval

CENTER FOR DRUG EVALUATION AND RESEARCH

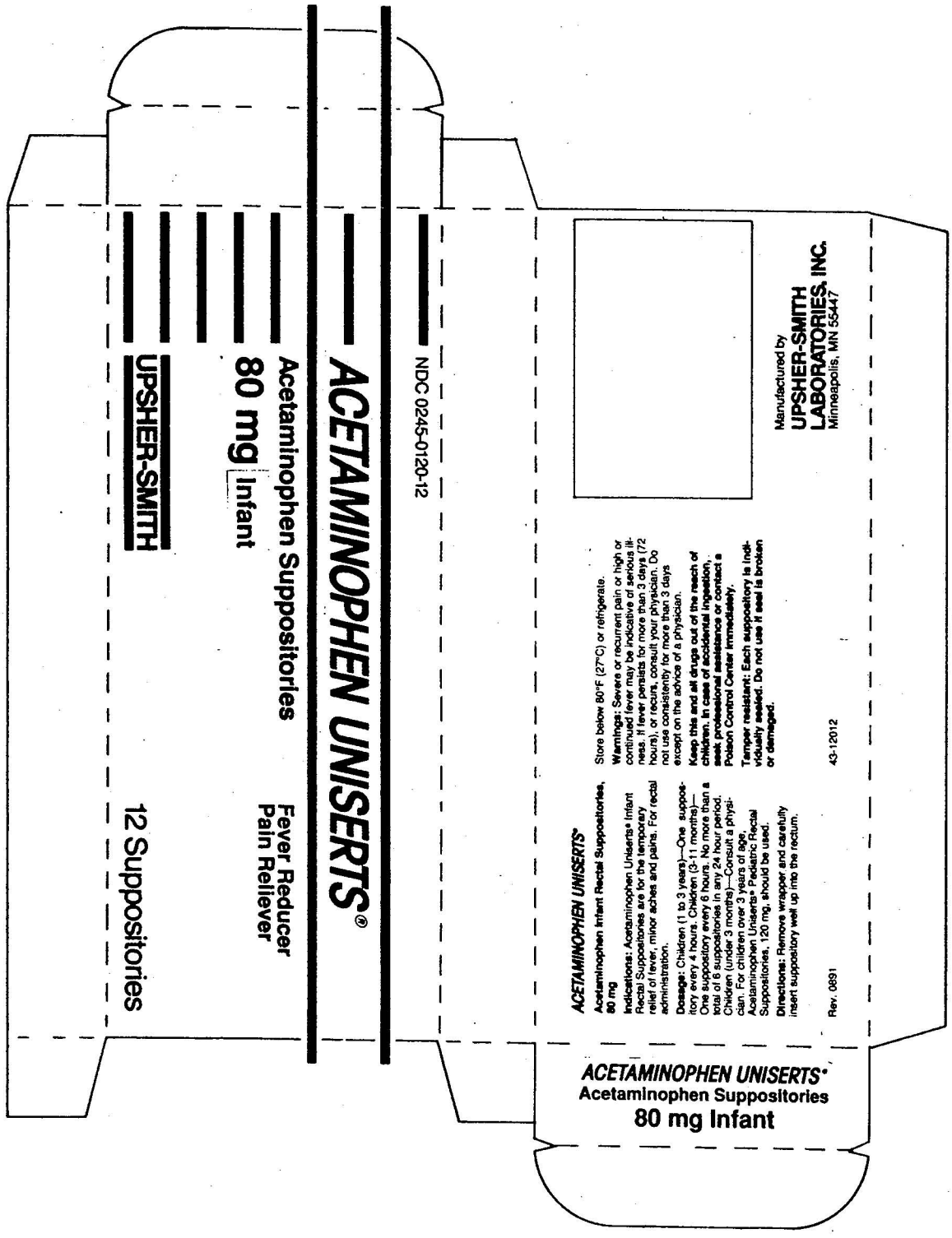
APPLICATION NUMBER:

18-337/S-013

LABELING

Acetaminophen Uniserts® 80 mg

Carton of 12 Suppositories



(b) (4)

Infants' Feverall® 80 mg Suppositories: Foil Samples
(Lot Number and Expiration Date are Printed on Foil Backing)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-337/S-013

MEDICAL REVIEW(S)

MAR 3 1 1997

Medical Officer's Review of NDA 18-337/S-013

NDA 18-337/S-013

Submission Dates: 9/30/92
Review Date: 3/31/97

Applicant:

Upsher-Smith Laboratories, Inc.
14905 23rd Avenue North
Minneapolis, MN 55447
(612) 473-4412

Drug:

Acetaminophen Uniserts Rectal Suppositories, 80 mg
(acetaminophen suppositories)

Pharmacologic Category:

Pain Reliever/Fever reducer - OTC

Submitted:

Supplement 13 provides for an additional strength (80 mg) of acetaminophen suppositories. The supplement was approved with draft labeling on August 26, 1992. The final printed labeling was submitted with changes made to the product labeling and identified as a supplement under 21 CFR 314.70(c).

Reviewer's comment:

The submission is not consistent with changes permitted under a Special Supplement 21 CFR 314.70(c). In addition, a number of deficiencies have been identified in the labeling and are listed below:

1. The name has been revised from "Acetaminophen Uniserts 80mg Suppositories" to "Infants' Feverall 80mg Suppositories."

Reviewer's comments:

This is not acceptable because the labeling no longer includes the statement of identity. In accordance with 21 CFR 201.61 (b) and (c), an accurate statement of the general pharmacological categories of the drug (i.e., pain reliever/fever reducer) must follow the established name. This statement should be presented in bold face type and be in a print size reasonably related to the most prominent printed matter on such panel. The established name should be "acetaminophen suppositories."

2. **INDICATIONS:** For the temporary relief of fever, minor aches and pains. For rectal administration.

Reviewer's comments:

The Indications section as written is potentially unclear. In accordance with the Center for Drug Evaluation and Research's OTC Analgesic Policy, the Indications section should be revised to read "For the temporary relief of occasional aches and pains, and for the temporary reduction of fever."

3. **WARNINGS:** Severe or recurrent pain or high or continued fever may be indicative of serious illness. If fever persists for more than 3 days (72 hours), or recurs, consult your physician. Do not use consistently for more than 3 days except on the advice of a physician. Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

Reviewer's comments:

The warning is not complete. If pain or fever persists, or gets worse, if new symptoms occur, or if redness or swelling is present, a physician should be consulted because these could be signs of a serious condition.

4. **Tamper resistant:** Suppositories are individually wrapped. Do not use if wrapper is opened or damaged.

Reviewer's comments:

The tamper-resistant packaging statement does not include an identifying characteristic as required in 21 CFR 211.132(c).

5. (b) (4) stored below 80°F (27°C).

Reviewer's comments: *The storage statement is potentially confusing. The statement should be revised to read: Store at 2°-27°C (35°-80°F).*

Recommendation:

The Final Printed Labeling is not acceptable because it is not in conformance with the approval letter for Supplement S-013. In addition, it is recommended that the deficiencies listed above be addressed.

Wiley A. Chambers, M.D.

cc: Orig NDA 18-337
HFD-550
HFD-560
HFD-105
HFD-830/Chem/Patel
HFD-550/CSO/Cook

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-337/S-013

CHEMISTRY REVIEW(S)

AUG 20 1992

Chemistry Review	1. Division HFD-007	2. NDA Number 18-337
3. Name and Address of Applicant Upsher-Smith Laboratories 14905 23rd Avenue North Minneapolis, MN 55441		4. Supplement Number SCS-013 Date (b) (4) SBarnes corrected see letter
5. Name of Drug Acetaminophen Unisert	6. Nonproprietary Name acetaminophen	
7. Supplement Provides for: addition of an 80 mg suppository		8. Amendment(s) AM 3-23-92 (FAX) AM 4-7-92 (FAX)
9. Pharmacological Category analgesic	10. How Dispensed OTC	11. Related Documents DMF (b) (4)
12. Dosage Form suppository, rectal	13. Potency(ies) 120 mg (approved); 80 mg (proposed)	
14. Chemical Name and Structure see USAN		

15. Comments

This application was originally submitted as ANDA (b) (4). It had various problems and it finally was decided to turn it into a supplement to the applicant's existing NDA hence the October 9, 1991 "submission" date. See the attached Review Notes for a summary of the information received. Note that the amendments referred to in the FAX documents were not received by the HFD-007 document room. On April 8, 1992 COMIS only listed one document, dated October 9, 1991, for this supplement number.

CGMP approval was requested on 11-14-91. The facilities were found acceptable on 2-28-92.

16. Conclusions and Recommendations

Issue an approval letter with the following recommendation. The production stability studies should be done at 27°C rather than at 22°C. The 22°C study may also be done as a "fall-back" temperature in case of failure at the higher temperature. Also 15 - 30°C is not an acceptable definition of ambient temperature for stability purposes.

17. Name	Signature	Date
Charlotte A. Yaciw	Charlotte A. Yaciw	4-8-92

/ / NDA #18-337 / / Div File / / C Yaciw / / S Barnes / / HFD-80

Doc ID: N18337S.012

J. McKeon 8/20/92

9 Pages have been Withheld as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-337/S-013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Acetaminophen
80 mg Pediatric Rectal Suppositories
NDA # (b) (4)
Reviewer: M. Chen
Wang # 1587f

NOV 12

Upsher-Smith Laboratories
Minneapolis, MN
Submission Date:
September 25, 1987

REVIEW OF DISSOLUTION DATA AND REQUEST OF WAIVER

The firm has previously conducted an acceptable bioequivalence study on Acetaminophen Uniserts^{R}, 120 mg Pediatric Rectal Suppositories, as compared to the reference product, Acephen^{R}, 120 mg Rectal Suppositories, manufactured by G & W Laboratories (NDA #18-337, submission dated June 25, 1982). Per 21 CFR 320.22 (d) (2), the firm has also requested a waiver of the in vivo bioavailability requirements for Acetaminophen, 80 mg Pediatric Rectal Suppositories (submission dated April 16 and September 19, 1986). The waiver request, however, was found incomplete by the Division of Bioequivalence.

In response to the comments made by the Agency, the firm has submitted further data on dissolution testing comparing its Acetaminophen suppository, 120 mg and 80 mg, with G & W Laboratories' Acetaminophen suppository, 80 mg, using the following conditions:

(i) Modified USP XXI apparatus I* at 75 rpm
900 ml of water at 37°
No. of samples: 12
Sampling time: 15, 30, 45 and 60 minutes

(ii) Modified USP XXI apparatus I* at 100 rpm
900 ml of water at 37°
No. of samples: 12
Sampling time: 15, 30, 45 and 60 minutes

(iii) Modified USP XXI apparatus I* at 75 rpm
900 ml of phosphate buffer (pH 7.2) at 37°
No. of samples: 12
Sampling time: 15, 30, 45 and 60 minutes

The results of the dissolution testings are attached.

*Modified U.S.P. XXI apparatus I

The make up of the apparatus is the same as U.S.P. XXI apparatus I, except that a special (b) (4) made by (b) (4) was employed. The (b) (4) fits the (b) (4) of the standard (b) (4) of U.S.P. XXI apparatus I.

This (b) (4) as (b) (4) described on pages 31 and 32 of his book (b) (4), is fabricated from (b) (4) with the same external dimensions as the official (b) (4).

Comment:

The dissolution profiles for the firm's 80 mg acetaminophen pediatric rectal suppositories have been found to be markedly different from those generated for its 120 mg rectal suppositories, regardless of the dissolution methodology used.

Recommendation:

The Division of Bioequivalence does not agree that the information submitted by Upsher-Smith Laboratories demonstrates that Acetaminopen Pedatric Rectal Suppositories, 80 mg, falls under Section 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in vivo bioequivalence study be denied. Accordingly, a bioequivalence study should be undertaken.

The firm should be informed of the recommendations.

Mei-Ling Chen

Mei-Ling Chen, Ph.D.
Division of Bioequivalence
Review Branch 2

RD INITIALED FPELSOR
FT INITIALED FPELSOR F. Pelsor

MChen/rw/10-21-87/Wang #1587f

cc: ANDA # (b) (4) original, HFN-230, HFN-200 (Hare), HFN-22 (Hooton), HFN-252 (Pelsor, Chen), Drug File

Results

Water, 75 rpm

Time (min)	Test Product (USL's 80 mg) Lot # 5139 Mean % Dissolved	Range	(CV)	Reference Product (USL's 120 mg) Lot # 5901 Mean % Dissolved	Range	(CV)
15	[redacted] (b) (4)		( )	[redacted] (b) (4)		( )
30			( )			( )
45			( )			( )
60			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

(G x D's 120 mg)

	Lot #			Lot # 6260-8		
15			( )	[redacted] (b) (4)		( )
30			( )			( )
45			( )			( )
60			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

Results — Water, 100 rpm

Time (min)	Test Product (USL's 80 mg) Lot # 5139 Mean % Dissolved	Range	(CV)	Reference Product (USL's 120 mg) Lot # 5901 Mean % Dissolved	Range	(CV)
15	[redacted] (b) (4)					
30						
45						
60						
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

(G & W's 120 mg)

Time (min)	Test Product Lot #	Range	(CV)	Reference Product Lot # 6260-8 Mean % Dissolved	Range	(CV)
15			( )	[redacted] (b) (4)		
30			( )			
45			( )			
60			( )			
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

Results — Phosphate buffer (pH 7.2), 75 rpm

Time (min)	Test Product (USL's 80 mg) Lot # 5139 Mean % Dissolved	Range	(CV)	Reference Product (USL's 120 mg) Lot # 5901 Mean % Dissolved	Range	(CV)
15	[redacted] (b) (4)					
30						
45						
60						
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )

Time (min)	Test Product (G & W's 120 mg) Lot # ____ Mean % Dissolved	Range	(CV)	Reference Product Lot # 6260-8 Mean % Dissolved	Range	(CV)
15	____	____	( )	[redacted] (b) (4)		
30	____	____	( )			
45	____	____	( )			
60	____	____	( )			
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )
____	____	____	( )	____	____	( )

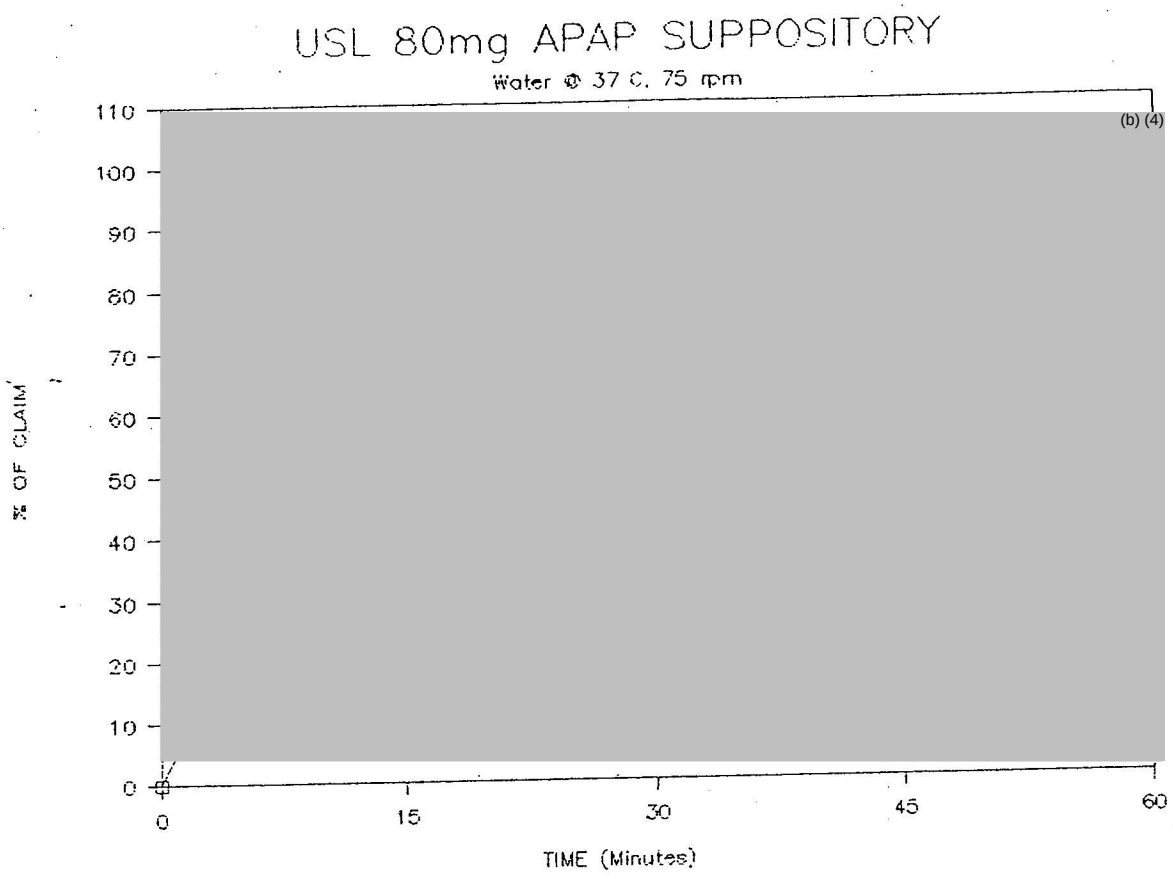
NDA # (b) (4) A-003

CONDITIONS: WATER @ 37 C, 75 RPM
SAMPLE: USL'S ACETAMINOPHEN, 80 MG SUPPOSITORY

LOT # 5139

	15 MINUTES (MG)	30 MINUTES (MG)	45 MINUTES (MG)	60 MINUTES (MG)
(b) (4)				
AVERAGE				
STD DEV				
%RSD				

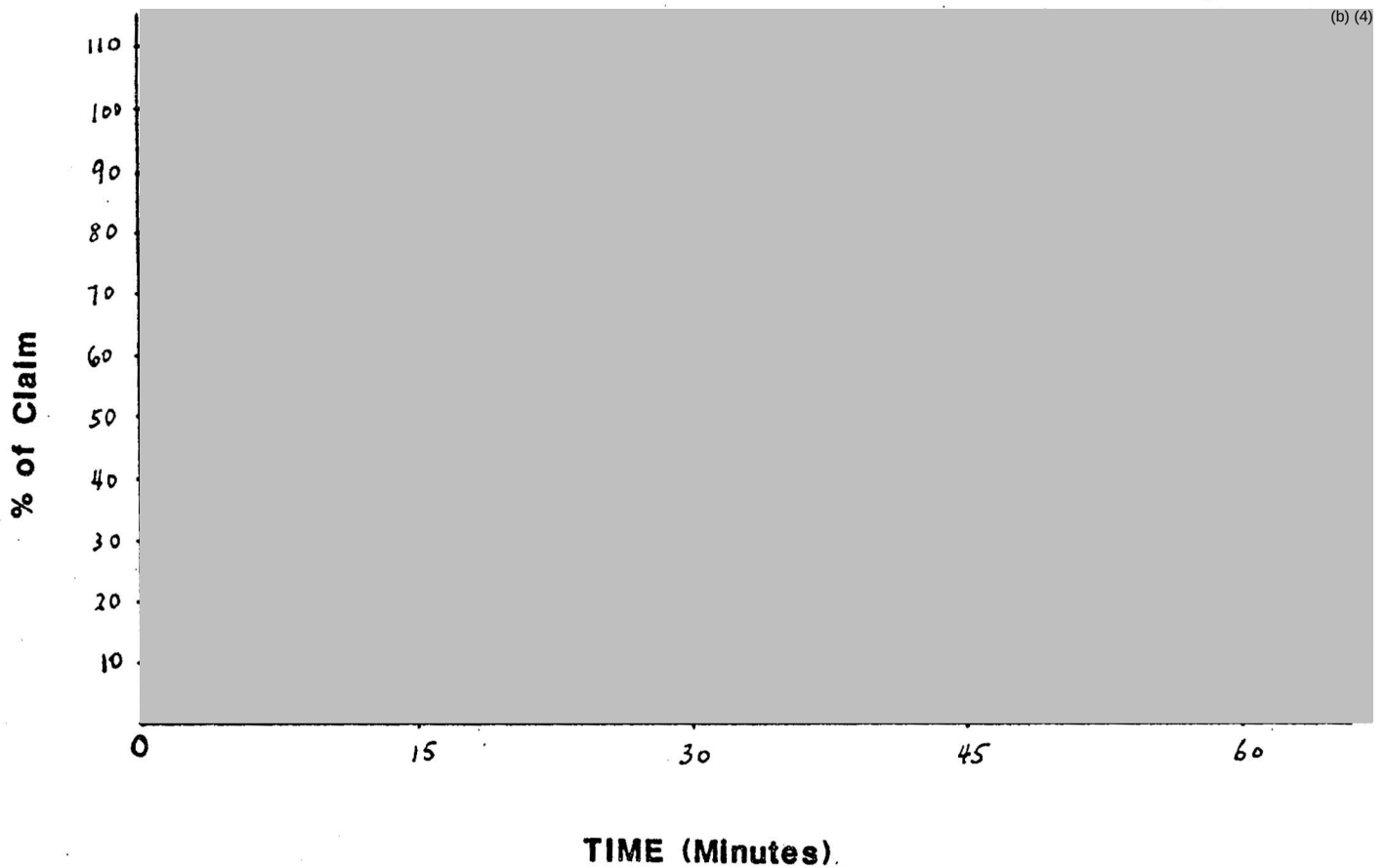
NDA # (b) (4) A-003



DISSOLUTION PROFILE:

TIME:	MG APAP:	% OF CLAIM:
0	(b) (4)	(b) (4)
15		
30		
45		
60		

DISSOLUTION PROFILES: WATER AT 37°C, 75 RPM



KEY

UPSHER-SMITH, 80 MG SUPPOSITORIES ———

UPSHER-SMITH, 120 MG SUPPOSITORIES —·—·—

G&W LABORATORIES, SUPPOSITORIES 120 MG — — —

NDA (b) (4)

acetaminophen suppositories
UNISERTS® (80 mg pediatric rectal suppos.)
NDA (b) (4) 18-337/S013
Reviewer: Victoria G. Hale, Ph.D.
S-

Upsher Smith Laboratories
Minneapolis, MN

Date: 6/19/91

Waiver of in vivo bioavailability study

Background:

In a 9/25/87 submission, the sponsor presented results from three dissolution methods, each comparing the dissolution of three suppositories (USL 80 mg, compared to USL 120 mg and G & W 120 mg suppositories). At this time, the firm requested a waiver for an in vivo bioequivalence study. A review by the Division of Biopharmaceutics dated 11/12/87 concluded that the dissolution profiles of the 80 mg suppositories were markedly different from the 120 mg products and the waiver request was denied. A subsequent review by the Pilot Drug Evaluation Staff uncovered an error in the Biopharmaceutics review (see review dated 6/19/91). The firm has now satisfied the requests of the Agency and may be granted a waiver for in vivo bioavailability studies.

This product is indicated for analgesia and antipyresis in young children. In theory, the bioavailability of the 80 mg suppository could be determined in adults. However, the rectal anatomy and circulation of children and adults may differ and therefore absorption characteristics in children may not be predictable.

At a May 1991 meeting at the Agency, it was agreed that it would not be necessary to perform bioavailability studies in children prior to marketing. However, the firm will need to agree to some post-marketing studies in this population to characterize the pharmacokinetic profile of acetaminophen who are given these new, lower strength rectal suppositories.

Conclusion:

A waiver of in vivo bioavailability studies is granted, provided that the sponsor agree to conduct population-type pharmacokinetic analyses in children of the appropriate age soon after marketing the 80 mg suppository.

Victoria G. Hale, Ph.D.
Pilot Drug Evaluation Staff

Peer Reviewed: EDB (Hale for Bashaw)

cc: Original NDA (b) (4)
HFD-007/Division file
HFD-007/CSO/Barnes
HFD-426/Drug file/Reviewer file/Chron
HFD-007/VHale//init. by EDBashaw
F/T 6/19/91

acetaminophen suppositories
UNISERTS® (80 mg pediatric rectal suppos.)
NDA (b) (4)
Reviewer: Victoria G. Hale, Ph.D.

Upsher Smith Laboratories
Minneapolis, MN
Date of original review: 11/12/87
Date of this review: 6/19/91

Addendum to a Pharmacokinetic Review

Background

The firm submitted dissolution data on 9/19/86 for their 80 mg suppository, comparing it to their 120 mg product and G & W Laboratories' 120 mg suppository. A review from the Division of Biopharmaceutics dated 12/31/86 concluded that the results were erratic and that dissolution tests should be repeated. The submission consisted of results using one dissolution method; this time, the firm was directed to use three methods (see review, Attachment 1).

The submission of the results from three dissolution methods, each comparing the three suppositories was received on 9/25/87. At this time, the firm requested a waiver for an in vivo bioequivalence study. A review by the Division of Biopharmaceutics dated 11/12/87 concluded that the dissolution profiles of the 80 mg suppositories were markedly different from the 120 mg products, regardless of the dissolution methodology used. The waiver request was denied.

Over the next few years, several communications between the Agency and the sponsor ensued, with little result. The product was transferred between the Division of Biopharmaceutics, the Division of Generic Drugs and the Pilot Drug Evaluation Staff. In May 1991, it was discovered that the Biopharmaceutics' review of 11/12/87 was in error: the review compared the mg acetaminophen dissolved, not the percentage of claim dissolved. Hence, the values obtained for the marketed products (Upsher Smith's and G & W's 120 mg suppositories) exceeded (b) (4) and those of the product under review were between (b) (4). A meeting was held on 5/21/91 between Pilot Drug and Upsher Smith Laboratories, during which these findings were communicated.

The purpose of this addendum is to correct the previous error and to permit the sponsor to pursue the development of the 80 mg acetaminophen pediatric rectal suppository. Additionally, a waiver for the performance of in vivo bioavailability/pharmacokinetic studies in pediatric patients will be granted. The firm, as per the May 1991 meeting, will conduct Phase IV pharmacokinetic/ biopharmaceutic studies in pediatric patients (see Waiver).

Evaluation of Dissolution Data

Attachment 2 contains one of the three dissolution method data sets testing the 80 mg suppository, that performed in water at 75 rpm. Here, it may be seen that the firm presented its data in tabular form as mg dissolved. The graphic presentation of the results is as % of claim dissolved. Below is the dissolution profile for the % dissolved of the 80 mg suppository in 37 °C water at 75 rpm.

	% of claim dissolved		
time (min)	mean	SD	range
15	82.9	(b) (4)	
30	92.3		
45	98.6		
60	100.8		

The dissolution data are acceptable for this product in this media. Furthermore, the data are acceptable for all three products using all three dissolution methods.

Recommendation

The Pilot Drug Evaluation Staff has found the dissolution data submitted by the sponsor of these 80 mg acetaminophen suppositories to be acceptable. This review supersedes that of the Division of Biopharmaceutics dated 11/12/87. A waiver is granted for performance of an in vivo bioequivalence study.

However, Pilot Drug believes that it is important to characterize the biopharmaceutics of this product in children whose age corresponds to that in which the product is to be used. These studies will be performed as Phase IV pharmacokinetic studies. The sponsor should consult with the Pilot Drug Staff regarding the performance of studies in this population, so as to optimize information gained while minimizing the discomfort of the children involved. Protocols should be submitted directly to the Division for review.

The first two pages of this review (no Attachments) should be forwarded to the firm.

Victoria G. Hale, Ph.D.
Pilot Drug Evaluation Staff

Peer Reviewed: Edb 6/18/91

cc: Original NDA (b) (4)
HFD-007/Division file
HFD-007/CSO/~~Schmidt~~ Barnes
HFD-426/Drug file/Reviewer file/Chron
HFD-007/VHale//init. by EDBashaw
F/T 6/5/91

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-337/S-013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date; August 31,1989.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 C.F.R. Part 314).*

NAME OF APPLICANT
Upsher-Smith Laboratories, Inc.

DATE OF SUBMISSION
October 1, 1992

TELEPHONE NO. *(Include Area Code)*
(612) 473-4412

ADDRESS *(Number, Street, City, State and Zip Code)*
14905 23rd Avenue North
Minneapolis, MN 55447

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
18-337

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Acetaminophen Suppositories

PROPRIETARY NAME *(If any)*
Acetaminophen Unserts® Rectal Suppositories

CODE NAME *(If any)*
N/A

CHEMICAL NAME
N-(4-Hydroxyphenyl) acetamide

DOSAGE FORM
Suppository

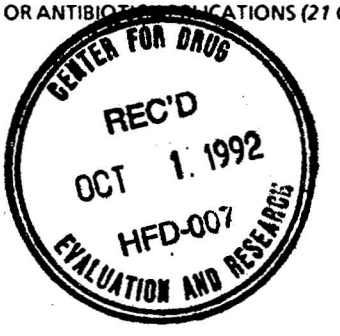
ROUTE OF ADMINISTRATION
Rectal

STRENGTH(S)
80 mg
120 mg
325 mg
650 mg

PROPOSED INDICATIONS FOR USE
Temporary relief of fever, minor aches, pains and headaches

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

N/A



INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION ☐ ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☒ SUPPLEMENTAL APPLICATION "Changes Being Effected"

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☒ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

FORM FDA 356h (3/87)

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
1. Index	
2. Summary (21 CFR 314.50 (c))	
3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))	
4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)	
b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))	
c. Labeling (21 CFR 314.50 (e) (2) (ii))	
i. draft labeling *(4 copies)*	
ii. final printed labeling (12 copies)	X
5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))	
6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))	
7. Microbiology section (21 CFR 314.50 (d) (4))	
8. Clinical data section (21 CFR 314.50 (d) (5))	
9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))	
10. Statistical section (21 CFR 314.50 (d) (6))	
11. Case report tabulations (21 CFR 314.50 (f) (1))	
12. Case reports forms (21 CFR 314.50 (f) (1))	
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. OTHER *(Specify)*	

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. 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.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Harvey M. Arbit, Pharm.D.		9/30/92

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
14905 23rd Avenue North Minneapolis, MN 55447	(612) 473-4412

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

☆ U.S GOVERNMENT PRINTING OFFICE:1987-181-338/55255

Approved Labeling for Acetaminophen Uniserts® 80mg Suppositories	Revised Labeling for Infants' Feverall® 80 mg Suppositories	Annotation
Front Side of Carton	**Front Side of Carton**	**Front Side of Carton**
NDC 0245-0120-XX	0245-0113-XX	• New NDC number to reflect Feverall® product line
	NDC number deleted from 2's cartons	• Cartons of 2's only
Acetaminophen Uniserts®	Infants' Feverall® Suppositories	• Incorporation of tradename
Acetaminophen Suppositories 80 mg Infant	Acetaminophen 80 mg	
Fever Reducer/Pain Reliever	Fever Reducer/Pain Reliever	• No change
12 Suppositories	6 (or 2) Rectal Suppositories (80 mg each)	• Describes dosage form as "Rectal"
Upsher-Smith logo	Deletion of logo	
	Added statement "Aspirin Free"	
	Added flag "80 mg per suppository"	
	Added statement "Safety Sealed"	• Cartons of 6's only
	Added picture of suppository and picture of infant	• Cartons of 6's only
	Added "new" to front riser card	• Cartons of 6's only

Approved Labeling for Acetaminophen Uniserts® 80mg Suppositories

Back Side of Carton

Acetaminophen Uniserts®

Acetaminophen Infant Rectal Suppositories, 80 mg

Indications: Acetaminophen Uniserts® Infant Rectal Suppositories are for the temporary relief of fever, minor aches and pains. For rectal administration.

Dosage: Children (1 to 3 years)--One suppository every 4 hours. Children (3-11 months)-- One suppository every 6 hours. No more than a total of 6 suppositories in any 24 hour period. Children (under 3 months)--Consult a physician. For children over 3 years of age, Acetaminophen Uniserts® Pediatric Rectal Suppositories, 120 mg, should be used.

Directions: Remove wrapper and carefully insert suppository well up into the rectum.

Store below 80°F (27°C) or refrigerate.

Warnings: Severe or recurrent pain or high or continued fever may be indicative of serious illness. If fever persists for more than 3 days (72 hours), or recurs, consult your physician. Do not use consistently for more than 3 days except on the advice of a physician.

Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center Immediately.

Tamper resistant: Each suppository is individually sealed. Do not use if seal is broken or damaged.

Lot number, expiration date, revision date, part number.

Manufactured by
UPSHER-SMITH
LABORATORIES, INC.
Minneapolis, MN 55447

Revised Labeling for Infants' Feverall® 80 mg Suppositories

Back Side of Carton

Annotation

Back Side of Carton

(b) (4)

[redacted]

Approved Labeling for Acetaminophen Uniserts® 80mg Suppositories	Revised Labeling for Infants' Feverall® 80 mg Suppositories	Annotation
End Flap Acetaminophen Uniserts® Acetaminophen Suppositories 80 mg Infant	**End Flap** [redacted]	**End Flap** (b) (4)
Foil Wrapper Acetaminophen Uniserts® Suppository 80 mg Upsher-Smith Minneapolis, MN 55447	**Foil Wrapper** [redacted]	**Foil Wrapper** (b) (4)

For your review of this supplement, attached are 12 sets of final printed labeling for the following:

1. Infants' Feverall®, 80 mg (cartons of (b)(4) suppositories)
2. Infants' Feverall®, 80 mg (cartons of 6 suppositories)
3. Samples of foil for the Infants' Feverall®, 80 mg Suppositories

For ease of review, four copies of the approved labeling (for cartons of 12 suppositories and foil) for our Acetaminophen Uniserts®, 80 mg Suppositories are included for comparison.

This supplement is being submitted in duplicate for incorporation into our file. Should you have any questions or comments regarding this submission, please contact:

Dianne Gibbs
Regulatory Affairs Specialist
(612) 449-7261

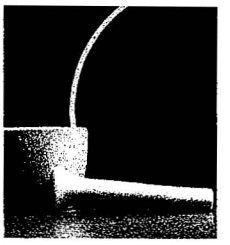
Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Harvey M. Arbit, Pharm.D.
Director of Scientific Affairs

HMA/DG/bac

enclosure



NDA SUPPL AMEND
SLR-013
(FA)

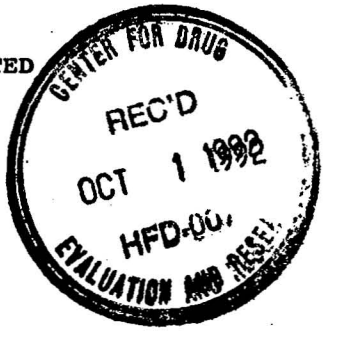
Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

September 30, 1992

FEDERAL EXPRESS

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED



John Harter, M.D.
Director
Pilot Drug Evaluation Division
(HFD-007), Room 9B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Harter:

RE: Final Printed Labeling for Approved Supplement NDA 18-337/S-013 with Changes Being Effected; Minor Editorial Labeling Changes Acetaminophen Uniserts® Rectal Suppositories, 80 mg

Reference is made to Supplement 013, which provides for an additional strength (80 mg) of acetaminophen suppositories, which was approved by FDA on August 26, 1992.

Submitted herewith please find twelve copies of final printed labeling as requested in the Agency's August 26, 1992 approval letter. Minor editorial changes have been made to the product labeling, therefore this labeling is being submitted as a supplement under 21 CFR 314.70(c) for a minor change in labeling for the above referenced drug product. There is no change in the suppository dosage form itself.

This supplement extends the Feverall® tradename to the 80 mg strength of this product and establishes a more consumer oriented layout of the overall package design.

The cartons we are submitting herewith for Infants' Feverall® 80 mg Suppositories are: cartons of (b)(4) suppositories (sample size), and 6 suppositories (retail package). Samples of the foil used to wrap the suppositories are also included.

This new labeling using the Feverall® tradename is intended as a replacement to our currently approved labeling for Acetaminophen Uniserts®, 80 mg. However, we reserve the option to still use our Acetaminophen Uniserts® labeling for many of our health-professional customers.

For ease of review, the labeling changes included are compared to the approved labeling in S-013 for Acetaminophen Uniserts®, 80 mg (carton of 12 suppositories), and are summarized as follows:

ORIGINAL

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN 55447
Telephone 612-473-4412 Telex# 6502644714 FAX# 612-476-4026

AUG 26 1992

CSO Overview

NDA 18-337/S012

Sponsor: Upsher-Smith Laboratories

Drug: Acetaminophen Suppositories, 80 mg

This supplement was originally submitted to The Division of Generic Drugs as a new ANDA # (b) (4). At that time the sponsor requested a waiver for an in vivo bioequivalence study, however they had not used the correct conditions in the in vitro dissolution testing. They submitted the corrected dissolution data on September 19, 1986 and again requested a waiver. A review by the Division of Biopharmaceutics dated 12/31/86 again recommended the waiver not be granted due to errors in the dissolution data. The corrected comparative dissolution data was submitted on September 25, 1987. A review by the Division of Biopharmaceutics dated 11/12/87 again recommended the waiver not be granted.

At that time a consultative review by the Division of Neuropharmacological drug products also recommended that the application not be approved based a lack of data in children <3 years of age and the sponsor labeling which recommended that the (b) (4).

As it appeared clinical trials may be necessary the application and the original acetaminophen suppository, 120 mg application, 18-337 were transferred to the Pilot Drug Evaluation Staff.

The file on the this application was reviewed by John G. Harter, M.D. and Victoria G. Hale, Ph.D. in preparation for a May 21, 1991 meeting with the sponsor. At the meeting Dr. Hale noted that it appeared an error had been made in the biopharmaceutics review dated 12/31/86 and the requested waiver should have been granted. Dr. Hale subsequently did a complete review of the application and her original suspicions were confirmed. Additional details are contained in Dr. Hale's review dated June 19, 1991.

Dr. Harter indicated at the meeting that he felt there is sufficient information available to approve this additional strength suppository. He recommended that the sponsor explore the development of a 40 mg dosage form to widen the range of available products and to eliminate the widespread practice of breaking a suppository in order to titrate the dose.

It was agreed that the supplemental application for an 80 mg dose could be approved after submission of the following items;

1. a commitment to perform a Phase IV pharmacokinetic study in children of the appropriate ages,

2. submission of the protocol for the Phase IV study,

3. submission of acceptable labeling as discussed at the meeting (deletion of the reference to [redacted] (b) (4), dosage and administration re-adjusted and cross reference made to the available 120 mg suppository for older children).

These items have been submitted to the application and found to be acceptable.

It was later discover that numerous changes had been made to the chemistry portion of the application since the original submission and review by Generic drug and a new chemistry review was needed including an inspection of the sponsor's facilities.

At this time a satisfactory inspection has been received and it is recommended that the application can now be approved.

Sandy Barnes
Consumer Safety Officer

Dulcan
8.25.92

8-26-92

DEPARTMENT OF HEALTH & HUMAN SERVICES 0972 Public Health Service

Memorandum

Date 11-14-91 FUR 5-19-92

From Division of Pilot Drug Evaluation Staff HFD- 007

Requestor's Name Charlotte Yaciw Phone 443-5074

Subject ESTABLISHMENT EVALUATION REQUEST

PRIORITY

To Division of Manufacturing & Product Quality (HFD-320)

Sterile Product _____ Non Sterile Product XXX

Application and Supplement No. NDA 18-337/S012

Brand Name *(if any)* ~~Acetaminophen Unicerts~~

Establishment Name, Dosage Form and Strength ~~acetaminophen pediatric rectal suppositories 80 mg each~~ Profile Class Code: ~~SUP~~

Priority Classification: _____ *(See SMG BD-4820.3)*

Applicant's Name: ~~Upsher-Smith Laboratories~~

Address: ~~14095 23rd Avenue, North, Minneapolis, MN~~

Facilities to be Evaluated: (*Name, full Address, DMF No., and responsibility*) **For HFD 320 Use** Status & Date of Inspection:

1. (b) (4) (b) (4)
2. _____
3. Upsher-Smith Laboratories, 14905 23rd Avenue, North, Minneapolis, MN Manufacture suppositories UPSP 10-DAY AC 2/24/92
4. (b) (4)
5. _____

Other Information or Special Requests: _____

****

New dosage level suppository

For HFD-320 Use Only: Date Received: 5/22/92

CGMP Compliance Status of Facilities Evaluated: acceptable

CSO: Melissa Garcia Date Completed: 7/27/92

Distribution: Original and First Copy: HFD-320
Remaining Copies: Requesting Office Use

FORM FDA 3274 (3/90)

7.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

4-13-1992

NDA 18337

UPSHER-SMITH
14905 23rd Avenue North
Minneapolis, MN 55447

Attention: Harvey M. Arbit, Pharm.D.
Director of Scientific Affairs

Dear :

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Acetaminophen Suppositories, 80 mg

NDA Number: 18337

Supplement Number: S-013

Date of Supplement: 4-7-1992

Date of Receipt: 4-8-1992

Should you have any questions, please contact:

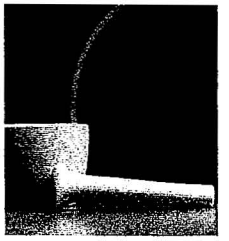
Sandy Barnes
Project Manager
(301) 443-3741

Sincerely yours,

For Jeanette Nyanfore
Project Manager
Center for Drug Evaluation and Research

cc:
Original NDA
HFN-007/150
HFN-007/150/CSO

SUPPLEMENT ACKNOWLEDGEMENT



NDA NO 18337 REF. NO. 013

NDA SUPPL FOR SE2

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

April 7, 1992

FEDERAL EXPRESS

Ms. Sandra Barnes
Pilot Drug Evaluation Division
HFD-007, Room 9B-23
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Barnes:

RE: NDA 18-337 Acetaminophen Suppositories, 80 mg

Per our conversation this morning, enclosed are another four copies of Upsher-Smith Laboratories, Inc.'s proposed carton and wrapper labeling for Acetaminophen Suppositories, 80 mg (as previously submitted to the Agency on March 5, 1992). Also enclosed is the updated stability data for Lot 5139 of this product.

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

If you have any other questions, please do not hesitate to call:

Dianne Gibbs
Regulatory Affairs Specialist
(612) 449-7261

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Harvey M. Arbit, Pharm.D.
Director of Scientific Affairs

HMA/DG/bac

enclosure

ORIGINAL

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN 55447
Telephone 612-473-4412 Telex# 6502644714 FAX# 612-476-4026