CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER: 75-135/S-001 to 007

Trade Name: Pacerone 200 mg tablets

Generic Name: (amiodarone hydrochloride)

Sponsor: Upsher-Smith Laboratories, Inc.

Approval Date: April 30, 1998

Indications: Provide an alternate site, a new site, for revisions to the WARNINGS AND PRECAUTIONS sections of the package insert labeling, the Food-Effect Bioequivalence study data, a facility addition, a manufacturing revision, and a labeling revision.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-135/S-001 to 007

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letters	X
Tentative Approval Letter	
ANDAs	
Approvable Letter	
Approved Labeling	X
Medical Review(s)	
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-135/S-001 to 007

ADMINISTRATIVE DOCUMENTS

OFFICE OF GENERIC DRUGS

REVIEW OF SUPPLEMENT TO
ABBREVIATED NEW DRUG APPLICATION

1. **ANDA NUMBER**
75-135/S-001

2. **NAME AND ADDRESS OF APPLICANT**
Upsher-Smith Laboratories, Inc.
Attention: Mark Robbins
14905, 23rd Avenue North
Minneapolis, MN 55447-4709

3. **PURPOSE OF AMENDMENT/SUPPLEMENT**
The Supplement provides for:

S-001: Facility Addition

Alternate site for [redacted]

4. **DATE(S) OF SUBMISSION(S)**
Firm:
02-15-1999 S-001-Original Supplement
Subject of this review

5. **PHARMACOLOGICAL CATEGORY**
Anti-arrhythmic

6. **TRADE NAME**
None

7. **NONPROPRIETARY NAME**
Amiodarone Hydrochloride

8. **DOSAGE FORM**
Tablets

9. **POTENCY**
200 mg

10. **RX OR OTC**
RX

11. **RELATED IND/NDA/DMF**
N/A

12. **STERILIZATION**
N/A

13. **LABELING**
Review Status: N/A

14. **BIOEQUIVALENCY STATUS**
Review Status: Satisfactory

The applicant has provided comparative dissolution data for Pacerone Tablets manufactured using [redacted] from [redacted] (lot# 64610 98-3966) and [redacted] (lot# 64333 98-2857). The profiles are comparable with an [redacted] value of [redacted] The results suggest that the finished product manufactured using [redacted] has dissolution profile similar to that from the [redacted] source [redacted].

15. **ESTABLISHMENT INSPECTION:** (Satisfactory)

Review Status: EER is pending (EER requested to OC). But [redacted] received a satisfactory FDA Inspection report, covering its [redacted] process within 2 years (Nov 1997).

[redacted]

The proposed changes meets the SUPAC-IR guidance definition of a Level 3 site change: It does not include any scale-up, changes in manufacturing, or changes in components or composition. The Firm commits that the same equipment, SOPs, environmental conditions, and controls will be used in the manufacturing process at the new site.

Brief description of the facility [redacted] Certification and Debarment certification are provided on pages 5-7 and are satisfactory.

In support of the alternate site for [redacted], the cGMP certification and description of [redacted] were submitted on pages 5-7. Raw material controls and USP testing results submitted in pages 8-15 are satisfactory.

Comparison of current [redacted] records and proposed [redacted] records and manufacturing information summary are within the approved limits.

The Upsher- Smith in-process specifications, methods and requirements for the receipt, testing and use of the Pacerone granules received from the new facility [redacted] are the same as those previously approved for Pacerone granules received from the [redacted] pages 171-181).

The Upsher- Smith in-process testing results for the Pacerone [redacted] manufactured from the new facility [redacted] Batch No 9807676) and used in the exhibit batch (Pacerone lot #64333) yielded acceptable results and within the specifications. The [redacted] testing results yielded satisfactory results and the [redacted] sample results are provided following the in-process testing results.

The finished product testing results of the Exhibit batch lot # 64333 are provided in pages 183-198. The identity, strength, quality, dissolution profile and purity of the finished product manufactured in the new facility [redacted] seems to meet all approved specifications for the Pacerone tablets 200 mg.

The post-approval stabilty commitment and the stability data for the drug product lot #64333 manufactured in the new facility [redacted] ,is submitted in pages 199-213 and data is satisfactory.

16. **COMPONENTS, COMPOSITION, MANUFACTURING & CONTROLS:**
No changes in Components, Composition, or Manufacturing is proposed.

The proposed change meets the SUPAC-IR guidance definition of a Level 3 site change: It does not include any scale-up, change in manufacturing, or changes in components or composition. The Firm commits that the same equipment, SOPs, environmental conditions, and controls will be used in the manufacturing process at the new site.

Brief description of the facility [redacted] , [redacted] CGMP Certification and Debarment certification are provided on pages 5-7 and are satisfactory.

Raw material controls and USP testing results submitted in pages 8-15 are satisfactory.

Comparison of current [redacted] batch records and proposed [redacted] batch records and manufacturing information summary are comparable and satisfactory.

The Upsher-Smith in-process specifications, methods and requirements for the receipt, testing and use of the Pacerone [redacted] received from the new facility are the same as those previously approved for Pacerone [redacted] received from the [redacted] (pages 171-181).

The Upsher-Smith in-process testing results for the Pacerone [redacted] manufactured at the new facility [redacted] No 9807676) and used in the exhibit batch (Pacerone lot #64333) yielded acceptable results and within the specifications. The [redacted] testing results yielded satisfactory results and the individual [redacted] sample results are provided following the in-process testing results.

The finished product testing results of the Exhibit batch lot # 64333 are provided in pages 183-198. The identity, strength, quality, dissolution profile and purity of the finished product manufactured in the new facility meet all approved specifications for the Pacerone Tablets 200 mg.

17. **PACKAGING:**
Review Status: N/A

18. **STABILITY:**
Review Status: Satisfactory

The post-approval stabilty commitment and the stability data for the drug product lot #64333 manufactured in the new facility [redacted], is submitted on pages 199-213 and data is satisfactory.

19. **REMARKS AND CONCLUSION:**
The proposed change meets the SUPAC-IR guidance definition of a Level 3 site change. The submitted data support the proposed site change. Hence this supplement is approved.

20. **ORDER OF REVIEW:**

The application submissions covered by this review were taken in the date order of receipt Yes X No
If no, explain reason(s) below:

21. **SPOT?** **Yes** **No** X

If yes, complete form

21. **REVIEWER AND DATE COMPLETED:**

Mouna P. Selvam, Ph.D., / September 23, 1999

cc: ANDA 75-135/S-001

/S/

/S/ 11/16/99

Approved

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 75135/001**
Stamp: **16-FEB-1999** Regulatory Due:
Applicant: **UPSHER SMITH**
14905 23RD AVE NORTH
MINNEAPOLIS, MN 55447

Priority: Org Code: **600**
Action Goal: District Goal: **16-JUL-1999**
Brand Name:
Established Name: **AMIODARONE HYDROCHLORIDE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **200 MG**

FDA Contacts: **M. SELVAM (HFD-647) 301-827-5859 , Review Chemist**

Overall Recommendation:

Establishment

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date **02-SEP-1999**

Responsibilities:

APPEARS THIS WAY
ON ORIGINAL

SUPAC / PAC ROUTING FORM

This form is to accompany all SUPAC / PAC supplements. Upon completion return to Document Room with appropriate letter (if required) for letter issuance, data entry, and filing.

I. To be completed by Document Room using industry cover letter:

DATE PROCESSED: 2.17.99

APPLICATION #: 75-135 SUPPLEMENT #: SC 001 S1

SUPAC modifier (amendment type code):
- X SI - (SUPAC-IR) Immediate release solid oral dosage forms
- ___ SS - (SUPAC-SS) Semisolid topical dosage forms
- ___ SE - (SUPAC-MR) Modified release oral dosage forms
- ___ ST - (SUPAC-TDS) Transdermal dosage forms
- ___ SP - (PAC-SAS) Sterile Aqueous Solutions
- ___ SL - (PAC-ATLS) Analytical Testing Laboratory Sites

Type of change (event code): (check all that apply)
- ___ S1 - Batch Size (Scale-Up/Scale-Down)
- ___ S2 - Components and Composition
- ___ S3 - Manufacturing Equipment
- ___ S4 - Manufacturing Process
- X S5 - Site (e.g. manufacturing, packaging, testing)

Supplement Type:
- ___ (PL) PRIOR APPROVAL *Skip to Item IV below*
- X (CBE) CHANGES BEING EFFECTED *Proceed with Items II, III, & IV*

II. To be determined by Chemistry Division:

___ (IS) INCORRECT SUPPLEMENT CATEGORY (non-SUPAC)
Chemistry Division Team Leader: _____ Date: _____

✓ (GR) QUALIFIES as CBE
Chemistry Division Team Leader: _____ Date: 3/3/99

___ (DN) DOES NOT QUALIFY as CBE NOTE: SUPAC CBE Checklist: Failure to Qualify, or other qualification statement required

Chemistry Division Team Leader: _____ Date: _____

Chemistry Division Director concurrence: _____ Date: _____

~~III. The (___ Project Manager ___ Chemistry Team Leader) will prepare notification of non-qualification letter in~~ accordance with ___ division policy on Chemistry, Manufacturing, and Control supplement letters.

IV. To Document Room:

Record SUPAC codes as special amendment for supplement.
File in archival submission.
cc: HFD-358, Project Manager/CSO

OFFICE OF GENERIC DRUGS

REVIEW OF SUPPLEMENT TO
ABBREVIATED NEW DRUG APPLICATION

1. **ANDA NUMBER**
75-135/S-002

2. **NAME AND ADDRESS OF APPLICANT**
Upsher-Smith Laboratories, Inc.
Attention: Mark Robbins
14905 23rd Avenue North
Minneapolis, MN 55447-4709

3. **PURPOSE OF AMENDMENT/SUPPLEMENT**
The Supplement provides for:

S-002: Facility Addition

New site for :

4. **DATE(S) OF SUBMISSION(S)**
Firm:
04-29-1999 S-002-Original Supplement
Subject of this review

5. **PHARMACOLOGICAL CATEGORY**
Anti-arrhythmic

6. **TRADE NAME**
None

7. **NONPROPRIETARY NAME**
Amiodarone Hydrochloride

8. **DOSAGE FORM**
Tablets

9. **POTENCY**
200 mg

10. **RX OR OTC**
RX

11. **RELATED IND/NDA/DMF**
N/A

12. **STERILIZATION**
N/A

13. **LABELING**
Review Status: N/A

14. **BIOEQUIVALENCY STATUS**
Review Status: N/A

15. **ESTABLISHMENT INSPECTION**
Review Status: EER is Acceptable (Attached).

The proposed change meets the "PAC-ATLS: Post Approval Analytical Testing Laboratory Sites" in accordance with the CDER April 1998 Guidance for Industry and persuant to 21 CFR 314.70 C

This Supplement provides for the addition of an alternate analytical testing laboratory site and the change in location of an analytical testing laboratory site included in the approved ANDA. It does not include any scale-up changes, changes in manufacturing, or changes in components or composition.

16. **COMPONENTS, COMPOSITION, MANUFACTURING & CONTROLS**
No changes in Components, Composition, or Manufacturing is proposed.

17. **PACKAGING**
Review Status: Satisfactory

18. **STABILITY**
Review Status: Satisfactory

19. **REMARKS AND CONCLUSION:**
The proposed change meets the "PAC-ATLS: 'Post Approval Analytical Testing Laboratory Sites" in accordance with the CDER April 1998 Guidance for Industry and pursuant to 21 CFR 314.70 C. This application is approved.

20. **ORDER OF REVIEW:**

The application submissions covered by this review were taken in the date order of receipt Yes X No
If no, explain reason(s) below:

21. **SPOT?** **Yes** **No** X

If yes, complete form

21. **REVIEWER AND DATE COMPLETED :**

Mouna P. Selvam, Ph.D., / September 22, 1999

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 75135/002**
Stamp: **03-MAY-1999** Regulatory Due:
Applicant: **UPSHER SMITH**
14905 23RD AVE NORTH
MINNEAPOLIS, MN 55447

Priority: Org Code: **600**
Action Goal: District Goal: **03-OCT-1999**
Brand Name:
Established Name: **AMIODARONE HYDROCHLORIDE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **200 MG**

FDA Contacts: **M. SELVAM** **(HFD-647)** **301-827-5859 , Review Chemist**

Overall Recommendation:

ACCEPTABLE on 02-SEP-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **01-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 75135/002**
Stamp: **03-MAY-1999** Regulatory Due:
Applicant: **UPSHER SMITH**
14905 23RD AVE NORTH
MINNEAPOLIS, MN 55447

Priority:
Org Code: **600**
Action Goal:
~~District Goal~~: **03-OCT-1999**
Brand Name:
Established Name: **AMIODARONE HYDROCHLORIDE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **200 MG**

FDA Contacts: **M. SELVAM** **(HFD-647)** **301-827-5859 , Review Chemist**

Overall Recommendation:

ACCEPTABLE on 02-SEP-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

APPEARS THIS WA
ON ORIGINAL

SUPAC / PAC ROUTING FORM

This form is to accompany all SUPAC / PAC supplements. Upon completion return to Document Room with appropriate letter (if required) for letter issuance, data entry, and filing.

SPECIAL

I. To be completed by Document Room using industry cover letter:

DATE PROCESSED: 5 4 99

APPLICATION #: 75-135 SUPPLEMENT #: SCB 002 SL

SUPAC modifier (amendment type code):
- ___ SI - (SUPAC-IR) Immediate release solid oral dosage forms
- ___ SS - (SUPAC-SS) Semisolid topical dosage forms
- ___ SE - (SUPAC-MR) Modified release oral dosage forms
- ___ ST - (SUPAC-TDS) Transdermal dosage forms
- ___ SP - (PAC-SAS) Sterile Aqueous Solutions
- X SL - (PAC-ATLS) Analytical Testing Laboratory Sites

Type of change (event code): (check all that apply)
- ___ S1 - Batch Size (Scale-Up/Scale-Down)
- ___ S2 - Components and Composition
- ___ S3 - Manufacturing Equipment
- ___ S4 - Manufacturing Process
- X S5 - Site (e.g. manufacturing, packaging, testing)

Supplement Type:
- ___ (PL) PRIOR APPROVAL *Skip to Item IV below*
- X (CBE) CHANGES BEING EFFECTED *Proceed with Items II, III, & IV*

To be determined by Chemistry Division:

___ (IS) INCORRECT SUPPLEMENT CATEGORY (non-SUPAC)
Chemistry Division Team Leader: _____ Date: _____

✓ (GR) QUALIFIES as CBE
Chemistry Division Team Leader: /S/ Date: 5/6/99

___ (DN) DOES NOT QUALIFY as CBE NOTE: SUPAC CBE Checklist: Failure to Qualify, or other qualification ment required

Chemistry Division Team Leader: _____ Date: _____

Chemistry Division Director concurrence: _____ Date: _____

~~The (___ Project Manager ___ Chemistry Team Leader) will prepare notification of not qualification letter in~~ rdance with ___ division policy on Chemistry, Manufacturing, and Control supplement letters.

To Document Room:

Record SUPAC codes as special amendment for supplement.
File in archival submission.
cc: HFD-358, Project Manager/CSO

OFFICE OF GENERIC DRUGS

REVIEW OF SUPPLEMENT TO
ABBREVIATED NEW DRUG APPLICATION

1. **ANDA NUMBER**
75-135/S-004

2. **NAME AND ADDRESS OF APPLICANT**
Upsher-Smith Laboratories, Inc.
Attention: Mark Robbins
14905, 23rd Avenue North
Minneapolis, MN 55447-4709

3. **PURPOSE OF AMENDMENT/SUPPLEMENT**
The Supplement provides for:

S-004: Bioequivalence data

4. **DATE(S) OF SUBMISSION(S)**

Firm:	
09-17-1999	S-004-Original Supplement
10-13-1999	Tel Amendment

Subject of this review

5. **PHARMACOLOGICAL CATEGORY**
Anti-arrhythmic

6. **TRADE NAME**
None

7. **NONPROPRIETARY NAME**
Amiodarone Hydrochloride

8. **DOSAGE FORM**
Tablets

9. **POTENCY**
200 mg

10. **RX OR OTC**
RX

11. **RELATED IND/NDA/DMF**

N/A

12. **STERILIZATION**
N/A

13. **LABELING**
Review Status: N/A

14. **BIOEQUIVALENCY STATUS:**
Satisfactory. Reviewed by J.Lee and the Approval letter sent to the Firm on 11/23/1999.
Recommendation:

1. The food-effect bioequivalence study conducted by [redacted] for Upsher-Smith Laboratories, Inc. on its amiodarone HCl 200 mg tablet, batch #64456, comparing it to Cordarone® 200 mg tablet (Wyeth) has been found acceptable by the Division of Bioequivalence.

2. The in-vitro dissolution testing data (DBE interim) is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability pogram. The dissolution testing should be conducted in 900 ml of 0.05M NaAc buffer w/1% polysorbate 80, pH 4.0 at 37°C using USP XXIII apparatus I (basket) at 50 rpm. The test product should meet the following specification: Not less than [redacted] of the labeled amount of the drug in the tablet is dissolved in 60 minutes.

3. All bioequivalence criteria for the food-effect BE study have been met for this supplement.

15. **ESTABLISHMENT INSPECTION**
N/A

16. **COMPONENTS, COMPOSITION, MANUFACTURING & CONTROLS**
No changes in Components, Composition, or Manufacturing is proposed.

17. **PACKAGING**
Review Status: N/A

18. **STABILITY**
Review Status: N/A

19. **REMARKS AND CONCLUSION:**
The Application is Approved.

20. ORDER OF REVIEW:

The application submissions covered by this review were taken in the date order of receipt Yes No X
If no, explain reason(s) below:

Telephone amendment

21. SPOT? Yes No X

If yes, complete form

21. REVIEWER AND DATE COMPLETED :

Mouna P. Selvam, Ph.D., / January 20, 2000

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 75135/005**
Stamp: **29-OCT-1999** Regulatory Due:
Applicant: **UPSHER SMITH**
14905 23RD AVE NORTH
MINNEAPOLIS, MN 55447

Priority: Org Code: **600**
Action Goal: District Goal: **29-MAR-2000**
Brand Name:
Established Name: **AMIODARONE HYDROCHLORIDE**
Generic Name:
Dosage Form: **TAB (TABLET)**
Strength: **200 MG**

FDA Contacts: **M. SELVAM** **(HFD-647)** **301-827-5859** **, Review Chemist**

Overall Recommendation:

Establishment: **2123200**
UPSHER SMITH LABORATORIES IN
14905 23RD AVE NORTH
MINNEAPOLIS, MN 55447

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **02-NOV-1999**

Responsibilities: **INTERMEDIATE MANUFACTURER**

OFFICE OF GENERIC DRUGS

REVIEW OF SUPPLEMENT TO
ABBREVIATED NEW DRUG APPLICATION

1. **ANDA NUMBER**
75-135/S-005, S-006, S-007

2. **NAME AND ADDRESS OF APPLICANT**
Upsher-Smith Laboratories, Inc.
Attention: Mark Robbins
14905, 23rd Avenue North
Minneapolis, MN 55447-4709

3. **PURPOSE OF AMENDMENT/SUPPLEMENT**
These Supplements provide for:

S-004: Facility Addition:

14905, 23rd Avenue North
Minneapolis, MN 55447-4709

S-005: Manufacturing Revision:
Scale up, Equipment and Process changes

S-006: Labeling Revision

4. **DATE(S) OF SUBMISSION(S)**
Firm:
10-28-1999 S-004- Facility Addition
S-005- Manufacturing Revision
S-006- Labeling Revision
Original Supplements
Subject of this review

5. **PHARMACOLOGICAL CATEGORY**
Anti-arrhythmic

6. **TRADE NAME**
None

7. **NONPROPRIETARY NAME**
Amiodarone Hydrochloride

8. **DOSAGE FORM**
Tablets

9. **POTENCY**
200 mg

10. **RX OR OTC**
RX

11. **RELATED IND/NDA/DMF**
N/A

12. **STERILIZATION**
N/A

13. **LABELING**
Review Status:
Acceptable, Review letter dated November 22, 1999.
Reviewer A.Vezza.

14. **BIOEQUIVALENCY STATUS**
Review Status: Satisfactory

The applicant has provided the comaparative dissolution data for Amiodarone Hydrochloride Tablets, 200 mg, manufactured at the proposed USL [redacted] facility (Lot# 65267) and Lot# 64984, manufactured at the approved [redacted] site. This drug product conforms to all currently approved release requirements (results presented from page 322-327). The data presented on page 323 is per SUPAC-IR guidance sampling intervals (15, 30, 45, and 60 minutes). And the same on page 325 is as per the approved sampling time (10, 20, 40 and 60 minutes.

15. **ESTABLISHMENT INSPECTION**
Review Status: EER is Acceptable on overall Compliance dated December 20, 1999.

Change of site for [redacted] :

Upsher-Smith Laboratories, Inc.
14905, 23rd Avenue North
Minneapolis, MN 55447-4709

Brief description of the facility (USL), USL's cGMP Certification and Debarment certification are provided on pages 13 & 14 and are satisfactory.

The proposed change meets the SUPAC-IR guidance definition of a Level 3 site change: It does include scale-up changes in manufacturing and there are no changes in components and composition. The Firm commits that the same equipment, SOPs, environmental conditions, and controls will be used in the manufacturing process at the new site.

16. COMPONENTS, COMPOSITION, MANUFACTURING & CONTROLS

The proposed changes meets the SUPAC-IR guidance definition of a Level 3 site change in manufacturing site to a different Campus in accordance with Section IV.C: The finished dosage form will be manufactured, processed, tested (release and stability), packaged and labeled at Upsher-Smith Laboratories, Inc.
14905, 23rd Avenue North
Minneapolis, MN 55447-4709.

The currently approved manufacturing process consists of combining [redacted]

The firm proposes to scale-up the manufacturing process [redacted]

The proposed manufacturing process consists of combining [redacted]

with subsequent compression into tablets.

Process step	Current site	Proposed site	Current equipment	Proposed equipment	Biolot Batch size	Current Production Batch size	Proposed Productio Batch siz
		USL					
	USL	USL					
	USL	USL					
	USL	USL					

Raw material controls, Executed batch records, Manufacturing records, controls for finished dosage form stability data, in vitro dissolution data and USP testing results submitted in Attachments 6-10, were satisfactory.

The Proposed (USL) Facility's in-process specifications, methods and testing requirements are the same as those previously approved for

The Manufacturing records, packaging records, label reconciliation and Batch Reconciliation data for Amiodarone Hydrochloride Tablets, 200 mg, manufactured at the proposed USL facility (Lot# 65267) were submitted and the data is satisfactory.

The identity, potency, uniformity of dosage units, dissolution profile and the purity of the finished product manufactured in the new Facility (USL Facility), meets all approved specifications for the Amidarone HCl tablets, 200 mg.

17. **PACKAGING**

Review Status: N/A

18. **STABILITY**

Review Status: Satisfactory

T The post-approval stability commitment is provided on page 339. 3 months accelerated and controlled room temperature stability data in the approved package sizes of 60 tablets/bottle, 500 tablets/bottle and 100 unit dose tablets/carton have been submitted on Amiodarone Hydrochloride Tablets, 200 mg (Lot # 65267) in Attachment 10 of the supplement.
A table summarizing the stability studies for each packaging configuration is provided followed by the individual stability profiles for the 3 months accelerated and controlled room temperature (CRT) studies.

The satisfactory stability results demonstrate the acceptability, quality, integrity and stability for the finished product manufactured using ——— produced at the proposed ——— manufacturing site, Upsher-Smith (pages 341-355).

19. **REMARKS AND CONCLUSION:**

The proposed change meets the SUPAC-IR guidance definition of a Level 3 site change. The submitted data support the proposed scale-up in the production. Labeling revision has been approved and hence these supplements are approved.

20. **ORDER OF REVIEW:**

The application submissions covered by this review were taken in the date order of receipt Yes X No
If no, explain reason(s) below:

21. **SPOT? Yes No** X

If yes, complete form

22. **REVIEWER AND DATE COMPLETED :**

Mouna P. Selvam, Ph.D., / March 30, 2000

REVIEW OF PROFESSIONAL LABELING # 1

SUPPLEMENT

FPL - Container Labels and Carton and Insert Labeling

DATE OF REVIEW: November 17, 1999

ANDA #: 75-135/S-007

NAME OF FIRM: Upsher-Smith

NAME OF DRUG: Pacerone® (Amiodarone HCl) Tablets, 200 mg

DATE OF SUBMISSION: October 28, 1999

COMMENTS:

The firm has successfully revised their container labels and carton and insert labeling to reflect the change in the manufacturer.

RECOMMENDATIONS:

Inform the firm of the above comments.

FOR THE RECORD:

1. Review based on the labeling of Cordarone® (Amiodarone HCl) Tablets, Wyeth, revised 10-20-98; approved 1-5-99.

2. This submission is a combined chemistry/labeling piece reflecting a change in the manufacturing site as well as scale-up, and incorporate equipment and process changes for the drug product.

3. I spoke to Cindy Farner of the firm about the new RLD changes and she said that they were already aware of them from our website and would be submitting a SS-CBE at their next printing. The firm will prepare and submit revised insert labeling to be in conformance with the recently approved labeling for Cordarone® Tablets (Wyeth - Approved 10-8-99; Revised 8-26-99). The submission will be a SS-CBE supplement.

cc: ANDA 75-135/S-007

/S/ 12/22/99

/S/

SUPAC / PAC ROUTING FORM

This form is to accompany all SUPAC / PAC supplements. Upon completion return to Document Room with appropriate letter (if required) for letter issuance, data entry, and filing.

I. To be completed by Document Room using industry cover letter:

DATE PROCESSED: 11-1-99

APPLICATION #: 75-135 SUPPLEMENT #: 75-135 — SCB-005 - SI SCR-006 - SI SL-007 - SI

SUPAC modifier (amendment type code):

- ✓ SI - (SUPAC-IR) Immediate release solid oral dosage forms
- ___ SS - (SUPAC-SS) Semisolid topical dosage forms
- ___ SE - (SUPAC-MR) Modified release oral dosage forms
- ___ ST - (SUPAC-TDS) Transdermal dosage forms
- ___ SP - (PAC-SAS) Sterile Aqueous Solutions
- ___ SL - (PAC-ATLS) Analytical Testing Laboratory Sites

Type of change (event code): (check all that apply)

- ✓ S1 - Batch Size (Scale-Up/Scale-Down)
- ___ S2 - Components and Composition
- ___ S3 - Manufacturing Equipment
- ___ S4 - Manufacturing Process
- ✓ S5 - Site (e.g. manufacturing, packaging, testing)

SPECIAL

Supplement Type:

- ___ (PL) PRIOR APPROVAL *Skip to Item IV below*
- ✓ (CBE) CHANGES BEING EFFECTED *Proceed with Items II, III, & IV*

To be determined by Chemistry Division:

___ (IS) INCORRECT SUPPLEMENT CATEGORY (non-SUPAC)
Chemistry Division Team Leader: _____ Date: _____

✓ (GR) QUALIFIES as CBE
Chemistry Division Team Leader: /S/ Date: 11/8/99

___ (DN) DOES NOT QUALIFY as CBE NOTE: SUPAC CBE Checklist: Failure to Qualify, or other qualification

ient required

Chemistry Division Team Leader: _____ Date: _____

Chemistry Division Director concurrence: _____ Date: _____

~~The (___ Project Manager ___ Chemistry Team Leader) will prepare notification of non-qualification letter in~~
iance with ___ division policy on Chemistry, Manufacturing, and Control supplement letters.

To Document Room:

Record SUPAC codes as special amendment for supplement.
File in archival submission.
HFD-358, Project Manager/CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-135/S-001 to 007

CORRESPONDENCE

ANDA 75-135

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

APR 1 1999

Dear Dr. Robbins:

This is in reference to your approved abbreviated new drug application dated May 19, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Amiodarone Hydrochloride tablets, 200 mg.

This letter is to inform you that the Food and Drug Administration (FDA) is preparing to initiate proceedings to change the therapeutic equivalence evaluation code for your drug product, Amiodarone Hydrochloride 200 mg Tablets, from "AB" to "BX". These codes are listed in the agency's publication Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Please refer to page xxi, paragraph 1.10, "Change of the Therapeutic Equivalence Evaluation for a Single Product" in the Preface to the 18th Edition of the Orange Book. The procedure that the agency uses to change a therapeutic equivalence evaluation code is outlined in the Orange Book.

The following provides an overview on the events leading to this recommendation:

Subsequent to the approval of your ANDA, the Agency determined that the absorption of amiodarone hydrochloride is significantly increased by food. As a result a food-effect study is now needed to fully demonstrate bioequivalence of generic amiodarone hydrochloride products to the Reference Listed Drug (RLD). Since there is no information regarding your product's is bioequivalence to Cordarone® when used under fed conditions, the Agency is requesting that you submit a food-effect study to evaluate food-effect differences between your drug product and Wyeth-Ayerst's drug product. We should receive the study as soon as possible.

The following steps should be followed to maintain your therapeutic equivalence evaluation code:

A single dose, two-treatment, two-period, two-sequence crossover study comparing your drug product to Wyeth-Ayerst's drug product under fed conditions is requested. The agency will initiate proceedings to change the therapeutic equivalence evaluation code of your amiodarone hydrochloride tablets from "AB" to "BX" in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book), unless within 30 days of receipt of this letter, you notify the Office of Generic Drugs that you will take the following steps:

(1) Within 60 days of the receipt of this letter, you will initiate a food-effect bioequivalence study. You may use a new bioequivalence batch, if your original bioequivalence batch is expired.

(2) Within one hundred and eighty days after initiation of the study, ANDA 75-135 will be supplemented with the written report of the food-effect study results.

(3) If the food-effect study demonstrates that the test and reference drug products are bioequivalent, the therapeutic equivalence evaluation code will not be changed. However, if bioequivalence of your amiodarone hydrochloride tablets is not demonstrated under fed conditions, the therapeutic equivalence evaluation code will be changed to "BX".

You may request expedited review based upon legal or regulatory actions (Please refer to the Office of Generic Drugs Policy and Procedure Guide 18-90).

If you have any questions regarding this letter, you may contact Lizzie Sanchez, Pharm.D. of my staff at 301-827-5847.

Sincerely yours,

/S/

Douglas L. Sporn,
Director, Office of Generic Drugs
Center for Drug Evaluation and Research

MESSAGE CONFIRMATION

04/01/99 13:30
ID=FDA/CDER/OGD

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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-615)
7500 STANDISH PLACE, ROCKVILLE, MD 20855

DATE: 4/1/99

TO: Mark Robbins **FROM:** P Rickman

PHONE: 612 493 4412 **PHONE:** (301) 827-5862

FAX#: 612 4764026 **FAX#** (301) 594-1174

TOTAL NUMBER OF PAGES: 2
(Excluding cover sheet)

SPECIAL INSTRUCTIONS:

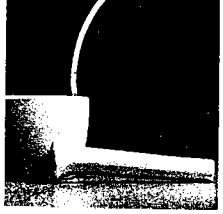
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-615)
7500 STANDISH PLACE, ROCKVILLE, MD 20855

DATE: 4/1/99

TO:	Mark Robbins	FROM:	P Rickman
PHONE:	612 473 4412	PHONE:	(301) 827-5862
FAX#:	612 476 4026	FAX#	(301) 594-1174

TOTAL NUMBER OF PAGES: 2
(Excluding cover sheet)

SPECIAL INSTRUCTIONS:



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

SUPAC-IR SUPPLEMENT

February 15, 1999

NDA NO. _____ REF NO. SC001
NDA SUPPL FOR Facility Add.
SC001 SL

FEDERAL EXPRESS

ARCHIVAL COPY

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

SUBJECT: **ANDA #75-135: Pacerone® (Amiodarone HCl) Tablets, 200 mg**
Alternate Manufacturing Site Supplement

SPECIAL SUPPLEMENT- CHANGES BEING EFFECTED (SUPAC-IR)

Dear Mr. Sporn:

Reference is made to the above referenced subject original abbreviated new drug application (ANDA), and to the agency's approval letter for that application dated April 30, 1998. Pursuant to 21 CFR 314.70(c), and in accordance with the CDER *November 1995 Guidance for Industry: Immediate Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes...* (SUPAC IR), we herewith submit a supplement to use an alternate manufacturing facility for the drug product.

Specifically, Upsher-Smith is notifying the agency of its intention to incorporate as an alternate site for the portion of the manufacturing process. The and therefore represents a different campus than the currently approved

FEB 16 [illegible]

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX# 612-476-4026 Sales & Distribution 1-800-654-2299

GENERIC DRUGS

The proposed change meets the SUPAC-IR guidance definition of a Level 3 site change: it does not include any scale-up changes, changes in manufacturing, or changes in components or composition. The same equipment, SOP's, environmental conditions, and controls will be used in the manufacturing process at the new site. Although [redacted] are separate entities, both are wholly owned subsidiaries of the same company, [redacted] id Upsher-Smith maintains one quality contract with with [redacted] which covers both the [redacted] Additionally, the alternate facility, [redacted] received a satisfactory FDA inspection covering its [redacted] within the previous 2 years (November 1997).

Key test documentation enclosed includes an executed batch record, accelerated stability data for finished product utilizing material [redacted], and a [redacted] profile comparing material from the current and proposed sites. Additionally, we have enclosed a CGMP compliance letter from

In summary, we have enclosed the following in support of this supplement:

- Index/Table of Contents.
- Application Form FDA 356h and Field Copy Certification.
- [redacted] Debarment and Convictions Certification letters.
- Raw Material Controls Information and Applicable Testing Results.
- Manufacturing Information, including [redacted]
- In-Process Controls Information, including [redacted] and In-Process Specifications and Testing Results.
- Finished Product Testing Results for the Exhibit Batch, including Comparative Dissolution Profiles (Current vs. Proposed).
- Post-Approval Stability Commitment and Stability Data for the Exhibit Batch.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

This supplement is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

Pursuant to 21 CFR 314.70(a), we hereby certify that a field copy of this supplement, which is a "true" copy, has been sent to the applicant's district FDA office in Minneapolis, Minnesota.

If there are any questions regarding the information in this submission, please contact Cindy Farner, Senior Regulatory Affairs Specialist at (612) 449-7267.

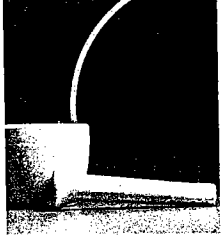
Sincerely,

Mark S. Robbins

Mark Robbins, Ph.D.
Vice President, Scientific Affairs

Enclosure: *Supplement to ANDA #75-135: Pacerone® (Amiodarone HCl) Tablets, 200 mg*

APPEARS THIS WAY
ON ORIGINAL



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

NEW CORRESP

NC to Bio

FEDERAL EXPRESS

April 28, 1999

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

RE: ANDA 75-135: Pacerone® (Amiodarone HCl) Tablets, 200 mg
Supplement Responding to the Agency's April 1, 1999 Letter Regarding the Therapeutic Equivalence Evaluation

Dear Mr. Sporn:

Reference is made to the Upsher-Smith Laboratories, Inc. original ANDA 75-135 for the above referenced drug product, and to the Agency's approval letter for the application dated April 30, 1998.

Reference is also made to the Agency's letter dated April 1, 1999 regarding the therapeutic equivalence evaluation for the above referenced drug product.

Via this letter, Upsher-Smith is notifying the Agency of its intention to perform the requested food-effect study to fully demonstrate bioequivalence of our product to the reference listed drug product.

Specifically, Upsher-Smith provides the following commitments with respect to this product application:

RECEIVED

APR 29 1999

GENERIC DRUGS

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX# 612-476-4026 Sales & Distribution 1-800-654-2299

(1) Within 60 days of the receipt of the Agency's April 1, 1999 letter, Upsher-Smith will initiate a food-effect bioequivalence study comparing the Upsher-Smith Pacerone® drug product to the Wyeth-Ayerst Cordarone® reference listed drug product under fed conditions. A currently marketed production lot of Pacerone®, as well as a currently marketed production lot of Cordarone®, will be used in the food-effect bioequivalence study.

(2) Within one hundred and eighty days after initiation of the study, ANDA 75-135 will be supplemented with the written report of the food-effect study results.

(3) If the food-effect study demonstrates that the test and reference drug products are bioequivalent, the therapeutic equivalence evaluation code will not be changed. However, Upsher-Smith acknowledges that if bioequivalence is not demonstrated under fed conditions, the FDA may initiate proceedings to change the therapeutic equivalence evaluation code to "BX".

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of your office.

This supplement is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

If there are any questions or further information is required, please contact Mark Halvorsen, Pharm.D., Manager, Clinical and Regulatory Affairs at (612) 449-7315.

Sincerely,

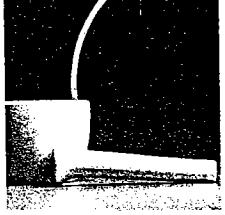
UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac

desk copy: Dale Conner, Pharm.D., Director, Division of Bioequivalence
Donald Hare, Special Assistant to the Director



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

April 29,1999

NDA NO. _____ REF NO. SCB 002
NDA SUPPL FOR Facility Add.
SC

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

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

RE: ANDA 75-135; Pacerone® (Amiodarone HCl) Tablets, 200 mg
Supplement to Provide for Analytical Laboratory Testing Site Changes
SPECIAL SUPPLEMENT—CHANGES-BEING-EFFECTED (PAC-ATLS)

Dear Mr. Sporn:

Reference is made to the Upsher-Smith Laboratories, Inc. (Upsher-Smith) ANDA 75-135 for the above referenced drug product, and to the Agency's approval letter for the application dated April 30, 1998.

Pursuant to 21 CFR 314.70(c) and in accordance with the CDER April 1998 Guidance for Industry "PAC-ATLS: Postapproval Change—Analytical Testing Laboratory Sites", this supplement provides for the addition of an alternate analytical testing laboratory site and the change in location of an analytical testing laboratory site included in the approved ANDA.

Specifically, Upsher-Smith proposes to add [redacted] as an alternate analytical testing facility to perform [redacted] Purified Water, USP, is a raw material used in the manufacturing process for Pacerone® (Amiodarone HCl) Tablets, 200 mg.

[redacted] is currently approved as the manufacturing site for the [redacted] operation for Pacerone®. The Purified Water, USP raw material used in the [redacted] operation is produced at [redacted] as indicated in the approved ANDA. Subsequently, [redacted] has implemented an [redacted] testing laboratory at the facility for Purified Water, USP raw material chemical testing (i.e., total organic

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX= 612-476-4026 Sales & Distribution 1-800-654-2225

carbon and water conductivity tests). The laboratory was evaluated as part of a May 28-June 9, 1998 general FDA inspection by the New Jersey FDA District Office. A copy of the Form FDA 483 dated June 9, 1998, the response letter dated June 18, 1998, and the FDA acknowledgment letter dated July 20, 1998, are included as Attachment 1. The CFN for the

In addition, approved in the original ANDA for routine testing of raw materials, has expanded their laboratory facilities. The testing services applicable to this product are performed at a new facility located at The corporate headquarters, and other laboratory functions, remain at

The facility was evaluated as part of a February 22-23, 1999 preapproval FDA inspection by the Minneapolis FDA District Office. A copy of the Form FDA 482 and the FDA approvable recommendation letter are included as Attachment 2. The CFN for the

These proposed analytical laboratory changes meet the following criteria specified in the PAC-ATLS Guidance for submission as a Changes-Being-Effected (CBE) Supplement:

- Current compendial test methodology will be used, consistent with approved application requirements for each raw material.
- There are no outstanding postapproval commitments relating to test methods for this product application.
- Both have the capability to adequately perform the intended testing. Information to support the capability of each laboratory to perform the intended testing is on file at the respective laboratory, and is available for FDA review, upon request.
- Both the have had a satisfactory cGMP inspection within the past 2 years.

In conclusion, the criteria for the proposed addition of an alternate laboratory for Purified Water, USP chemical testing, and the criteria for the relocation of the facility for routine testing of pharmaceutical raw materials, as presented in the PAC-ATLS Guidance, have been met. Therefore, Upsher-Smith is submitting the proposed changes as a postapproval Changes-Being-Effected Supplement, effective May 31, 1999, unless otherwise notified by the Agency.

This supplement is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

Pursuant to 21 CFR 314.70(a), we hereby certify that a field copy of this supplement has been submitted to the Minneapolis District FDA for their information as well. This third (field) copy is a "true" copy of this supplemental application.

If there are any questions regarding the information provided, please contact Cindy Farner, Sr. Regulatory Affairs Specialist at (612) 449-7267.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac

Enclosures

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-135

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

MAY 17 1999

Dear Sir:

This is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Amiodarone Hydrochloride Tablets, 200 mg.

Due to recent and significant changes in the labeling of the reference listed drug (Cordarone®; Approved January 5, 1999; Revised October 20, 1998) please revise your insert labeling to be in accord with the enclosed copy of the approved labeling of the reference listed drug.

In addition to the above revisions, please make the following changes:

1. Replace the "CAUTION: Federal law ..." statement with the "Rx only" symbol on all labels and labeling. It should be prominently displayed on the main panel.

2. The established name should include "tablet" on all container labels and carton labeling.

Within 90 days of the receipt of this letter, please submit revised insert labeling as a Special Supplement - Changes Being Effected to your approved application.

The changes to the container label and carton labeling may be submitted in an annual report providing that the changes are described in full.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-~~side~~ comparison of your proposed labeling with your last submission with all the differences annotated and explained.

Sincerely yours,

/S/ 1/17/89

Robert L. Welt, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures: Reference listed drug insert labeling and approval letter

cc: ANDA 75-135

LETTER OUT

/S/

APPEARS THIS WAY
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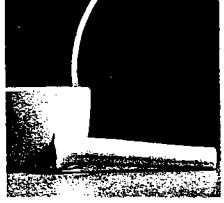

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

FEDERAL EXPRESS

NDA NO. 75/35 REF NO. SL 003
NDA SUPPL FOR Labe/ Revision
AI

September 16, 1999

Approval letter
drafted 9/22/99
A. Vezza

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

RE: ANDA 75-135: Pacerone® (Amiodarone HCl) Tablets, 200 mg
Supplement Providing Revised Package Insert Final Printed Labeling, Requested per the Agency's May 17, 1999 Letter Regarding Reference Listed Drug Labeling Changes

SPECIAL SUPPLEMENT—CHANGES-BEING-EFFECTED

Dear Mr. Sporn:

Reference is made to the Upsher-Smith Laboratories, Inc. original ANDA 75-135 for the above referenced drug product, and to the Agency's approval letter for the application dated April 30, 1998.

Reference is also made to the Agency's letter dated May 17, 1999, regarding requested labeling changes for the above referenced drug product.

Upsher-Smith is submitting the final printed package insert labeling, incorporating the Agency requested changes and in accordance with the currently approved reference listed drug labeling. To facilitate review of the labeling revisions, a side-by-side comparison of the Pacerone® revised package insert labeling (Rev. 0799) to the previously approved package insert labeling (Rev. 1297) is provided. The revision 1297 package insert was approved with the original application. Subsequent editorial changes to the package insert labeling (i.e. Rev. 0598

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP 17 1999
OGD

9-21-99

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX 612-476-4026 Sales & Distribution 1-800-654-2299*

incorporated "®" trademark registration designation; Rev. 0499 incorporated the 90 count bottle and patent information) are also annotated in the side-by-side labeling comparison.

The changes requested for the Pacerone® labels and carton will be implemented and submitted in the next annual report.

This supplement is being submitted in duplicate as an archival and a review copy, for incorporation into our file. The archival copy contains twelve copies of the final printed package insert; the review copy contains one copy of the final printed package insert. In addition, one copy of the final printed package insert is provided in the field copy.

Pursuant to 21 CFR 314.70(a), we hereby certify that a field copy of this supplement, which is a "true" copy, has been sent to the applicant's district FDA office in Minneapolis, Minnesota.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of your office.

If there are any questions regarding this submission, please contact Cindy Farner, Senior Regulatory Affairs Specialist, at (612) 449-7267.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins

Mark S. Robbins, Ph.D., J.D.
Vice President, Scientific Affairs

MSR/bac

Enclosures

APPEARS THIS WAY
ON ORIGINAL

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q:\firms\amiodarone upsher smith

D.S. A.V.
G.B.
D.H.
R.W
P.R.
C.P.
D.C.
R. Patnaik
L. Sanchez
Vezza
Selvam
Ames
Venkatarum

ANDA 75-135

UPSHER-SMITH LABORATORIES, INC.
14905 23RD AVENUE NORTH
MINNEAPOLIS, MN 55447
TELEPHONE: (612) 473-4412
FAX: (612) 476-4026

FAX

TO: **Donald Hare**
Special Assistant to the Director

FAX: **(301) 594-0183**

FROM: **Cindy Farner**
Sr. Regulatory Affairs Specialist

DATE: **September 20, 1999**

RE: **ANDA 75-135, Pacerone® (Amiodarone HCl) Tablets, 200 mg**
Supplement Providing Food-Effect Bioequivalence Data
Requested per the Agency's April 1, 1999 Letter Regarding
Therapeutic Equivalence Evaluation of Amiodarone HCl Tablets

NUMBER OF PAGES (INCLUDING COVER PAGE): 3

This telefax is to inform you of the Upsher-Smith Laboratories, Inc. submission of the requested food-effect bioequivalence study data to ANDA 75-135, Pacerone® (Amiodarone HCl) Tablets, 200 mg. This submission is in response to the Agency's April 1, 1999 letter regarding the therapeutic equivalence evaluation and the corresponding requirement to perform a food-effect bioequivalence study. The food-effect bioequivalence study data provide the Agency with adequate demonstration of bioequivalence to the reference listed drug product, Cordarone®, under fed conditions and, therefore, the current "AB" therapeutic equivalence evaluation code remains appropriate.

If there are any questions or further information is required, please contact Mark Halvorsen, Pharm.D., Director, Clinical and Regulatory Affairs at (612) 449-5315. An expedited review of this submission has been requested.

Upsher-Smith Laboratories, Inc.
Innovative Pharmaceuticals Since 1919

FEDERAL EXPRESS

September 17, 1999

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

RE: ANDA 75-135; Pacerone® (Amiodarone HCl) Tablets, 200 mg
Supplement Providing Food-Effect Bioequivalence Data, Requested per the Agency's April 1, 1999 Letter Regarding the Therapeutic Equivalence Evaluation

SUPPLEMENT—EXPEDITED REVIEW REQUESTED

Dear Mr. Sporn:

Reference is made to the Upsher-Smith Laboratories, Inc. original ANDA 75-135 for the above referenced drug product, and to the Agency's approval letter for the application dated April 30, 1998.

Reference is also made to the Agency's letter dated April 1, 1999, regarding the therapeutic equivalence evaluation and the corresponding requirement to perform a food-effect bioequivalence study for the above referenced drug product, and to the Upsher-Smith response letter dated April 28, 1999.

As stated in the Agency's April 1, 1999 letter, expedited review of this supplement is requested.

Upsher-Smith is submitting the final bioequivalence study report for a randomized, single oral dose, three-treatment, three-period crossover study, titled "A Relative Bioavailability Pilot Study of Pacerone® 200 mg Tablets and Cordarone® 200 mg Tablets Under Fed and Fasting

Conditions." This bioequivalence study was initiated prior to receiving the Agency's April 1, 1999 letter requesting food-effect bioequivalence data from a single dose, two-treatment, two-period, two-sequence crossover study. The Upsher-Smith bioequivalence study was entitled a pilot study, intended for information purposes, and the design was adapted from the single dose, three-way crossover food/fasting study section of the Oral Extended (Controlled) Release Dosage Forms *In Vivo* Bioequivalence and *In Vitro* Dissolution Testing Guidance. The enclosed data provide the Agency with adequate demonstration of bioequivalence. Therefore, the Upsher-Smith product, Pacerone®, is bioequivalent to the reference listed drug, Cordarone®, and the current "AB" therapeutic equivalence evaluation code remains appropriate.

This supplement is being submitted in duplicate as an archival and a review copy, for incorporation into our file. The archival copy (blue jackets) and the review copy (orange jackets) consist of 5 volumes each. In addition, the bioequivalence clinical data are provided on disk in ASCII format. The disk is located in Volume 1 of the archival copy.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of your office.

If there are any questions or further information is required, please contact Mark Halvorsen, Pharm.D., Director, Clinical and Regulatory Affairs at (612) 449-7315.

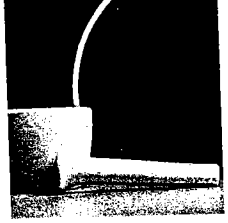
Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins, Ph.D., J.D.
Vice President, Scientific Affairs

MSR/bac

c: Dale Conner, Pharm.D., Director, Division of Bioequivalence (letter only)
Donald Hare, Special Assistant to the Director (letter only)



Upsher-Smith Laboratories, Inc.
Innovative Pharmaceuticals Since 1919

FEDERAL EXPRESS

NDA NO. _____ REF NO. SB 004
NDA SUPPL FOR Bioavailability

September 17, 1999

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

RE: ANDA 75-135: Pacerone® (Amiodarone HCl) Tablets, 200 mg
Supplement Providing Food-Effect Bioequivalence Data, Requested per the Agency's April 1, 1999 Letter Regarding the Therapeutic Equivalence Evaluation

SUPPLEMENT—EXPEDITED REVIEW REQUESTED

Dear Mr. Sporn:

Reference is made to the Upsher-Smith Laboratories, Inc. original ANDA 75-135 for the above referenced drug product, and to the Agency's approval letter for the application dated April 30, 1998.

Reference is also made to the Agency's letter dated April 1, 1999, regarding the therapeutic equivalence evaluation and the corresponding requirement to perform a food-effect bioequivalence study for the above referenced drug product, and to the Upsher-Smith response letter dated April 28, 1999.

As stated in the Agency's April 1, 1999 letter, expedited review of this supplement is requested.

Upsher-Smith is submitting the final bioequivalence study report for a randomized, single oral dose, three-treatment, three-period crossover study, titled "A Relative Bioavailability Pilot Study of Pacerone® 200 mg Tablets and Cordarone® 200 mg Tablets Under Fed and Fasting

Conditions." This bioequivalence study was initiated prior to receiving the Agency's April 1, 1999 letter requesting food-effect bioequivalence data from a single dose, two-treatment, two-period, two-sequence crossover study. The Upsher-Smith bioequivalence study was entitled a pilot study, intended for information purposes, and the design was adapted from the single dose, three-way crossover food/fasting study section of the Oral Extended (Controlled) Release Dosage Forms *In Vivo* Bioequivalence and *In Vitro* Dissolution Testing Guidance. The enclosed data provide the Agency with adequate demonstration of bioequivalence. Therefore, the Upsher-Smith product, Pacerone®, is bioequivalent to the reference listed drug, Cordarone®, and the current "AB" therapeutic equivalence evaluation code remains appropriate.

This supplement is being submitted in duplicate as an archival and a review copy, for incorporation into our file. The archival copy (blue jackets) and the review copy (orange jackets) consist of 5 volumes each. In addition, the bioequivalence clinical data are provided on disk in ASCII format. The disk is located in Volume 1 of the archival copy.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of your office.

If there are any questions or further information is required, please contact Mark Halvorsen, Pharm.D., Director, Clinical and Regulatory Affairs at (612) 449-7315.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins, Ph.D., J.D.
Vice President, Scientific Affairs

MSR/bac

c: Dale Conner, Pharm.D., Director, Division of Bioequivalence (letter only)
Donald Hare, Special Assistant to the Director (letter only)

labeling review
digital 11/17/99
A. Vega

NDA NO. 75135 REF NO. SCB-005
NDA SUPPL FOR Facility Addition
SI

NDA NO. 75135 REF NO. SCR-006
NDA SUPPL FOR Manufacturing Revision
SI

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

SUPAC-IR SUPPLEMENT

NDA NO. 75135 REF NO. SL-007
NDA SUPPL FOR Labeling Revision
SI

October 28, 1999

OVERNIGHT COURIER 10/28/99

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

ARCHIVAL COPY

Marks SUPAC-IR
Changes Being Effected
Pursuant to
21 CFR 314.70 (c)
Concur by
Mowra Selvam
11/5/99.

SUBJECT: **ANDA #75-135: Pacerone® (Amiodarone HCl) Tablets, 200 mg**
SUPAC-IR Supplement for Change of Manufacturing Site, Scale-Up, Equipment and Process Changes

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED (SUPAC-IR)

Dear Mr. Sporn:

Reference is made to the above referenced original abbreviated new drug application (ANDA), and to the Agency's approval letter for that application dated April 30, 1998.

Reference is also made to the Agency's October 25, 1999 letter confirming that the multiple changes described below are acceptable as a SUPAC-IR Changes-Being-Effected Supplement. Pursuant to 21 CFR 314.70 (c), and in accordance with CDER's November 1995 *Guidance for Industry: Immediate Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes...* (SUPAC IR), we herewith submit a supplement to change the manufacturing site, scale-up, and incorporate equipment and process changes for the drug product.

OCT 29 1999

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4112 FAX= 612-476-4026 Sales & Distribution 1-800-654-2299

Specifically, Upsher-Smith is notifying the agency of its intention to change the site for the portion of the manufacturing process to Upsher-Smith Laboratories Inc. The Upsher-Smith manufacturing site is located at 14905 23rd Avenue North, Minneapolis, Minnesota. Although this represents a different campus than the currently approved sites, refer to the SUPAC-IR CBE Supplement dated February 15, 1999), the proposed Upsher-Smith site is the same site used for completion of the manufacturing and packaging processes for the finished product approved in this application.

The supplement also includes a scale-up change within 10 times of the bioequivalence batch (from for the bioequivalence batch to a proposed for commercial production batches), and a equipment change from a the same equipment class. Although no subclass is identified in the SUPAC-IR/MR Manufacturing Equipment Addendum, the current and proposed equipment have the same design and operating principles.

It is also noted that process parameter adjustments to accommodate the larger equipment are incorporated as process changes. The process changes, attributable to scale-up and equipment changes, are necessary to obtain with the same characteristics as produced via the currently approved manufacturing process and equipment. Because the larger on the proposed equipment, to obtain the the total An therefore, to achieve the In addition, to avoid the potential for rate, the The parameter changes specified in the batch record include a kg/min and an No other process changes have been made to the manufacturing process approved in this application.

It is further noted that the same SOP's, environmental conditions, and controls will be used in the manufacturing process at the new site. Upsher-Smith Laboratories, Inc., received a satisfactory FDA inspection covering its ~~~~ within the previous 2 years (May 18-28, 1998).

Key test documentation enclosed includes an executed finished product batch record, including ~~~~ manufactured at the proposed site, accelerated stability data for finished product utilizing material ~~~~ at the proposed site, and a Case B multi-point dissolution profile comparing material from the current and proposed sites. Additionally, we have enclosed a cGMP compliance letter from Upsher-Smith.

In summary, the following documents are enclosed in support of this supplement:

- Index/Table of Contents
- Application Form FDA 356h and Field Copy Certification
- Upsher-Smith and FDA Letters regarding SUPAC-IR CBE Supplement Acceptability
- Site Information with cGMP Certification
- Side-by-Side Comparison Labeling and Final Printed Labeling
- Scale-Up Quantities and Formulation Comparison
- Raw Material Controls, including Purified Water, USP Testing
- Manufacturing Information, including Master Batch Records
- In-Process Controls, including Executed Batch Records and In-Process Testing
- Finished Dosage Form Controls, including Finished Product Testing and Comparative Dissolution Profiles
- Stability Commitment Addendum and 3 Month Accelerated and Controlled Room Temperature Stability Data

Upsher-Smith requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be publicly released, through FOI or any other means, without the applicant's written consent to an authorized member of your Office.

This supplement is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

Pursuant to 21 CFR 314.70(a), we hereby certify that a field copy of this supplement, which is a "true" copy, has been sent to the applicant's district FDA office in Minneapolis, Minnesota.

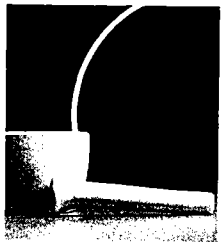
If there are any questions regarding the information in this submission, please contact Cindy Farner, Senior Regulatory Affairs Specialist at (612) 449-7267.

Sincerely,

Mark Robbins, Ph.D.
Vice President, Scientific Affairs

Enclosure: *Supplement to ANDA #75-135: Pacerone® (Amiodarone HCl) Tablets, 200 mg*

APPEARS THIS WAY
ON ORIGINAL



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

FEDERAL EXPRESS

October 13, 1999

SUPPL APPROVED
SB 004
AB

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

RE: ANDA 75-135: Pacerone® (Amiodarone HCl) Tablets, 200 mg
Amendment to Food-Effect Bioequivalence Supplement, Providing Requested Information per the Agency's October 1, 1999 Telephone Communication

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to the Upsher-Smith Laboratories, Inc. original ANDA 75-135 for the above referenced drug product, and to the Agency's approval letter for the application dated April 30, 1998.

Reference is also made to the Upsher-Smith supplement dated September 17, 1999, providing food-effect bioequivalence study data for the above referenced drug product to support the current therapeutic equivalence evaluation and to the Agency's October 1, 1999 telephone communication requesting additional information.

As stated in the Agency's October 1, 1999 telephone communication, this amendment is being submitted as a TELEPHONE AMENDMENT. The requested information is enumerated below.

CENTER FOR DRUG

APPEARS THIS WAY
ON ORIGINAL

ADMINISTRATION AND

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX= 612-476-4026 Sales & Distribution 1-800-654-2299

1. **Provide comparative dissolution profiles for the test and reference products used in the food-effect bioequivalence study.**

   The requested comparative dissolution data, presented in tabular and graphic format, for Pacerone® (Amiodarone HCl) Tablets, 200 mg, Packaging Lot 17890, Manufacturing Lot 64456, and Cordarone® (amiodarone HCl) Tablets, 200 mg, Lot 9980849, are provided in Attachment 1. The profiles were generated using USP Apparatus 1 (Baskets) at 50 rpm with 900mL 0.05M Sodium Acetate Buffer, pH 4.0, and 1% Polysorbate 80 as the dissolution medium. A copy of the test method is also provided, for the reviewer's reference.

2. **Provide comparative potency and content uniformity data for the test and reference products used in the food-effect bioequivalence study.**

   The requested assay and content uniformity data for Pacerone® (Amiodarone HCl) Tablets, 200 mg, Packaging Lot 17890, Manufacturing Lot 64456, and Cordarone® (amiodarone HCl) Tablets, 200 mg, Lot 9980849, are provided in Attachment 2.

3. **Provide the batch size for Pacerone® (Amiodarone HCl) Tablets, 200 mg, Packaging Lot 17890, Manufacturing Lot 64456.**

   Pacerone® Tablets Manufacturing Lot 64456 was a full-scale commercial production lot, with a final blend yield of [redacted], producing [redacted] during compression and was packaged as Packaging Lot 17890.

4. **Provide the sample processing and QC sample processing procedures used for the food-effect bioequivalence study.**

   [redacted] which includes details of the sample processing and QC sample processing procedures for the analysis of amiodarone and desethylamiodarone in human plasma, is provided in Attachment 3. Please note that this information is proprietary to [redacted] and should be kept confidential.

5. **Provide information for the internal reference standard used in the food-effect bioequivalence study sample analysis.**

   The internal reference standard, designated as L8040 in the food-effect bioequivalence study report, is 2-ethyl-3-(3,5-dibromo-4-β-dipropylaminopropoxybenzoyl)benzofuran. This is the same compound used as an internal reference standard for the bioequivalence study submitted and approved in the original application A Compound Data Sheet for the L8040 internal reference standard used for sample analysis is provided in Attachment 4.

6. **Provide the complete randomization scheme for the food-effect bioequivalence study subjects, including dropouts.**

   A copy of the dosing schedule showing the randomization scheme, including dropouts, for the food-effect bioequivalence study, is provided in Attachment 5.

7. **Provide the food-effect bioequivalence study data on a computer disk.**

   The food-effect bioequivalence study clinical data are provided on a computer disk in ASCII format. The disk is provided in Attachment 6 of the archival copy only.

This amendment is being submitted in duplicate as an archival and a review copy, for incorporation into our file.

We request that all information related to this application be treated as confidential within the meaning of 21 CFR 314.430, and that no information, except as provided in 21 CFR 314.430, be released without our written consent to an authorized member of your office.

If there are any questions or further information is required, please contact Cindy Farner, Senior Regulatory Affairs Specialist, at (612) 449-7267.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins, Ph.D., J.D.
Vice President, Scientific Affairs

MSR/bac

c: Jennifer Fan, Project Manager, Division of Bioequivalence (telefax letter only)