CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-623

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.1 ZARS, Inc. PATENT INFORMATION

Patent No. 6,465,006
Expires: July 28,2015
Method of Use
Patent Owner ZARS, Inc.

The undersigned declares that Patent No. 6,465,006 covers the formulation, composition, and/or method of use of S-Caine Patch. This product is the subject of this application for which approval is being sought.

Patent No. 6,340,472
Expires: July 28, 2015
Method of Use
Patent Owner ZARS, Inc.

The undersigned declares that Patent No. 6,340,472 covers the formulation, composition, and/or method of use of S-Caine Patch. This product is the subject of this application for which approval is being sought.

Patent No. 6,306,431
Expires: July 28, 2015
Method of Use
Patent Owner ZARS, Inc.

The undersigned declares that Patent No. 6,306,431 covers the formulation, composition, and/or method of use of S-Caine Patch. This product is the subject of this application for which approval is being sought.

Patent No. 6,245,347
Expires: July 28, 2015
Method of Use
Patent Owner ZARS, Inc.

The undersigned declares that Patent No. 6,245,347 covers the formulation, composition, and/or method of use of S-Caine Patch. This product is the subject of this application for which approval is being sought.

Patent No. 5,919,479
Expires: July 28, 2015
Formulation
Patent Owner ZARS, Inc.

The undersigned declares that Patent No. 5,919,479 covers the formulation, composition, and/or method of use of S-Caine Patch. This product is the subject of this application for which approval is being sought.

Patent No. 5,658,583
Expires: July 28, 2015
Method of Use
Patent Owner ZARS, Inc.

The undersigned declares that Patent No. 5,658,583 covers the formulation, composition, and/or method of use of S-Caine Patch. This product is the subject of this application for which approval is being sought.

Authorized Signature _____ Date 3/30/07

1.2 ZARS, INC. PATENT CERTIFICATION

In the opinion and to the best knowledge of ZARS, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

EXCLUSIVITY SUMMARY

NDA # 21-623 SUPPL # HFD # 170

Trade Name Synera

Generic Name Lidocaine 70 mg and Tetracaine 70 mg topical patch

Applicant Name Zars

Approval Date, If Known 6-21-05

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-575	Lidocaine patch
NDA# 20-612	Lidoderm patch
NDA# 20-962	Emla Disc

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

sc-54-04 and sc-55-04

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

sc-54-04 and sc-55-04

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 58,823	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 58,823	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Allison Meyer
Title: Regulatory Project Manager
Date: June 21, 2005

Name of Office/Division Director signing form: Bob Rappaport, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # :21-623 Supplement Type (e.g. SE5): _____ Supplement Number: N000

Stamp Date: April 4, 2003 Action Date: 06/21/05

HFD 170 Trade and generic names/dosage form: Synera™ / lidocaine and tetracaine

Applicant: ZARS, INC. Therapeutic Class: Topical local anesthetic

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): One

Indication #1: is indicated for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodessication and shave biopsy of skin lesions

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ___Partial Waiver __x_Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.** 0	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.** 4	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

❑ **Products in this class for this indication have been studied/labeled for pediatric population**
❑ **Disease/condition does not exist in children**
❑ **Too few children with disease to study**
❑ **There are safety concerns**
x **Adult studies ready for approval**
❑ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): 12/31/06

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.** 4	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.** 16	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-623**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-623
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Allison Meyer
6/23/05 05:17:13 PM

DEBARMENT STATEMENT

ZARS, Inc. herewith certifies that the services of any persons debarred under Section 306 (a) or (b) were not and will not be used in any capacity in conjunction with this application.

Signed: _____ Date: 3/30/03

Andrew Crockett
Director
Clinical & Regulatory Affairs

350 WEST 800 NORTH, SUITE 320 - SALT LAKE CITY, UTAH 84103
PHONE 801.350.0202 - WWW.ZARS.COM - FAX 801.350.0303

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
	See Attached

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Larry Rigby	C.E.O.
FIRM / ORGANIZATION: ZARS, Inc.	
SIGNATURE	DATE: 3/31/03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Meyer, Allison

From: Patricia Richards [prichards@zars.com]
Sent: Tuesday, June 21, 2005 5:14 PM
To: Allison Meyer
Cc: 'Michael Ashburn'; 'Andy Crockett'; [redacted]
Subject: NDA 21-623: Synera Container/Carton Labeling Change
Importance: High

Allison,

The following statement will appear in equal prominence (with adequate spacing) after the "Use immediately after opening the pouch" statement:

[redacted]

This change will be made to the container (pouch) and carton (2 and 10 patches) labeling tomorrow. An electronic copy will be sent with a hard copy to follow.

Thank you.

Patricia

Patricia J Richards
ZARS, Inc.
801.350.0202 (telephone)
801.350.0909 (fax)
prichards@zars.com

Office of Drug Safety

Memo

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia and Rheumatology Drug Products
HFD-170

From: Denise Toyer, PharmD
Deputy Director, Division of Medication Errors and Technical Support; Office of Drug Safety, HFD-420

Through: Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support; Office of Drug Safety, HFD-420

Date: June 17, 2005

Re: ODS Consult 05-0090-2; Synera (Lidocaine and Tetracaine Transdermal Patch) 70 mg/70 mg; NDA 21-623

This memorandum is in response to a June 17, 2005 request from your Division for a review of the container labels and carton labeling Synera. Please note that we did not receive revised Patient Application Instructions or insert labeling. We refer you to our June 6, 2005 review for comments on these two items. Listed below are our comments on the Synera container label, pouch and carton labeling.

A. Top Cover Film

1. The sponsor proposes to [redacted] DMETS has several concerns with this proposal.

   a. [redacted]

   b. [redacted]

2. [redacted]

3. [redacted]

B. Carton Labeling (Packaging Sizes #2 and #10)

1. DMETS notes that the labeling was submitted in a black and white presentation. Therefore, we were unable to evaluate the affect color, company logos, etc would have on the readability of the labels. However, we recommend [redacted]

2. DMETS questions the use of the term topical patch as the dosage form. DMETS recommends that the Division contact Dr. Guirag Poochikian of the CDER Labeling and Nomenclature Committee (LNC) for the proper designation of the established name prior to approval.

3. Increase the prominence of the established name in proportion to the proprietary name. In the current presentation (i.e., font size, format, bolding) the established name, dosage form and strength are not prominently displayed.

4. Insert a space between the strength and units of measurement (i.e., 70 mg instead of 70mg).

5. It appears that the statement "For Local Dermal Analgesia" is an indication of use instead of a route of administration. Therefore, we recommend that this information be deleted.

6. The Usual Dosage statement should be revised to include information pertaining to both Venipuncture or Intravenous Cannulation and Superficial Dermatological Procedures and not only the former.

7. Increase the prominence of the route of administration statement "For Topical Use Only." Additionally, relocate this statement to the main display panel.

8. Relocate the "Rx Only" statement to the main display panel.

C. Pouch Labeling

1. See Comments B1 through B8.

2. [redacted]

If you have any questions or need clarification, please contact the medication errors project manager, Diane Smith at 301-827-1998.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Denise Toyer
6/17/05 04:31:02 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

TE RECEIVED: 4/1/05 **DATE OF DOCUMENT:** 3/17/05	**DESIRED COMPLETION DATE:** 4/29/05 **PDUFA DATE:** 6/21/05	**ODS CONSULT #:** 05-0090

TO: Bob Rappaport, MD
Director, Division of Anesthetic, Analgesia and Rheumatology Drug Products
HFD-170

THROUGH: Allison Meyer
Project Manager
HFD-170

PRODUCT NAME: **Synera** (Lidocaine and Tetracaine [redacted] Patch) 70 mg/70 mg **NDA#: 21-623**	**NDA SPONSOR:** Zars, Inc.

SAFETY EVALUATOR: Felicia Duffy, RN

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Synera. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Synera acceptable from a promotional perspective.

Denise Toyer, PharmD Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664	Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 27, 2005

NDA# 21-623

NAME OF DRUG: **Synera**
(Lidocaine and Tetracaine [redacted] Patch)
70 mg/70 mg

NDA HOLDER: Zars, Inc.

*** **NOTE: This review contains proprietary and confidential information that should not be released to the public.** ***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Analgesia and Rheumatology Drug Products (HFD-170), for assessment of the proprietary name, "Synera", regarding potential name confusion with other proprietary or established drug names. Container labels, carton labeling and insert labeling were not provided for review and comment.

The sponsor previously submitted the proprietary name as [redacted] The Division of Drug Marketing, Advertising and Communications (DDMAC) found the name unacceptable. The Division agreed with DDMAC's objection, therefore, DMETS did not conduct a safety review of the proprietary name, [redacted] (ODS consult #05-0015). The sponsor submitted the following alternate proprietary names: [redacted] "Synera", and [redacted] DDMAC and the Division found the names [redacted] unacceptable from a promotional perspective (see section IIA). Thus, DMETS will only proceed with the review of the proprietary name, Synera.

PRODUCT INFORMATION

The Synera Patch is a topical product for the administration of two anesthetics, lidocaine and tetracaine, to intact skin. Each Synera Patch contains a eutectic mixture of lidocaine 70 mg and tetracaine 70 mg. The delivery of the anesthetics into the skin is enhanced with heat by the activation of an oxygen-activated heating element contained within the patch. The heating element is activated once the patch is removed from the package and is exposed to oxygen in the air. The heating element generates a mild warming effect for the duration of the application. The product is indicated as a topical anesthetic for the use on intact skin for local dermal anesthesia. Synera should be applied for 20-30 minutes prior to a procedure.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2,] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Synera to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for Synera consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Synera. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Synera acceptable from a promotional perspective.

2. The Expert Panel identified six (6) proprietary names that were thought to have the potential for confusion with Synera. These products are listed in table 1 (see below and on page 4), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Synera	Lidocaine and Tetracaine [redacted] Patch: 70 mg/70 mg	Apply 20-30 minutes prior to venipuncture, IV insertion, or superficial dermatologic procedures	
Synalar	Fluocinolone Acetonide Cream: 0.01%, 0.025% Ointment: 0.025% Topical Solution: 0.01%	Apply sparingly to affected areas 2 to 4 times daily.	LA
Synarel	Nafarelin Acetate Metered Nasal Spray: 0.2 mg/spray	Endometriosis: 1 spray in one nostril QAM, 1 spray in the other nostril QPM. Central precocious puberty: 2 sprays into one nostril QAM and 2 sprays in the other nostril QPM.	LA/SA

[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Synera	Lidocaine and Tetracaine [redacted] atch: 70 mg/70 mg	Apply 20-30 minutes prior to venipuncture, IV insertion, or superficial dermatologic procedures	
Synercid	Dalfopristin and Quinupristin Injectable: 350 mg/vial;150mg/vial	Vancomycin-resistant *E. faecium*: 7.5 mg/kg IV Q8hrs. Complicated skin and structure infection: 7.5 mg/kg IV Q12hrs.	LA
Cynara-SL	Artichoke Extract Capsule: 320 mg	1-2 capsules daily.	LA/SA
			LA
Femara	Letrozole Tablet: 2.5 mg	2.5 mg po QD.	SA

*Frequently used, not all-inclusive.
**LA (look-alike), SA (sound-alike)
*** **Name pending approval. Not FOI releasable.**

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Synera were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Synera with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses) for each. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Synera (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION

Outpatient RX:	Synera As directed in clinic today Dispense 1
Synera as dir in clinic today #1	
Inpatient RX:	
Synera to be applied for 20 min prior to procedure today as directed	

2. Results:

One respondent interpreted the proposed name as "Synara", which may look and sound similar to the currently marketed herbal product, Cynara-SL. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Synara, the primary concerns related to look-alike and sound-alike confusion with Synalar, Synarel, Synercid, Cynara-SL, [redacted]***, and Femara. Upon further review of the names gathered from EPD, the name [redacted]*** was not further reviewed due to a lack of strong orthographic similarities to Synara, in addition to numerous differentiating product characteristics such as product strength, indication for use, frequency of administration, route of administration, and dosing formulation. Although Synera may appear orthographically similar to Synalar and Synercid, neither name was further reviewed due to the lack of overlapping product characteristics such as product strength, indication for use, frequency of administration, route of administration, and dosage form.

DMETS conducted prescription studies to simulate the prescription ordering process. One respondent from the verbal prescription study misinterpreted the name Synera as "Synara", which may look and sound similar to the currently marketed herbal product, Cynara-SL (if the "SL" is omitted). However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, Synera.

1. Sound-Alike and/or Look-Alike Concerns

   a. Synarel may look and sound similar to Synera. Synarel is a nasal spray indicated for the treatment of endometriosis and precocious puberty. Synarel looks similar to Synera because they share the same first three letters "Syn". In addition, the "el" at the end of Synarel may look like an open "a" if it is not prominent. Both names share phonetic similarities since they each contain three syllables and the first syllable is the same ("Syn"). The second and third syllables help to give each name a slight phonetic differentiation ("arel" vs. "era"). Synarel and Synera are both available in a single strength; however, they differ in indication for use (endometriosis/precocious puberty vs.

*** **Note: This review contains proprietary and confidential information that should not be released to the public.*****

dermal analgesia), frequency of administration, route of administration, and dosage form. Despite the orthographic similarities between Synera and Synarel, both drug products have will have different areas of distribution. Synarel will be available in the retail setting, whereas Synera will be primarily in an outpatient clinic or inpatient setting. Additionally, according to the 2004 annual report for Synarel, the distribution from December 2003 – February 2005 was [redacted] Since the distribution of Synarel is low, the likelihood of confusion between the two products is minimized. Based on the distribution levels and differentiating product characteristics, the potential for confusion between Synera and Synarel is minimal.

Synera Synarel

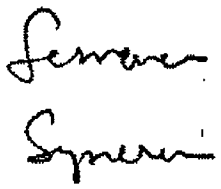
b. Cynara may look and sound similar to Synera when scripted or pronounced. DMETS identified two different citations including Cynara. The first citation was found in the USPTO website as 'Cynara' listed as gas separation and purification services using membranes and membrane equipment. The second citation is Cynara-SL, an herbal over-the-counter product indicated for relief from occasional discomfort associated with heartburn, acid indigestion, upset stomach, and irritable bowel syndrome. Only the latter, Cynara-SL, will be discussed further. Cynara (without the modifier 'SL') and Synera may look and sound similar because they both contain six letters and three syllables that are almost identical. Although Synera begins with an "S" and Cynara begins with a "C", both letter can look similar if they are not prominent. In addition, the ending of Cynara can look very similar to the ending of Synera ("-ara" vs. "-era"). Furthermore, the beginning and ending of each name can have the same pronunciation ("Cyn" vs. "Syn" and "ara" vs. "era").

Cynara

Synera

Despite orthographic and phonetic similarities, Cynara and Synera have differentiating product characteristics such as indication for use (acid indigestion vs. dermal analgesia), frequency of administration (as needed or once daily vs. prior to procedure), route of administration (oral vs. topical), strength (320 mg vs. 70 mg/70 mg), and prescription status (over-the-counter vs. rx only). The potential may exist for confusion between Cynara and Synera if a health care provider is taking a patient's medication history and misinterprets Cynara as Synera or vice versa. Either way, upon further clarification, confusion between the two drug products can be resolved. If a healthcare provider receives a verbal order for Synera and they are unsure of what the product is, they may attempt to retrieve information about the product on the internet. If the healthcare provider spells the name (e.g. Senara), they may be directed to the Cynara product's website. Once they read about Cynara, the healthcare provider will likely question the order (i.e., for artichoke extract) and call the ordering provider for clarification. Although there may be some initial confusion with the names, the situation will be rectified upon further investigation. It is also unlikely to see prescription orders for an herbal supplement (Cynara) in either an inpatient or outpatient setting. Furthermore, according to Thomson and Thompson, the last record of sales of Cynara-SL was in 2002 and the product is not able to be purchased from the company's website (*www.lichtwer.com*). Due to the unavailability of Cynara-SL, the different product characteristics and conditions of use, the risk of medication errors between theses two products are minimal.

c. Femara may look and sound similar to Synera when written or pronounced. Femara is indicated for the treatment of advanced breast cancer. Femara may look similar to Synera if the letter "F" is written in lower-case and the downstroke of the "f" is dragged while crossing the "f" (see example below). Additionally, both names contain six letters and the endings may look similar when scripted ("mara" vs. "nera"). Although the first letters may look similar, the downstroke of the letter "y" in Synera helps to differentiate the two names. Femara and Synera may sound similar since they each contain three syllables and there endings share a rhyming quality. Despite some phonetic similarities, the beginning of each name is phonetically different ("Fem" vs. "Syn"). Femara and Synera are available in single strengths (2.5 mg vs. 70 mg/70 mg); however, they differ in indication for use (breast cancer vs. acid indigestion), usual dosage (1 tablet vs. 1 patch), frequency of administration (once daily vs. prior to procedure), route of administration (oral vs. topical), and dosage form (tablet vs. patch). Although both drug names can be written with "take as directed" instructions, the concern for confusion between Femara and Synera is minimal due to the lack of convincing orthographic and phonetic similarities along with differentiating product characteristics such as indication for use, strength, usual dosage, route of administration, frequency of administration and dosage form.



2. Other Safety Related Concerns

DMETS considered the following issues as potential safety related concerns: exposure to external heat sources and the primary area of use of the product. DMETS contacted the Division's Medical Officer, Howard Josefberg, via telephone to gain clarification on the use of this product.

a. DMETS was initially concerned with the potential for dose dumping if the patch is exposed to an external heat source or if the patient had an internal fever. This concern stemmed from postmarketing reports of patients receiving overdoses of Fentanyl, after their patch was exposed to external heating sources such as sunlight and heating blankets. After the discussion with Dr. Josefberg, this issue of concern is minimized due to the fact that Synera has its own internal heating element which is designed to enhance delivery of the medication. Additionally, outside sources of heat will unlikely increase absorption or affect the internal heating element. Thus, external heat is not likely to cause an overdose. Additionally, since Synera will primarily be used in an outpatient clinic or inpatient setting rather than be dispensed in the retail setting, the patient will be in a controlled environment and will probably not be exposed to external heat sources.

b. As previously mentioned, Dr. Josefberg noted that the primary area of use will most likely be in an inpatient or outpatient clinic setting rather than being dispensed in a retail setting. Healthcare practitioners could apply the unit immediately prior to a medical procedure. This is likely because the application and onset time (20-30 minutes) is rapid enough that there is no additional benefit to provide Synera to a patient days or hours prior to arrival at the hospital or clinic for a procedure. Additionally, if the patient or procedure is postponed/delayed the patient would have been exposed to the drug

prematurely. The use of Synera in the clinical setting by healthcare practitioners will help to ensure the proper administration of Synera. The proposed packaging of Synera may also discourage use in the retail setting. Since Synera may not commonly be used in the retail setting, pharmacies will unlikely routinely stock this product. Although, one box of Synera will contain ten individually packaged units, if a retail pharmacy receives a prescription for one Synera unit, they would have to order a box of ten units in order to dispense one individual unit. The remaining nine units would remain on their shelf until they receive another prescription or expires. Retail pharmacies do not routinely stock pharmaceuticals that have a limited patient population but generally will order the product specifically for an individual patient. Thus, a packaging configuration of a multiple of ten (when a patient may only use one unit) may not be conducive to the retail setting.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES:

Since the sponsor did not re-submit revised carton and container labeling, please refer to ODS consult #03-0263 for previous labeling recommendations from DMETS. We re-reviewed the insert labeling and patient application instructions from a safety perspective. DMETS has identified the following areas of improvement, which may minimize potential user error.

A. PACKAGE INSERT LABELING

1. General comment:

   The sponsor utilizes the "µg" abbreviation for micrograms. We recommend using "mcg" to abbreviate micrograms in order to avoid confusing "µg" with "mg". We note that the Joint Commission for Accreditation of Hospitals (JCAHO), 2005 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must "Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization." The use of "µ" is specifically listed as a dangerous abbreviation, acronym, or symbol. Other healthcare organizations, such as ISMP have also published similar lists containing symbols that can lead to medication errors. Please revise throughout the package insert.

2. Overdose section:

   The first sentence of this section addresses the maximum peak plasma concentrations of lidocaine and tetracaine for adults (< 9 ng/mL), however the maximum peak plasma concentrations for pediatric patients are not addressed. Since both patient populations will be using this product, we recommend adding the pediatric information to this section to adequately inform the user.

3. Dosage and Administration section:

   This section should state what age range the product has been approved for use in children as noted in the "Precautions (pediatric use)" section.

4. Handling and Disposal section:

   A "used" patch contains a large quantity of active ingredients (at least 61 mg of lidocaine and [redacted] of tetracaine). Therefore, this section should provide detailed instructions of how to properly dispose of the patch to prevent a child from inappropriately applying the patch to their skin (e.g., fold the sticky surface of the patch together, flush down the toilet, etc…).

B. PATIENT APPLICATION INSTRUCTIONS

1.

   a.

   b.

   c.

   d.

2.

   a.

   b.

3.

   a.

   b.

4. [redacted]

5. [redacted]

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Synera. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days for the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with this use of this product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name Synera acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-1998.

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh, MS
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. Syenra Prescription Study Results

Written Inpatient	Written Outpatient	Verbal
Synera	Sinira	Cenera
Synera	Syncia	Cinera
Synera	Syncream	Sanara
Synera	Syncrem	Scenara
Synera	Synera	Senara
Synera	Synera	Senara
Synera	Synera	Senara
Synera	Syneren	Senera
Synera	Synira	Sinara
Synera	Synira	Synara
Synera	Synira	
Synera	Synira	
Synera	Syniren	
Synera	Synua	
Synera		
Sypera		

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/s/

Felicia Duffy
6/10/05 09:19:55 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/10/05 09:33:53 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/10/05 02:11:29 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/10/05 04:08:26 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-623

INFORMATION REQUEST LETTER

ZARS, Inc.
1142 West 2320 South, Suite A
Salt Lake City, UT 84119

Attention: Patricia Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your December 17, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for S-Caine™ Patch (lidocaine and tetracaine topical patch) 70 mg/70 mg.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Review of your application reveals several discrepancies between protocol and amendment dates cited in final study reports, and those found within the IND itself. For example, the amendments to SC-23-01 and SC-24-01 were dated between June 2001 and July 2002, but most seem to have been first submitted in October 2002.

For each study that utilized the final product formulation (heated and/or non-heated) provide the original protocol date, the actual submission date and serial number, and the dates of enrollment. The same information should be provided for each protocol amendment (amendment date and actual submission date).

Clarify, protocol by protocol, when each investigator completed the necessary documentation, what date that material was actually submitted to the IND, and in which protocol amendment and volume.

Provide sample study drug from SC-55-04, in its foil packaging, specifically the non-heated patches, and the unaltered, to-be-marketed patches as well.

If you have any questions, call Allison J. Meyer, Regulatory Project Manager, at 301-827-7426.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
6/2/05 09:03:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-623

INFORMATION REQUEST LETTER

ZARS, Inc.
1142 West 2320 South
Suite A
Salt Lake City, UT 84119

Attention: Patricia Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to your March 31, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for S-Caine™ Patch (lidocaine and tetracaine topical patch) 70 mg/ 70 mg.

We also refer to your May 7, 2004, submission, proposing [redacted] as a tradename for this product.

We have reviewed the tradename [redacted] and we find it unacceptable for the reasons listed below:

1. [redacted]

2. The name is misleading because it overstates the efficacy of the drug by suggesting that use of the drug will prevent all pain, irregardless of the source or type. In the absence of substantial evidence demonstrating that ALL patients using this drug will not experience ANY pain, the name is misleading.
3. The name is misleading because it is overly fanciful and implies that the drug has some unique effectiveness or composition, when, in fact, the active ingredients are common substances (Lidocaine and Tetracaine). This name would be highly problematic from a promotional perspective because it confers a promotional advantage compared to other topical anesthetic products currently on the market such as Emla, Lidopatch, and lidocaine gel.

We request a prompt written response, including a new proposed tradename, in order to continue our evaluation of your NDA.

If you have any questions, call Allison J. Meyer, Regulatory Project Manager, at 301-827-7431.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
1/27/05 11:39:53 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-623

ZARS, Inc.
1142 West 2320 South, Suite A
Salt Lake City, UT 84119

Attention: T. Andrew Crockett
Director, S-Caine Projects

Dear Mr. Crockett:

We acknowledge receipt on December 21, 2004 of your December 17, 2004 resubmission to your new drug application for S-Caine™ Patch (lidocaine and tetracaine topical patch) 70 mg/70 mg.

We consider this a complete, class 2 response to our February 4, 2004 action letter. Therefore, the user fee goal date is June 21, 2005.

If you have any question, call me, at (301) 827-7431.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Regulatory Project Manager
Division of Anesthetic, Critical Care
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Allison Meyer
1/7/05 02:31:26 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-623

ZARS, Inc.
350 West 800 North, Suite 320
Salt Lake City, UT 84103

Attention: T. Andrew Crockett
Director, Clinical and Regulatory Affairs

Dear Mr. Crockett:

Please refer to the meeting between representatives of your firm and FDA on May 3, 2004. The purpose of the meeting was to discuss the deficiencies noted in the action letter dated February 4, 2004.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7412.

Sincerely,

{See appended electronic signature page}

Pratibha Rana, M.S.
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Date/Time: May 3, 2004 / 3:00-4:30 pm

Location: Parklawn, Chesapeake Room C

Application: NDA 21-263

Sponsor: ZARS, Inc.

Drug Name: S-Caine Patch

Indication: [redacted]

Type of Meeting: Type B

Meeting Chair: Nancy Chang, M.D., Team Leader, Anesthetics Drug Products

Minutes Recorder: Pratibha Rana, M.S., Regulatory Project Manager

ZARS, Inc	Title
Michael Ashburn, MD, MPH	VP, Clinical & Regulatory
[redacted]	
Andrew Crockett	Director, Clinical & Regulatory
Richard Hamer	VP, Clinical & Regulatory (Ferndale)
Sara Hotchkiss	Technical Operation Manager
Wade Hull, MS	Director, Engineering
[redacted]	
Jerry Williams	Director, Quality Assurance
[redacted]	

FDA HFD-170	Title
Bob A. Rappaport, MD	Division Director
Rigoberto A. Roca, MD	Deputy Director
Nancy Chang, MD	Team Leader, Anesthetic Drug Products
Howard Josefberg, MD	Medical Officer
Dan Mellon, PhD	Supervisor, Pharmacology/Toxicology
Suzanne Thornton-Jones, PhD	Pharmacology/Toxicology Reviewer
Eric Duffy, PhD	Director, Division of New Drug Chemistry II
Jila Boal, PhD	Chemistry Reviewer
Dominic Chiapperino, PhD	Chemistry Reviewer
Suresh Doddapaneni, PhD	Team Leader, Biopharmaceutics
Srikanth Nallani, PhD	Biopharmaceutics Reviewer
Thomas J. Permutt, PhD	Team Leader, Statistics
Allison Meyer	Regulatory Project Manager
Pratibha Rana, MS	Regulatory Project Manager

Meeting Objective(s): The purpose of the meeting was to discuss the plans for resolving the outstanding issues prior to submitting a response to the S-Caine Patch action letter dated February 4, 2004.

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the April 2, 2004, meeting package. The slides containing the Sponsor's questions and Agency responses are presented below in *italicized* text. Discussion is presented in normal text.

CMC Questions

Question 1: Regarding item 2b in the action letter

Item2b. There are inadequate controls over the acceptance testing for the raw materials and the components of the S- Caine Patch at Tapemark. Provide revised specifications for [redacted] with the following tests:

1) A specific ID test such as [redacted]
2) Assay based on actual testing at Tapemark

Is the information provided sufficient to justify the addition of [redacted] as an alternate supplier for the [redacted]

FDA Response:

- *Yes, the specifications provided for [redacted] by the new supplier, [redacted] seem adequate.*

Discussion:

The Division informed the Sponsor that raw materials can be supplied by any qualified vendor.

Question 2: Regarding item 2c, is the information provided herein by the Sponsor sufficient to properly address your request?

Item 2c: Provide a justification for the stated shelf life of [redacted] and also describe the nature of the container- closure system in which this is stored.

FDA Response:

- *Yes.*

Discussion:

There was no additional discussion beyond the information provided in the above slide.

Question 3: Regarding item 2d, is the information provided herein by the Sponsor sufficient to properly address your request?

Item 2d: The absorption capacity of [redacted] is listed as a reference property only and it is not listed under the product specifications. Since the absorption capacity is a critical quality attribute to ensure adequate absorption of [redacted] in the patch, this should be listed under specifications. Therefore, provide a revised specification sheet from [redacted] listing absorption capacity as a required specification.

FDA Response:

- *Data demonstrating equivalency between [redacted] are needed.*

Discussion:

The Division stated that equivalency has to be demonstrated whenever the grades are changed.

Question 4: Regarding item 2e, is the information provided sufficient to properly address your request?

Item 2e: Provide a letter of authorization from [redacted] to reference their DMF for the manufacture and controls for the [redacted] Alternatively, provide a description of the manufacturing process of this film and list all components.

FDA Response:

- *Yes.*

Discussion:

There was no additional discussion beyond the information provided in the above slide.

Question 5: Regarding item 2h, is the information provided herein by the Sponsor sufficient to properly address your request?

Item 2h: [redacted] certificate of analysis (COA) for the CHADD pods, provided on page 326/Vol. 3C of the NDA is inadequate. Provide a revised representative COA from [redacted] with the actual observed values of the test results for CHADD™ pods.

FDA Response:

- *This information appears, on its face, to be sufficient.*

Discussion:

There was no additional discussion beyond the information provided in the above slide.

Question 6: Regarding item 2k, is the information provided herein by the Sponsor sufficient to properly address your request?

Item 2k: The description of the container closure system for CHADD heating pods is unclear as to how much protection the [redacted] would provide to the CHADD pods against moisture and oxygen ingress during the anticipated duration of storage of CHADD pods. Therefore, provide data on the moisture vapor transmission rate and oxygen transmission rate of the [redacted] used for storage and the [redacted] capacity of the [redacted]

FDA Response:

- *The information provided appears as if it will be adequate.*
- *Detailed comments will be provided based upon your complete response.*

Discussion:

There was no additional discussion beyond the information provided in the above slide.

Question 7: Regarding item 3a, is the information provided adequate?

Item 3a: The acceptance testing criteria and the impact of the hold time of S-Caine bulk material on the expiration dating of the S-Caine Patch are not described clearly and adequately. Provide a description of [redacted] SOP 02-35 on quantitation of syneresis and the acceptance criteria for the extent of syneresis if observed in the visual inspection of S-Caine bulk material.

FDA Response:

- *It appears that there is no separation of the oil and aqueous phase of the S-Caine bulk material. We will review the additional information in volume 3D of the NDA at the time of complete response.*

Discussion:

The Sponsor notified the Division that they had already submitted the information for review. The Division agreed to verify and review the data.

Question 8: Regarding item 3e, is the proposal acceptable?

Item 3e: Provide a revised specification sheet for the S-Caine bulk material with viscosity testing as part of the release and stability testing. Alternatively, justify why viscosity measurement is irrelevant for ensuring the physical integrity of the emulsion form of the bulk material.
ZARS response: "Quantitation of syneresis is not applicable to the S-Caine bulk material"

FDA Response:

- *Submit the data for the viscosity test demonstrating that it remains constant during the period.*

Discussion:

The Sponsor notified that the data has already been submitted to the Division for review. The Division agreed to verify and review the data.

Question 9: Regarding item 4a, is the Sponsor's proposal acceptable to FDA?

Item 4a: Manufacturing batch records and process controls for the S-Caine Patch should be revised to reflect the process used to manufacture the product used in the pivotal clinical studies, and to produce the drug product consistently.

Note that the revised master production batch record submitted on December 30, 2003, is the official batch record for commercial production, since this reflects more accurately the executed batch records of the primary NDA batches used in the pivotal clinical studies and stability studies. Proposed changes in the [redacted] and other manufacturing changes should be submitted with comparative stability data for the patches made with the current and the revised processes.

FDA Response:

- *Your proposal, as agreed in 3/16/2004 teleconference is acceptable*

Discussion:

There was no additional discussion beyond the information provided in the above slide.

Question 10: Regarding item 4b is the information provided herein by the Sponsor sufficient to properly address your request?

Item 4b: Provide the following additional in-process controls in the [redacted] operations of the [redacted] and of the form-fill pouch during the manufacture of the S-Caine Patch:

- *Dwell times*
- [redacted]

FDA Response:

- *On its face the information provided is acceptable.*

Discussion:

There was no additional discussion beyond the information provided in the above slide.

Question 11: Regarding item 5a, is the Sponsor's proposal acceptable to FDA?

Item 5a: The drug product specifications need to be revised to reflect the desired product performance. Some of the analytical methods need to be refined for better control. Provide additional system suitability criteria, namely the tailing factors and theoretical plates in the assay methods STM 04-104 and 04-103, for the determination of lidocaine, tetracaine, methylparaben, and propylparaben.

ZARS response: "We propose the following criteria..."

FDA Response:

- *These should be acceptable.*

Discussion:

There was no additional discussion beyond the information provided in the above slide.

Question 13: Regarding item 5f, does the Sponsor's response adequately address your request?

Item 5f: The actual temperatures achieved in the pivotal clinical studies by the CHADD heating pod were in the range [redacted] however, the drug release testing was carried out at 40°C. Reconcile this discrepancy and justify why conventional temperature of [redacted] was not deemed appropriate for this test.

FDA Response:

- *Release testing must be performed in the temperature range of [redacted] ^{0}C. Demonstrate temperature rise within the period of clinical use.*

Discussion:

The Division stated that the onset, rate of the rise in temperature, maximum temperature achieved, and rate and timing of temperate drop-off should be well characterized and put in the context of the intended manner of use for this product.

The Sponsor notified that they intend to provide the following two sets of data:

1. A well designed study of the performance of CHADD with respect to temperature achieved at the site of application in adults and elderly subjects of both genders.
2. A controlled study to determine the impact of heat on efficacy in human subjects.

The Sponsor added that the temperature will be close to the current specification, 40 ^{0}C, and they would provide the data to support this claim.

Clinical Question 14: Regarding item 5g, does the Sponsor's response adequately address your request?

Item 5g: Justify why [redacted] was used as an [redacted] in the drug release test media.

FDA Response:

- *Provide data demonstrating that the concentration of [redacted] is justified.*

Discussion:

The Division mentioned that the Sponsor should provide method development data showing progression from simple media to the [redacted] medium.

Question 15: Regarding item 5h, is the Sponsor's proposal acceptable to FDA?
Item 5h: Provide the following tighter acceptance criteria for the drug release for both lidocaine and tetracaine:

1) 20 min: [redacted]

2) 40 min: [redacted]

3) 60 min: [redacted]

FDA Response:

- *This information will be reviewed with your complete response.*
- *Provide comprehensive justification.*

Discussion:

The Division pointed out that the proposed specifications do not seem to be appropriate. The mean specification at the 40 minute time point [redacted] that at the 60 minute time point for both drugs. The Sponsor agreed to propose different specification on the available data.

Question 16: Regarding item 7, does this response adequately address your request?

Item 7: Accidental mishandling of the patch is likely to release the iron powder, and, if it is exposed to air, it may rapidly heat up and cause thermal injuries. Provide data indicating whether S-Caine Patch can release the iron powder, and, if so, indicate the rate and extent of heating.

ZARS response: "This has not occurred ..."

FDA Response:

- *Provide data indicating whether S-Caine Patch can release the iron powder, and, if so, indicate the rate and extent of heating.*

Discussion:

The Division stated that the Sponsor should evaluate the worst-case scenario. The Sponsor should address the safety aspects of the possibility of rapid exposure of the iron powder. The Division cited 2 examples where exposure of the iron powder to the atmosphere might occur in real use: A patch might be damaged or crushed during storage/transport, or users might cut open the wrapping (instead of peeling open) and inadvertently cut the patch itself. The objective is to appropriately label the product to ensure safe use. The Sponsor agreed to fully expose the heating element and report the results to the Agency. The Division clarified that if temperature achieved might burn human subjects, the study/studies should not be performed in humans.

Question 17: Regarding item 8, was [redacted] response sufficient to deem [redacted] adequate to support this NDA?

Item 8: [redacted] referenced in support of tetracaine was deemed inadequate to support this NDA. A deficiency letter was sent to the DMF holder, [redacted]
Was [redacted] response sufficient to deem [redacted] adequate to support this NDA?

FDA Response:

- *[redacted] response has not yet been reviewed.*

Discussion:

There was no additional discussion beyond the information provided in the above slide.

Question 20: Regarding item 1b in the items that are "non-approvability related," does the Sponsor's response adequately address your request?

Item 1b: Provide revised acceptance specifications for tetracaine, USP, with the following test attributes:

- *Specific ID test such as IR*
- *Impurities and degradation products in conformance with ICH Q3A*
- *Heavy metals*
- *Residual solvents*

FDA Response:

Yes.

Discussion:

The Sponsor informed the Division about their concerns with the immediate labeling. The Sponsor explained that [redacted], cross links the drug layer together and without it the

drug would just stick to the other side. Secondly, there is limited space for text and the Sponsor inquired if abbreviations could be used on the label. The Division recommended that the Sponsor make a formal proposal to the Division for review.

Preclinical Questions:

Question 19: Regarding item 12, does the Agency concur that this study design addresses the endpoints specified in the action letter?

FDA Response:

- *The study design for the male fertility study is acceptable.*
- *Submission of the final study reports for the Segment I and III reproduction studies with tetracaine to the NDA with the complete response is acceptable.*

Discussion:

There was no additional discussion beyond the information provided in the above slide.

Question 21: Regarding item 6 in the items that are "non-approvability related," Does the Agency concur that this equivocal response observed with tetracaine will be handled in the package insert?

FDA Response:

- *Yes the equivocal findings in the in vitro chromosomal aberration assay with tetracaine will be handled in the package insert.*

Discussion:

The clinical significance of the equivocal finding in the in vitro chromosomal aberration assay with tetracaine is a review issue and will be addressed in the package insert. Although not a requirement, a repeat study of the in vitro chromosomal aberration assay to clarify the equivocal finding can be conducted.

Clinical Questions

Question 12: Regarding action letter items 5d and 5e,

ZARS Response: "In order to adequately address the Agency's concerns with regard to the temperature profile of the S-Caine Patch on human skin, and with regard to the contribution of the heating component to product efficacy, the Sponsor proposes to conduct two additional studies in adult subjects"

FDA Response:

- *Following submission of finalized protocols further discussion may be required.*

- *The first study, patch effect on skin temperature in volunteers appears to be acceptable on its face.*

- *The second study (heating element contribution to efficacy, SC-54-04) also appears to be generally acceptable.*

- *Written comments will be provided on the proposed statistical analysis.*

Discussion:

The Sponsor agreed to conduct a pilot study first to better understand the patch to patch variability in heating profiles.

Regarding action letter items 2, 3 and 4
Efficacy evaluation in pediatric and in geriatric subjects (#s 2, 3)
Evaluation of anesthetic endpoints (#4)

Items 2, 3: "ZARS is considering options for addressing the Division's concerns about pediatric and geriatric efficacy data. A definitive response will be included with the complete response"

Item 4: "ZARS plans to conduct such a study as a Phase IV commitment ... and will submit a protocol with the complete response."

FDA Response:

- *If and when the S-Caine Patch is approved, the product label will reflect the completed studies.*

Discussion:

The Division stated that the clinical trials conducted do not provide strong support of efficacy in the pediatric and geriatric populations. The Division suggested that the Sponsor submit proposals for phase 4 commitments to address the concerns about efficacy in the pediatric and geriatric populations, and for evaluating neonatal pharmacokinetics.

Question 18: Regarding action letter item 9: "Does FDA concur with the (new) proposal for completion of the clinical study in infants less than 4 months of age?"

FDA Response:

- *We had already agreed that your SC-33-02 proposal was acceptable on its face, as described in submission #12 (6/4/2002).*

- *Enrollment was to have begun in 2002 (per submission # 12).*
- *Efficacy evaluations in newborns should not continue to delay study initiation.*
- *The protocol should be finalized and submitted, with a concrete timetable for enrollment and submission of the final study report.*
- *We encourage completion of this study prior to resubmission.*

Discussion:

The Division also recommended that the Sponsor focus on the new pediatric act, Pediatric Research Equity Act (PREA). The Division strongly recommended expanding the NDA submission to include all relevant age groups. The Division strongly encouraged the Sponsor to provide a thorough and high quality assessment of efficacy and safety in relevant pediatric age groups since the product is anticipated to be used largely in pediatric patients, including neonates and premature infants. The Sponsor informed the Division that the delay was due to unavailability of the patch. The Division suggested that the Sponsor also had the option of submitting a pediatric written request.

Action Items:

1. The Division will review data, included in volume 3D of the NDA, concerning the acceptance testing criteria and the impact of the hold time of S-Caine bulk material on the expiration dating of the S-Caine Patch.

2. The Division will verify that data has been submitted for viscosity tests demonstrating that it remains constant during a [redacted]

3. The Sponsor agreed to perform two additional studies including (1) test patch effect on facial skin temperatures in adult patients, (2) test heating element contribution to efficacy, SC-54-04.

4. The Sponsor will submit proposals for Phase 4 commitments in pediatric and geriatric patients, as well as neonatal pharmacokinetic studies.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Pratibha Rana
6/8/04 03:37:33 PM

EOP2 meeting minutes
May 9, 2000

IND 58,823

Zars, Inc.
49 Wanderwood Way
Sandy, Utah 84092

Attention: Anne T. Carter, R.A.C.
Director, Clinical and Regulatory Affairs

Dear Ms. Carter:

Please refer to the End of Phase 2 meeting between representatives of your firm and FDA on May 9, 2000. The purpose of that meeting was to review the clinical studies and to discuss the clinical plan for Phase 3 clinical trials for S-Caine™ (tetracaine base, USP and lidocaine base, USP) Local Anesthetic Patch.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: May 9, 2000 **IMTS#** 5722
Time: 1:30 am – 3:00 pm
Location: Conference RoomL
Drug: S-Caine™ Local Anesthetic Patch
Sponsor: Zars, Inc.
Indication: [redacted]
Type of Meeting: Type B Meeting, EOP2
Meeting Chair: Bob Rappaport, M.D., Deputy Director
Minutes Recorder: Laura Governale, Pharm.D., Regulatory Project Manager

FDA Attendees:	Titles:	Offices:
Cynthia McCormick, M.D.	Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD-170
Harold Blatt, D.D.S.	Medical Reviewer	HFD-170
Lucy Jean, Ph.D.	Pharmacology Team Leader	HFD-170
Kathleen Haberny, Ph.D.	Pharmacology Reviewer	HFD-170
Albinus D'Sa, Ph.D.	Chemistry Team Leader	HFD-170
Steve Koepke, Ph.D.	Chemistry Supervisor	HFD-170
Michael Theodorakis, Ph.D.	Chemistry Reviewer	HFD-170
Ramana Uppoor, Ph.D.	Biopharmaceutics Team Leader	HFD-870
Albert Chen, Ph.D.	Biopharmaceutics Reviewer	HFD-870
Tom Permutt, Ph.D.	Biostatistics Team Leader	HFD-170
Laura Governale, Pharm. D.	Regulatory Project Manager	HFD-170

Participants:	Titles:
Michael Ashburn, M.D.	Medical Director, Anesthesiologist
[redacted]	
Anne Carter, RAC	Director, Clinical & Regulatory Affairs
Andrew Crockett	Clinical & Regulatory Affairs
Wade Hull	Lead Engineer
[redacted]	
Larry Rigby	President
[redacted]	
Jie Zhang, Ph.D.	Chief Technical Officer

Meeting Objective: The primary objective of this meeting was to discuss the ongoing and proposed clinical studies for the S-Caine™ Local Anesthetic Patch and to discuss specific

questions regarding stability, manufacturing development and toxicology studies for the eventual NDA submission for the S-Caine™ Patch.

General Discussion: Following introductions, Dr. Rappaport led the discussion toward answering the sponsor's questions which were included in the April 7, 2000, meeting package. The sponsor's questions are listed in italics.

I. Clinical Program

1. Are the general format and extent of the clinical research reports presented in this meeting information packet representative of the reports required by FDA to support an NDA submission for the S-Caine™ Local Anesthetic Patch?

Dr. Hal Blatt stated that even though these reports are not from Phase 3 trials, generally speaking, yes, they appear to be of an acceptable format. However, that is something that will have to be determined at the time of the review of the NDA submission.

The sponsor inquired about the format of the electronic submission. Dr. Rappaport replied that the Agency would prefer Word format to use as reviewer aids. Furthermore, the Center policy on electronic submissions is available on the FDA web site. For questions regarding electronic submissions, please contact the project manger.

2. Are the proposed Phase-III clinical trials for the S-Caine™ Local Anesthetic Patch, as outlined in this meeting information package, acceptable to FDA to support an NDA submission for the label of [redacted]

Dr. Blatt replied that until we have a chance to review the final protocols, it is impossible to say for certain, but based on the limited outline provided so far, the trials appear to be adequate. In addition, he made the following suggestions regarding the trial designs:

a. The sponsor should specify one primary efficacy endpoint for each Phase 3 trial.
b. Conduct repeat dose application testing at the same site and testing of multiple sites concurrently. One study should suffice.
c. Study different populations, skin types, including patients over 75 years of age, and children under 7 years of age. [redacted]
d. Have patients return to the study site for visual inspection of the skin after 24 - 48 hours.

The sponsor replied that they are planning 2 special population studies: a single site study in geriatric patients aged 60 – 85; and another single site study in neonatal patients which will be conducted after the newborn piglet study. The sponsor inquired if the Agency found these planned studies acceptable. Dr. Rappaport replied that the above plan seemed acceptable and reasonable; however, if safety becomes an issue, then a single site study may pose a problem. Dr.

McCormick requested confirmation from the sponsor on the number of patients in the pediatric studies and the age limit. The sponsor replied that 120 pediatric patients down to age 4 are planned for the pediatric studies and that the largest exposure is in the age 7 group. Dr. McCormick commented that since this product has great potential for use in newborns and infants, the sponsor should consider studying lower age ranges. The sponsor inquired whether plasma sampling would be required for infants and newborns. Evidence of drug absorption in the plasma from the piglet studies would inform the decision to require plasma samples from humans. The sponsor requested clarification on the length of the time interval between repeat-dose application testing in regard to the second point raised in Dr. Blatt's slide. Dr. Rappaport replied that a 1-2 hour interval between applications is desirable for this study. The envisioned scenario would involve a patient in a hospital setting who is receiving multiple applications of the patch throughout the day for venous access. The main goals of this study are to obtain safety and pharmacokinetic (PK) information for the drug product in the event drug accumulation occurs.

The sponsor inquired if the Agency would prefer volunteers or patients for the repeat-application study. Dr. McCormick replied that from reading the meeting package material, it appears that most of the studies will be conducted on venipuncture patients. Approximately 540 total patient exposures are planned and of that, 300 patients will be exposed to the drug and 20 will be volunteers. 400 patients are recruited into Phase 3 trials with a 2-to-1 randomization scheme. Dr. McCormick asked the sponsor to comment on her understanding of the above statements. The sponsor replied that volunteers were used in the Phase 1 and 2 studies. For Phase 3 studies, the sponsor plans to recruit 200 patients of which 80 will be adults and 120 will be pediatric patients. The same population and the same indication will be sought for Phase 3 as in the Phase 1 and 2 studies. The special population studies will be comprised of a total of 120 patients half of which will be geriatric patients and half will be neonates. The total patient exposure in the Phase 3 trials is 320. Using a 2-to-1 randomization scheme for all studies, the total drug exposure in humans is 400. Dr. Permutt commented that this randomization scheme is satisfactory. An unequal randomization would result in better safety data, but may affect the power of the study.

Dr. McCormick brought up the issue that since S-Caine™ is a eutectic mixture of lidocaine and tetracaine, the drug may be held to a combination drug policy. The Division is currently seeking guidance from the medical policy staff in regard to the requirements for combination drugs. This would require a change in the proposed clinical studies to a 4-arm study evaluating the effects of each active ingredients. The sponsor replied that they would not have enough patients for such a design with the currently proposed study population. Dr. Rappaport stated that the Division will provide the sponsor with recommendations regarding the combination drug policy once the consult is received from the Agency medical policy staff. The sponsor replied that this policy was not applied to EMLA® Anesthetic Disc, another analgesic patch currently active in the Division. Dr. McCormick encouraged the sponsor to submit a rationale in writing for not being held to the combination drug policy to present to the medical policy staff.

The sponsor inquired how many pediatric patients between the ages of 2 – 7 would be satisfactory for the Agency. Dr. McCormick encouraged the sponsor to submit a proposal for pediatric studies for the Agency to review and comment. Dr. McCormick also stated that the

sponsor has the option to design a smaller patch for pediatric patients or totally redesign the patch to fit smaller patients. The sponsor inquired whether a redesigned patch would be part of the original NDA or a supplement to the NDA and whether it would be required to redesign the patch at all if the results of the newborn piglet study shows no drug absorption from the patch. Dr. McCormick reiterated that the sponsor should submit a proposal for pediatric development plan as a Phase 4 commitment.

In regard to the repeated-application study, Dr. McCormick stated that if the sponsor chooses not to conduct this study, then the product would have a restricted labeling. She further urged the sponsor to conduct this study as part of Phase 3 studies since the likelihood is high for repeat use. Volunteers may be used for this study and other studies to assess the effects, sensitization and PK with different skin types, and on geriatric patients, and patients with skin disorders.

II. Pharmacology and Toxicology

1. Are the completed and proposed pharmacology and toxicology studies outlined in this meeting information packet sufficient to support an NDA submission for the S-Caine™ Local Anesthetic Patch?

Dr. Haberny addressed the above question with the following comments from her slide.

a. In the proposed skin irritation study in rabbits, it is recommended that the sponsor evaluate irritation after 30-minute and 1-hour patch application times.

b. In the dermal irritation study in newborn pigs, it is recommended that the sponsor include 30-minute and 1-hour application times, and histopathology evaluation of the application sites.

c. The sponsor should conduct a 4-week GLP toxicity study in one appropriate species prior to the NDA submission. The sponsor may use the results from this study for both INDs. The observations should include clinical signs, mortality, body weight, food consumption, hematology, clinical chemistry, ophthalmology, organ weight, gross pathology, histology and toxicokinetics. Gross pathology and histopathology of the application sites should be included.

The Agency and the sponsor agreed that the S-Caine™ Patch would result in greater systemic absorption and should be used for the study. The Agency also agreed that the rabbit is an appropriate species to conduct the study.

d. For the 505(b)(2) NDA submission, the sponsor should address the following issues for the label: a) reproductive toxicity; b) genotoxicity. The sponsor can use data from the public domain or generate data. The requirements for study on reproductive toxicology may be waived if the clinical studies on the final formulation in a representative patient

population show little or no systemic exposure. However, this will be based on the Agency's judgment.

e. Carcinogenicity is not required for drugs intended to be used occasionally.

Dr. Theodorakis addressed the sponsor's questions regarding Chemistry, Manufacturing and Controls.

III. Chemistry, Manufacturing and Controls

1. *Is the proposed manufacturing scale-up and post scale-up testing plan sufficient for an NDA submission for the S-Caine™ Local Anesthetic Patch?*

Regarding the regulatory specifications and testing procedures, the sponsor should include an *in-vitro* release test of lidocaine and tetracaine from the patch, content uniformity according to USP <905>, pH of the cream in the patch, degradation products and volatile solvents tests. For guidance, the sponsor should refer to ICH Q3B, Q3C and Q6A. In addition, the sponsor needs to monitor parameters that will be related to the functionality of the heating patch, e.g. the amount of heat emitted. Also, include the controls used to qualify the materials in the heating patch.

2. *Is our proposed labeling claim of [redacted] of the label strength of lidocaine and tetracaine acceptable to FDA provided that the results of our proposed studies outlined in Section 4.7 demonstrate that the safety and efficacy of the product are unchanged in this concentration range and not compromised by two years storage at room temperature?*

Dr. Theodorakis responded that the proposal is not acceptable because the range of [redacted] is too wide; the current USP monograph for tetracaine topical solution has an assay range of 95 to 105%. If the [redacted] range is adopted, the content uniformity range will be even wider. Normally, the range for patches is 90 to 110% and the respective content uniformity range is 85 to 115%. We recommend that you improve the manufacturing process so that tetracaine remains within the range of 90 to 110% of the label claim.

The sponsor responded that the drug becomes more stable at lower pH ranges; however, the drug will become ionized and not go through the skin. The drug is an oil-in-water emulsion with a low concentration in the aqueous phase, but permeation occurs through the aqueous phase. If more drug is added to the eutectic mixture, then the concentration of the drug in the aqueous phase does not increase. The assay range of [redacted] does not change the quantity of the drug delivered to the body.

3. *Is our proposed stability program acceptable to FDA in support of an NDA submission for the S-Caine™ Local Anesthetic Patch?*

Dr. Theodorakis responded that this is not acceptable because the sponsor conducted the test conditions at 20°C and 60% RH. The recommended test conditions for room temperature storage under the ICH Guideline Q1B are 25°C and 60% RH. At 20°C, a 6.6% loss of tetracaine occurs in 9 months. At 40°C, up to 18.5% of tetracaine is lost in 4 months. Dr. Koepke stated that the real issue here is degradation of the product.

The sponsor presented their rationale for why the S-Caine™ Patch is not expected to deliver more degradation products than the commercially available tetracaine injectable solution. Assuming: 1) [redacted] 2) all degradation compounds penetrate as fast as nitroglycerin, and 3) all degradation compounds are available for permeation; only [redacted] of the degradation products will permeate through the skin. In comparison, the injectable tetracaine solution will deliver [redacted] of degradation products at [redacted] degradation, respectively. The S-Caine™ Patch will deliver significantly less degradation products than the commercially available tetracaine injectable solution even with the 3 assumptions described above.

Dr. Koepke responded that the reviewers will need to know if the degradation products for the S-Caine™ Patch are the same as the tetracaine injectable solution. The Agency will determine the appropriate expiration dating after reviewing the data. This is a review issue for the NDA submission. The sponsor asked if there was a guidance for stability and whether a [redacted] expiration dating will be granted [redacted] of the drug degrades per year. Dr. Koepke inquired whether a different/lower temperature storage condition will be selected. The sponsor replied that the temperature storage condition will not be changed from the one proposed due to marketing reasons. If the product is kept in the refrigerator, the product will take longer to heat up and therefore delay the onset of effect.

Dr. Theodorakis reiterated that to his knowledge, the Agency has not approved any products with an assay range as wide as [redacted] The USP only allows an assay range of 95 – 105%. The Agency will allow an assay range of 90 – 110% for tetracaine.

Dr. McCormick inquired which products are being evaluated for efficacy. The sponsor replied that they are planning a 3-arm study which would include [redacted] and placebo. Dr. McCormick encouraged the sponsor to prepare a second meeting with the Agency to discuss in detail the pivotal studies, the pediatric studies, and the final number necessary for safety assessment. The materials presented for this meeting falls short on details for an end-of-phase-2 meeting. The Agency would like more CMC information at the next meeting. The sponsor agreed to prepare for another meeting. They will identify all degradation products for the next meeting with the Agency.

4. *Are our proposed long-term and accelerated stability storage conditions acceptable based upon the rationale provided in section 4.8?*

Dr. Theodorakis responded that this is not acceptable because the studies should be conducted at 25°C and 60% RH in order to label the drug product for storage at controlled room temperature

(20°C - 25°C). The accelerated stability conditions are acceptable. However, the studies should be conducted for 12 months.

Dr. Koepke added that stability testing should be conducted under ICH conditions: 40°C, 25°C 60% RH, and 30°C for 1 year. The CMC policy will allow up to 1-year expiration dating if the product remained stable at 6 months of accelerated testing. This product does not appear to be stable for 1 year. The Agency would require real-time data for this product.

The sponsor replied that the 12-month data generated [redacted] degradation products. The majority of the drug degrades [redacted] Dr. Koepke replied that the Agency guidance is based on a linear process. This is a review issue for the Agency to address at the NDA stage. If the formulation is stable at 90 – 110%, then this will be acceptable for the Agency.

Dr. Uppoor asked the sponsor to clarify the differences in the products for the clinical studies and the commercial product. The sponsor responded that the Phase 3 studies will use the commercial product. Dr. Uppoor replied that a pivotal bioequivalence study would not be necessary to link the commercial and the clinical batches if the commercial product is used in Phase 3 clinical trials.

5. *Is the submission of 18 months pilot-scale manufactured product stability data with 6 months long-term and 6 months accelerated stability data from commercial-scale manufactured product acceptable to FDA in support of an NDA submission for the S-Caine™ Local Anesthetic Patch?*

Dr. Theodorakis responded that this is not acceptable. For this product we need at least 1-year stability data on three lots of commercially manufactured products.

IV. Pharmacokinetics (PK)

The sponsor did not provide pharmacokinetic (PK) information in the meeting materials. The following PK information is needed:

a. Literature information on PK (ADME) of both lidocaine and tetracaine.

b. Singe-dose PK study for S-Caine patch for evaluation of plasma levels of lidocaine and tetracaine in healthy subjects using sensitive/specific assay method(s).

Note: A human toxicity safety profile study (pilot?) in 20 healthy adult volunteers was conducted, application of a patch (70 mg lidocaine/70 mg tetracaine) over a 10 cm^2 area for 30 min (p.366). Analysis of PK data (0 up to 4 hr post initial exposure) is currently underway.

c. The same patch formulation should be used for the above PK study and proposed clinical trials and for future commercial manufacturing. Animal data for assessing BE is not adequate and a pivotal BE study will be needed if the clinically tested formulation and the commercial formulation are not the same.

The sponsor inquired whether separate PK studies are required when pharm/tox studies are conducted. Dr. Jean replied that separate studies would be required. Dr. Uppoor added that if a pivotal BE assessment becomes necessary, then human bioequivalence study (most likely based on clinical data) is needed, and the Agency cannot rely on animal data for BE assessment.

d. Multiple applications of S-Caine™ patches at the same site (if repeated) and at different sites (related to actual use clinically) should be assessed. According to preliminary PK data, blood sampling should be conducted for adequate time (to characterize terminal phase and half-life). Information on multiple-dose PK may be needed based on the actual clinical use.

The sponsor replied that a 30-minute application is sufficient for clinical effect. The maximum recommended application time is 1 hour. The clinical effect will last 4-6 hours. It will be difficult to assess progressive absorption. Dr. Chen added that the sponsor should measure plasma levels for more than 4 hours for determination of terminal half-life.

e. Special Population ⇒ PK in pediatrics (if proposed including neonates and infants) and in elderly need to be assessed. Issues of gender and patients with renal or hepatic insufficiency need to be addressed.

Dr. Chen stated that separate PK studies are not necessary for the pediatric population; however, blood samples should be collected within clinical trials. Dr. Uppoor added that conventional PK studies are not required for infants and neonates but limited number of blood samples should be collected to assess systemic exposure. Dr. McCormick urged the sponsor to submit a protocol for these studies. The sponsor added that they may study patients with renal insufficiency and hepatic insufficiency or not include these populations in the label.

f. For pediatric patients to be enrolled in the clinical trials (if proposed), the sparse sampling technique and optimal sampling strategy may be employed for population PK analysis.

g. In addition, *in vitro* dissolution/release testing method needs to be proposed and discussed with the Agency for mutual agreement preferably prior to pivotal stability tests.

In conclusion, Dr. McCormick outlined the outstanding issues from this meeting.

a. Potentially serious CMC issues require further thought from the sponsor.
b. Need proposal for pediatric studies.
c. Need details on pivotal studies and the number for safety exposure.

The discussion of these issues may necessitate another meeting with the Agency. The sponsor should also request a pre-NDA meeting. The sponsor stated that the studies are planned to start on September 1, 2000, with the commercial product. The sponsor also inquired what would be the implications if the clinical formulation is different from the commercial product. Dr. McCormick replied that bridging studies would be required and these should be submitted before the NDA.

Dr. Rappaport adjourned the meeting.

Action Items:

- The Agency will provide the sponsor with a copy of the official meeting minutes.

Minutes prepared by: Laura Governale, Pharm.D.

_____

Minutes concurred by Chair: Bob Rappaport, M.D., Deputy Director

_____

CC:

HFD-170/Division Files
HFD-170/L. Governale
HFD-170/K.Haberny, L.Jean, R.Uppoor, A.Chen, A.D'Sa, M.Theodorakis, H.Blatt, T.Permutt, S.Koepke
HFD-170/C.Schumaker, B.Rappaport, C.McCormick

Drafted by: L. Governale/5-24-00
Initialed by: C. Schumaker/5-24-00, H.Blatt/5-25-00, K.Haberny/5-25-00, M.Theodorakis/5-25-00, L.Jean/5-25-00, A.D'Sa/5-25-00, A.Chen/5-27-00, R.Uppoor/5-26-00, B.Rappaport/5-26-00, 6-6-00, S.Koepke/5-31-00, C.McCormick/6-6-00
Final: B.Rappaport/6-7-00, L.Governale/6-7-00

FILE NAME: 58823(Zars)EOP2.MM.050900.doc

12/10/03

MEMORANDUM OF TELECON

DATE: December 10, 2003

APPLICATION NUMBER: NDA 21-623, S-Caine Patch

BETWEEN:

Name: Andrew Crockett, Director, Clinical & Regulatory
And other Representatives of: Zars, Inc.

AND

Name: Nancy Chang, MD, Team Leader, Anesthetics
Howard Josefburg, MD, Medical Officer
Lisa Malandro, Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: NDA 21-623 Teleconference to discuss progress of response to Division requests

In a teleconference held on December 10, 2003, Dr. Chang asked the Sponsor to provide the Division with an update on their progress with the response to the Division requests (December 2, 2003). Dr. Chang stated that the Division would prioritize their needs for the Sponsor since the application is late in the review cycle. The Sponsor stated that the erythema scale was consistent in each protocol. Dr. Chang requested that the Sponsor correct the inconsistent categorical values in the datasets. The Sponsor asked if, in the interest of time for the S-Caine Patch application, this be completed only for the combined database rather than each individual one. Dr. Chang agreed that this would be satisfactory, [redacted]

The Sponsor stated that they were submitting a new file to the Integrated Summary of Safety (ISS) containing the categorical values. Dr. Chang encouraged the Sponsor to also correct the individual datasets for the S-Caine Peel application. The Sponsor stated that they would submit the information for the S-Caine Patch application in one week.

Dr. Josefberg stated that the contribution of the heating element of the S-Caine Patch has not been demonstrated. He asked the Sponsor if they had any other data to support the contribution of the heating element. The Sponsor stated that the pain stimulus in the study that was meant to address this issue was ineffective. Dr. Chang stated that the Sponsor has an opportunity to provide more justification as to why the product should be approved with the heating element. The Sponsor asked if this could be done as part of a Phase 4 commitment. Dr. Chang stated that there were numerous possibilities for addressing this, but at this time, the Sponsor should make a proposal for justifying the heating element and the Division will review it.

Lisa Malandro
Regulatory Project Manager

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/s/

Lisa Malandro
1/14/04 12:39:01 PM
CSO

7/14/03

MEMORANDUM OF TELECONFERENCE

DATE: July 14, 2003

APPLICATION NUMBER: NDA 21-623, S-Caine Patch

BETWEEN:

Andrew Crockett and other representatives of Zars Inc.

AND

Name: Ken Edmunds
Howard Josefberg, MD, Medical Officer
Lex Schultheis, MD, Medical Officer
Lisa Malandro, Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: NDA 21-623: Request for Electronic Data

A teleconference was held on July 24, 2003, so that reviewers could discuss electronic formatting of data. The Sponsor had asked the reviewers if there were particular files that would assist their review if they were submitted in an electronic format. Dr. Josefberg stated that it would be helpful to have the Integrated Summary of Safety (ISS), the efficacy data from the pivotal trials and the individual line listings of the safety data for the pivotal trials. The data files should be submitted in SAS Transport files while other items such as text, diagrams and copies of articles must be in PDF format, as discussed in the Guidance. The Sponsor stated that this information could be submitted with the 120-day update.

Lisa Malandro
Regulatory Project Manager

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/s/

Lisa Malandro
1/14/04 12:42:16 PM
CSO

12/8/03

MEMORANDUM OF TELECON

DATE: December 8, 2003

APPLICATION NUMBER: NDA 21-623, S-Caine Patch

BETWEEN:

Name: Andrew Crockett,
Representing: Zars, Inc.

AND

Name: Ravi Harapanhalli, Ph.D., Acting Team Leader, Chemistry
Parinda Jani, Chief, Project Management Staff
Lisa Malandro, Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: NDA 21-623 Teleconference to discuss manufacturing inspection

A teleconference was held on December 8, 2003, in response to a request from the Sponsor to discuss their options for responding to the field inspection report. The Sponsor stated that there was a difference between the batch records filed with the NDA and those actually used during the clinical study. The Sponsor stated that the FDA inspector suggested that the Sponsor amend the NDA with the new batch records. The Sponsor asked the Division how an amendment at this time would affect the review of the NDA. Dr. Harapanhalli asked what the differences were in the batch records. The Sponsor stated that they had changed the procedure for [redacted] Dr. Harapanhalli stated that the Sponsor is required to provide data to prove that the two different processes do not change the quality or performance of the product by testing old and new patches. As an alternative to providing this data, the Sponsor should revert back to the older process and submit the appropriate data to support that process. Ms. Jani stated that the amendment should be submitted and the Division would review it and give the Sponsor feedback following the primary review. Dr. Harapanhalli reiterated that if the application was approved based on the submission of these data, the Sponsor would only be able to manufacture the patch using the old process until a supplement containing the comparative data of seal integrity was received, reviewed and approved.

Lisa Malandro
Regulatory Project Manager

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/s/

Lisa Malandro
1/14/04 02:40:48 PM
CSO

12/2/03

MEMORANDUM OF TELECONFERENCE

DATE: December 2, 2003

APPLICATION NUMBER: NDA 21-623, S-Caine Patch

BETWEEN:

Name: Andrew Crockett, Director, Clinical & Regulatory
And other Representatives of: Zars, Inc.

AND

Name: Howard Josefburg, MD, Medical Officer
Nancy Chang, MD, Team Leader, Anesthetics
Lisa Malandro, Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: NDA 21-623 Teleconference regarding clinical efficacy data

In a teleconference held on December 2, 2003, Dr. Chang informed the Sponsor there appeared to be inaccuracies and missing data within the application. Dr. Josefberg stated that, additionally, given the number of protocol amendments and the extent of the changes, it was difficult to follow the progression of events and difficult to interpret the Sponsor's intent with respect to the study design. The Division requested that the Sponsor submit a copy of the original protocol, the amended changes and the dates when the changes occurred for each of the four pivotal studies. For NDA 21-623, the Sponsor should concentrate on only the pivotal studies. The Sponsor was also asked to clarify the data definition tables for each NDA to include the expected values and the format of the expected values.

Lisa Malandro
Regulatory Project Manager

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/s/

Lisa Malandro
1/13/04 03:30:09 PM
CSO

6/17/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-623

ZARS, Inc.
350 W. 800 N. Suite 320
Salt Lake City, UT 84103

Attention: T. Andrew Crockett
Director, Clinical & Regulatory

Dear Mr. Crockett:

Please refer to your April 4, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for S-Caine Patch (lidocaine 70 mg and tetracaine 70 mg).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is filed under section 505(b) of the Act on June 3, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. We note that [redacted] for lidocaine is deficient.

2. [redacted]

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information with the 120-day safety update:

1. Complete data from Study SC-30-01 which evaluates the systemic exposure of lidocaine and tetracaine in 30 pediatric patients.

2. Data from a study evaluating the sensitization and cumulative irritation potential of the S-Caine Patch in 200 subjects. As agreed upon with the Agency, data from 100 subjects will be included in the update and data from the remaining 100 subjects will be submitted shortly thereafter.

3. Quantitative test results associated with the specifications for drug product stability at 18 months.

4. [redacted]

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Victoria Kao, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Celia Winchell
6/17/03 05:13:08 PM
for Bob A. Rappaport, Acting Division Director

6/17/03

Memo to File

Re: N21-623 S-Caine Patch (lidocaine 70mg and tetracaine 70mg)/I58,823
Sponsor: Zars, Inc.
PDUFA due date: February 4, 2004

This NDA was filed June 3, 2003. Upon drafting a 74-day letter (duedate June 17, 2003), I was asked by Dr. Nancy Chang for clarification on a commitment that I had included in the letter. This commitment had been made by the Sponsor in the cover letter of the NDA and reads:

> "Completion of Study SC-30-01 (to be included in the 120-day safety update). This study is evaluating the systemic exposure of lidocaine and tetracaine in 30 pediatric patients and is currently ongoing."

The 74-day letter reminds the Sponsor of this commitment.

To get documentation for this commitment, I subsequently called Andrew Crockett (cell 801-913-5164), at Zars, Inc. for clarification.

He explained that this commitment had been discussed at the December 5, 2002 pre-NDA meeting and the arrangement was concurred by both Dr. Bob Rappaport and Dr. Nancy Chang. Furthermore, he clarified that SC-30-01 is but one study in a broader pediatric program which includes studies SC-04, -09, -10, -20, -21, -29. Complete study data of all those other studies have already been submitted in the NDA. In addition, there is a P4 commitment to study systemic exposure in neonates.

Memo prepared by Victoria Kao
June 17, 2003

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/s/

Victoria Kao
6/17/03 11:54:33 AM
CSO

5/29/03

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-623 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: S-Caine Patch
Generic Name: lidocaine 70 mg/tetracaine 70 mg
Strengths:

Applicant: Zars, Inc.

Date of Application: March 31, 2003
Date of Receipt: April 4, 2003
Date clock started after UN: N/A
Date of Filing Meeting: May 19, 2003
Filing Date: June 3, 2003
Action Goal Date (optional): User Fee Goal Date: **February 4, 2004**

Indication(s) requested: [redacted]

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA ___X___
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S ___X___ P _____
Resubmission after a withdrawal? ___NA___ Resubmission after a refuse to file? ___NA___
Chemical Classification: (1,2,3 etc.) ___4___
Other (orphan, OTC, etc.) _____

User Fee Status: Paid _____ Waived (e.g., small business, public health) X - Sm Business
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: **YES** NO
User Fee ID #
Clinical data? YES __X_____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO

If yes, explain: Sponsor will be eligible for 3 year exclusivity

Does another drug have orphan drug exclusivity for the same indication? YES **NO**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES **NO**
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? **YES** NO
- Was form 356h included with an authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? **YES** NO
  If no, explain:

- If an electronic NDA, does it follow the Guidance? **N/A** 1YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? **N/A** YES NO

- Is it an electronic CTD? **N/A** YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information included with authorized signature? **YES** NO

- Exclusivity requested? YES, _____years **NO**
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure information included with authorized signature? **YES** NO
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES** NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES** NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: **I58,823**

- End-of-Phase 2 Meeting(s)? Date(s) _5/9/00 (DFS'd)_ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _12/5/02 (DFS'd)_ NO
  If yes, distribute minutes before filing meeting.

Project Management

Vkao 5-19-03 - These will be done after filing meeting, if the application is filed.

- Package insert consulted to DDMAC? YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?
  N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **YES** NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

  It will be initiated when/if the application is deemed fileable
- If parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

NOT APPLICABLE

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: EMLA Disc (lidocaine 2.5% and prilocaine 2.5%)

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

  S-Caine is lidocaine/tetracaine, not lidocaine/prilocaine.

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)
  YES **NO**

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).
  YES NO

NOT APPLICABLE

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).
  YES NO

NOT APPLICABLE

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

__X_ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES **NO**

    N20962 EMLA (disc) has no unexpired patent or exclusivity.

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES NO

- EITHER
  The number of the applicant's IND under which the studies essential to approval were conducted.

  YES, IND # _____ NO

  OR
  A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 5-19-03

BACKGROUND:
Zars, Inc. submitted the S-Caine application as 505(b)(2) referencing EMLA® Disc (lidocaine 2.5% and prilocaine 2.5%). It should be noted that there is currently no approved NDA for tetracaine, either alone or in combination. After checking Comis, we discovered that there was a tetracaine/benzocaine product (N008076) that was approved in August 29, 1951 and WITHDRAWN June 24, 1976. We are validating that this withdrawn NDA can be referenced for this (b)(2). Dr. Dale Koble classified this NDA as Type 4 - New Combination chemical classification (based on a search of the Orange Book and Comis); both Lidocaine and Tetracaine have been previously approved in NDAs separately (though the NDA for tetracaine has since been WD) but not as a combination.

Note #1: Since the Sponsor did not cite a reference NDA for tetracaine, each discipline has had to review the application for filability for tetracaine as a "stand alone" program. That is, tetracaine should be viewed as a "(b)(1)" and a review should be done to ensure that the Sponsor cited adequate literature or studies for review of tetracaine to be used in combination with lidocaine.

Note #2: At 120 Days, the Agency is to expect:

1) Data of Study SC-30-01 which evaluates the systemic exposure of lidocaine and tetracaine in 30 pediatric patients.
2) Data of a study evaluating the sensitization and cumulative irritation potential of the S-Caine Patch in 200 volunteers. As agreed with FDA, data from 100 subjects will be included in the 120-day safety update and data from the remaining 100 subjects will be submitted shortly thereafter.

ATTENDEES:

Bob Rappaport, M.D.
Srikanth Nallani, Ph.D.
Nancy Chang, M.D.
Suresh Doddapaneni, Ph.D.
Tom Permutt, Ph.D.
Howard Josefberg, M.D.
Ravi Harapanhalli, Ph.D.
Dale Koble, Ph.D.
Milton Fan, Ph.D.
Dominic Chiapperino, Ph.D.
Dan Mellon, Ph.D.
Khairy Malek, M.D.
Tim McGovern, Ph.D.

Kim Compton, R.Ph.
Adam Wasserman, Ph.D.
Jerry Cott, Ph.D.

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Howard Josefberg, M.D.
Secondary Medical:	Nancy Chang, M.D.
Statistical:	Milton Fan, Ph.D.
Pharmacology:	Dan Mellon, Ph.D.
Statistical Pharmacology:	N/A
Chemist:	Ravi Harapanhalli, Ph.D.
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Srikanth Nallini, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	
DSI:	Khairy Malek, M.D.
Regulatory Project Manager:	Victoria Kao, B.S.
Other Consults:	ODS, DDMAC, CDRH etc. to be consulted

Per reviewers, are all parts in English or English translation? **YES** NO
If no, explain:

CLINICAL FILE __X___ REFUSE TO FILE _____

- Clinical site inspection needed: YES **NO**

  Inspection will not be requested at the current time; reviewers, however, reserve the right to request at later stage.

- Advisory Committee Meeting needed? YES, date if known _____ **NO**

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

			N/A	YES	NO
CLINICAL MICROBIOLOGY	FILE _____	REFUSE TO FILE _____			**N/A**
STATISTICS	FILE _X____	REFUSE TO FILE _____			
BIOPHARMACEUTICS	FILE _X____	REFUSE TO FILE _____			

- Biopharm. inspection needed: YES NO

PHARMACOLOGY FILE __X___ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE __X___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? **YES** NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments:

Sponsor will be sending in quantitative test results associated with the specifications for drug product stability (12-, 15-, 18-month timepoints) electronically at 120-day update.

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

____X___ Filing issues to be communicated by Day 74. List (optional):

74 DAY ISSUES/ISSUES DISCUSSED AT FILING MEETING:

Clinical:

1) The Sponsor is to be reminded of their commitment to submit data in the 120-day safety update for several studies which evaluate sensitization and cumulative irritation potential and systemic exposure in pediatric patients.

2) [This will not be in the 74 day letter] Discussions with the Sponsor regarding the phrasing of the indication will most likely be necessary. The current wording "The S-Caine Patch...is indicated as a [redacted] will need to be reconciled with the scope of various sections of the PI, e.g. Dosage and Administration. Separate indications may need to be teased out of what is currently proposed.

Chemistry:

1) The Sponsor is to be reminded that cited [redacted] for lidocaine is deficient (it has not been updated since 1999).

2) The Sponsor should be reminded that quantitative test results associated with the specifications for drug product stability at 18 months should be submitted in the 120-day update.

[redacted]

PharmTox:

1) [redacted]

2)

3)

BioPharm:

[This will not be in the 74 day letter] As requested by the Agency, the Sponsor submitted in the NDA information to address our concerns regarding clinically significant systemic levels observed in a PK study that were apparently unpredictable and dose-independent. The Division had flagged this as a safety concern in the 12/05/02 Pre-NDA meeting. This will not be a filing issue.

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_____
Regulatory Project Manager, HFD-

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/s/

Parinda Jani
5/29/03 10:40:56 AM

5/27/03

45 DAY MEETING CHECKLIST
(Answer Yes or No to the questions below)

FILEABILITY:

On initial overview of the NDA application:

STATISTICAL:

(1) On its face, is the statistical section of the NDA organized in a manner to allow substantive review to begin? Yes

(2) Is the statistical section of the NDA indexed and paginated in a manner to allow substantive review to begin? Yes

(3) On its face, is the statistical section of the NDA legible so that substantive review can being? Yes

(4) On its face, do there appear to be at least two adequate and well-controlled studies in the application? Yes

(5) Are the pivotal efficacy studies of appropriate design to meet the basic requirements for approvability of this product based on proposed draft labeling? Yes

(6) Are all the data sets for pivotal efficacy studies 'complete for all indications (infections) requested? Yes

   (a) Line listings by Center

   (b) Intermediate analysis summary tables

   (c) Pathogen listing

   (d) Adverse events listing by Center

   (e) Lost subject/patient tables by reason, time of loss, and center

(7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? Yes

(8) From a statistical perspective, is this NDA fileable? If "no", please state below why it is not. Yes, but the sponsor has not submitted electronic datasets.

Reviewing Statistician Date

Supervisory Statistician Date

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/s/

Milton Fan
5/27/03 11:49:08 AM
BIOMETRICS

Pl sign it off

Thomas Permutt
5/27/03 01:03:49 PM
BIOMETRICS
concur

5/23/03

Review For Filing

NDA # 21-623, S-Caine Patch (lidocaine 70 mg and tetracaine 70 mg)

Sponsor: ZARS, Inc., Salt Lake City, Utah

CMC Reviewer: Dominic Chiapperino, Ph.D.

FILEABILITY:

On initial overview of the NDA application: 21-623 **YES** **NO**

MANUFACTURING AND CONTROLS:

(1) On its face, is the M&C section of the NDA organized in a manner to allow substantive review to begin?

Yes. The CMC information is presented in Volumes 2, 3A-F, and 4, corresponding roughly to sections for drug substance, drug product, and methods validation, respectively.

(2) Is the M&C section of the NDA indexed and paginated in a manner to allow substantive review to begin?

Yes. Tabs, section headings, and pagination appear to be accurate and appropriate.

(3) On its face, is the M&C section of the NDA legible so that substantive review can begin?

Yes.

(4) Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?

Yes. The following facilities are listed in the CMC summary section (Vol. 1, Tab 3.4, p.1-59):

[redacted]

Tapemark Company
1685 Marthaler Lane, West St. Paul, MN 55118

Review of all detailed CMC sections was conducted to identify any other facilities that may have involvement in drug substance and drug product manufacturing, release and stability testing, sterilization, packaging, or labeling activities for commercial batches. [redacted] to conduct microbial testing (see Vol.3F, p.6). Regarding the drug substances, lidocaine base is supplied by [redacted] (Vol.2, p.76), and tetracaine base is supplied by [redacted] (Vol.2, p.78). It was thought that these two companies

may be transfer points for the drug substances manufactured abroad. Clarification was needed as to whether any release testing or repackaging of the drug substances is done at either of these companies. An email request was sent through the PM, asking for a complete list of facilities necessary for setting up site inspections, and requesting confirmation of facility readiness for inspection (see DFS). The response was satisfactory, and the EER can be made post-filing meeting. [redacted] . will not need to be inspected. [redacted] will be added to the other four facilities for site inspections. More detailed contact information for facility representatives can be found in the sponsor's response to our IR.

(5) Has the applicant submitted a complete environmental impact assessment?

No. The applicant claims categorical exclusion under 21CFR25.31(b). Less than 1 ppb is estimated for the maximum amount of drug substance entering the aquatic system. No extraordinary circumstances exist, according to the applicant.

(6) Has the applicant developed appropriate controls assessment procedures that are presently ready for FDA verification?

Yes.

(7) For an antibiotic, has the applicant submitted an appropriate validation package and committed to the readiness of exhibit samples?

N/A. The drug product is not an antibiotic.

(8) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?

Yes. There were several commitments made by ZARS with FDA during the pre-NDA stage of development. All recommendations of the agency, with regard to CMC issues, appear to have been addressed by the applicant.

(9) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?

Yes. The sections of the package insert labeling, including "description", "dosage and administration", and "how supplied", appear to be consistent with the CFR sections above.

(10) Has the applicant submitted stability data to support and justify the proposed expiry?

Yes. There may be issues relating to expiry date and impurity levels that will be addressed in the review cycle. The proposed expiry for the drug product is [redacted] (see Vol.3F, p.4). The [redacted] Currently, data is submitted up through the 12 month time point, but the sponsor states that 15, 18 and 24 month data will be submitted to the Agency in support of the 18 month expiry. (This was reconfirmed in a teleconference on the topic of electronic stability data submission, something the agency has requested of the sponsor for purposes of facilitated statistical analysis.)

Three lots of the finished drug product (1261, 1262, and 1263) were tested and submitted as part of the ongoing stability studies. Each lot is made on a [redacted] from a different batch of S-

Caine Bulk Material (658, 659, and 663, respectively). Storage conditions for samples of each lot have six variants, as follows:

The data appear to be complete up to the twelve-month mark, and suitable for review. The specifications incorporate some suggestions made by FDA in EOP2 and pre-NDA meetings.

Aside from the formal stability studies, the applicant has acknowledged that the expiry would be dictated by [redacted] The proposed specifications for the finished product allow a mean% (based on tetracaine label claim) [redacted] these two degradants respectively. Discussion of these impurity levels with the P/T reviewer may result in a potential issue for the 74-day FI letter.

(11) Has the applicant stated that they are ready now (Priority Drugs) for inspections of the facilities or that they will be ready within the next 6 months (Standard Drugs)?

Yes. A fax was submitted to the sponsor requesting confirmation of facilities requiring inspection, and confirmation of facility readiness for inspections, which was not stated explicitly in the application. They have provided the necessary information by email, and a list of five facilities will be entered into EES following the filing meeting (if appropriate to do so). The facilities are ready for inspection, as per the applicant's comments.

(12) From a manufacturing and controls perspective, is the NDA fileable? If "no", please state below why it is not.

Yes. The NDA is fileable at this time. One potential filing issue was the fact that a DMF for one of the two drug substances [redacted], Lidocaine) had not been updated with annual reports since 1999, rendering it inactive. A teleconference was held with a US agent for [redacted] A commitment was obtained from the agent, [redacted] that the DMF would be updated appropriately, within a month, so as to be of use to the applicant. No other filing issues came to light.

Dominic Chiapperino Ph.D. (for Ravi Harapanhalli, Ph.D.) 5/16/03
Reviewing Chemistry Office Date

Dale Koble, Ph.D.
Supervisory Chemistry Officer Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dominic Chiapperino
5/23/03 01:48:14 PM
CHEMIST

Dale Koble
5/23/03 02:11:24 PM
CHEMIST

TC 5/12/03

AMENDED Memo of Teleconference 5/12/03
[the following was emailed to Andrew Crockett of Zars, Inc. as amended minutes of the teleconference on 5/16/03

Andy,

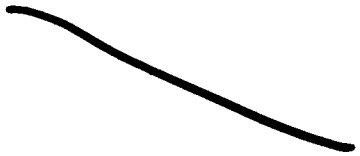
As we discussed earlier today (5/20/03), I am sending an amended summary of the 5/12/03 teleconference regarding the electronic submission of N21-623 S-Caine Patch's stability data. The addition is in bold.

FDA attendees:

Tom Permutt, Ph.D., Statistical Team Leader
Dale Koble, Ph.D., Chemistry Team Leader
Dominic Chiapperino, Ph.D., Chemistry Reviewer
Victoria Kao, B.S., Regulatory Project Manager

Zars, Inc. Attendees:

Wade Hull (Director of Engineering, ZARS)
Andrew Crockett (Director of Clinical/Regulatory, ZARS)
Jerry Williams (Director of Quality Assurance, ZARS)
Sara Hotchkiss (Technical Operations Manager, ZARS)



)

Summary:

Regarding the stability data that we are requesting in electronic format, all electronic datasets submitted as part of New Drug Applications should be in SAS XPORT transport format, also called Version 5 SAS transport format. Detailed guidance on electronic submissions is available at http://www.fda.gov/cder/guidance/2867fnl.pdf. To further summarize what was discussed in the teleconference, the scope of the data we would like in the submission would include all quantitative test results associated with the specifications for drug product stability (from tabulated data in Volume 3F, Section 4.2.7.1). **If statistical analysis is not provided for a particular test, provide appropriate rationale.** We have indicated that the timeline for this submission may coincide with the 120-day update to the NDA, and include additional stability data for the 15- and 18-month timepoints.

If you have any questions, please let me know.

Victoria Kao
Regulatory Project Manager
Division of Anesthetic, Critical Care
and Addiction Drug Products
301-827-7416

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/s/

Victoria Kao
5/20/03 04:27:59 PM
CSO

Memo of Teleconference 5/12

[the following was emailed to Andrew Crockett of Zars, Inc. as minutes of the teleconference on 5/16/03]

Hi Andy,

As we discussed at our teleconference 5/12 regarding the electronic submission of N21-623 S-Caine Patch's stability data, I'm forwarding you a summary of our discussion.

The FDA attendees were:

Tom Permutt, Ph.D., Statistical Team Leader
Dale Koble, Ph.D., Chemistry Team Leader
Dominic Chiapperino, Ph.D., Chemistry Reviewer
Victoria Kao, B.S., Regulatory Project Manager

Various Zars, Inc. attendees were present, of which Andrew Crockett was the project manager.

Summary:

Regarding the stability data that we are requesting in electronic format, all electronic datasets submitted as part of New Drug Applications should be in SAS XPORT transport format, also called Version 5 SAS transport format. Detailed guidance on electronic submissions is available at http://www.fda.gov/cder/guidance/2867fnl.pdf. To further summarize what was discussed in the teleconference, the scope of the data we would like in the submission would include all quantitative test results associated with the specifications for drug product stability (from tabulated data in Volume 3F, Section 4.2.7.1). We have indicated that the timeline for this submission may coincide with the 120-day update to the NDA, and include additional stability data for the 15- and 18-month timepoints.

If you have any questions, please let me know.

Victoria Kao
Regulatory Project Manager
Division of Anesthetic, Critical Care
and Addiction Drug Products
301-827-7416

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/s/

Victoria Kao
5/16/03 04:26:47 PM
CSO

5/15/03

Memo to File
NDA 21- 623 S-Caine Patch
Zars, Inc.

[The following was emailed to Mr. Andrew Crockett of Zars, Inc. on May 6, 2003; a hard copy of the response is expected to be submitted by the Sponsor.]

Hi Andrew [Crockett], thank you for you help thus far regarding N21-623. Per our conversation, I'm forwarding the additional request from our CMC reviewer:

"We refer you to NDA 21-623...

Regarding the manufacture of S-Caine Local Anesthetic Patch, you have specified the following facilities in the CMC Summary section (Vol.1, p.59):

[redacted]

Tapemark Company
1685 Marthaler Lane, West St. Paul, MN 55118

We have further identified the following companies mentioned in your application as potentially having a role in manufacturing, testing (including stability testing), packaging, or labeling activities:

[redacted]

Please confirm for us which of the above facilities, including contract facilities, will have any involvement in manufacturing, testing (including stability testing), packaging, or labeling activities for either the drug substance and drug product for commercial batches. Also, please list any additional facilities that will have involvement in any of these activities. The information that you provide will be used to schedule the necessary FDA site inspections in connection with NDA 21-623. Please provide the full addresses for each of the specified facilities, as well as CFN numbers, and the name and phone number of a suitable contact person at each facility.

Finally, please confirm that all of the involved facilities are currently ready for site inspections."

Please Let me know if you need further clarification.

Thanks,

Victoria Kao
Regulatory Project Manager
Division of Anesthetic, Critical Care
and Addiction Drug Products
301-827-7416

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/s/

Victoria Kao
5/15/03 12:22:19 PM
CSO

4/15/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-623

ZARS, Inc.
350 West 800 North
Suite 320
Salt Lake City, Utah 84103

Attention: T. Andrew Crockett
Director, Clinical and Regulatory Affairs

Dear Mr. Crockett:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ZARS, Inc.

Review Priority Classification: Standard (S)

Date of Application: March 31, 2003

Date of Receipt: April 4, 2003

Our Reference Number: NDA 21-623

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 4, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care
And Addiction Drug Products, HFD-170
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Victoria Kao, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Victoria Kao
Regulatory Project Manager
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Victoria Kao
4/15/03 01:49:59 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER 21-623

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ZARS, Inc.	March 31, 2003
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
(801) 350-0202	(801) 350-0909
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: RECEIVED 350 W. 800 N. Suite 320 Salt Lake City, UT 84103 APR 04 2003 CDR/CDER	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-623

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	CODE NAME *(If any)*
lidocaine 70mg and tetracaine 70mg	S-Caine™ Patch (lidocaine 70mg and tetracaine 70mg)	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
patch	lidocaine 70mg and tetracaine 70mg	topical

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
X NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) X 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug EMLA® Disc (lidocaine 2.5% and prilocaine 2.5%) Holder of Approved Application ASTRAZENECA

TYPE OF SUBMISSION *(check one)* X ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
New Drug Application

PROPOSED MARKETING STATUS *(check one)* X PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 68 (No. 1-63) THIS APPLICATION IS X PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached sheet

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Caine Patch IND 58,823
MFs (See attached sheet)

This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Labeling *(check one)* X Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
X	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
X	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
X	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
X	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
X	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. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (l)(3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. 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.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	T. Andrew Crockett, Director Clinical & Regulatory	March 31, 2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
350 W. 800 N. Suite 320, Salt Lake City, UT 84103	(801) 350-0202

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

ZARS, Inc.
350 W. 800 N. Suite 320
Salt Lake City, UT 84103

2. TELEPHONE NUMBER *(Include Area Code)*

(801) 350-0202

3. PRODUCT NAME

S-Caine Patch (lidocaine 70mg and tetracaine 70mg)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NO21-623

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

N/A

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☒ YES ☐ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Pres & CEO	31 MAR 03

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 10, 2003

Larry Rigby
President and CEO
Zars, Inc.
350 West 800 North, Suite 320
Salt Lake City, UT 84103

RE: Zars, Inc., Small Business Waiver Request 2003.035 for S-Caine Patch, NDA 21-623

Dear Mr. Rigby:

This responds to your December 17, 2002, letter requesting a waiver of the human drug application fee for new drug application (NDA) 21-623 for S-Caine Patch (lidocaine 70 mg and tetracaine 70 mg) under the small business waiver provision, section 736(d)(1)(D)[1] of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2003.035). For the reasons described below, the Food and Drug Administration (FDA) grants the request from Zars, Inc. (Zars) for a small business waiver of the application fee for NDA 21-623 for the S-Caine Patch.

According to your waiver request, Zars is a small business with fewer than 500 employees, including employees of your affiliates. You note that the S-Caine Patch NDA is the first Zars application submitted to FDA for review under section 505(b) of the Act. You also note that you do not have any affiliates who have previously filed NDAs. You anticipate submission of the NDA in March 2003.

Under section 736(d)(3)(B) of the Act,[2] a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate[3] submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant Zars' request for a small business waiver for NDA 21-623 for lidocaine 70 mg and tetracaine 70 mg is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated January 30, 2003, that Zars has fewer than 500 employees. Zars does not have any affiliates.

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[1] 21 U.S.C. 379h(d)(1)(D).
[2] 21 U.S.C. 379h(d)(3)(B).
[3] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

Second, according to FDA records, the marketing application for S-Caine Patch, NDA 21-623, is the first human drug application, within the meaning of the Act, to be submitted to FDA by Zars or its affiliates. Consequently, your request for a small business waiver of the application fee for NDA 21-623 is granted, provided that FDA receives the marketing application for S-Caine Patch no later than January 30, 2004, 1 year after the effective date of the size determination made by SBA.

If FDA refuses to file the application or Zars withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Zars should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for NDA 21-623.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman, Michael Jones, or Tawni Schwemer at 301-594-2041.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Pre-NDA meeting minutes
December 5, 2002

IND 58, 823

Zars, Inc.
350 West 800 North, Suite 320
Salt Lake City, Utah 84103

Attention: T. Andrew Crockett
Director, Clinical and Regulatory Affairs

Dear Mr. Crockett:

Please refer to the meeting between representatives of your firm and FDA on December 5, 2002. The purpose of the meeting was to provide feedback for you on your preparation for submitting a new drug application for your S-Caine Product by providing responses to the questions in your meeting package.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7432.

Sincerely,

{See appended electronic signature page}

Kimberly Compton
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: December 5, 2002

Location: Parklawn Building, Conference Room L

Sponsor: ZARS Inc.

IND: 58, 823

Drug Name: S-Caine Patch

Type of Meeting: Type B, Pre-NDA Meeting

Meeting Chair: Nancy Chang, M.D.
Division of Anesthetics, Critical Care and Addiction Drug Products

Minutes Recorder: Kimberly Compton, Regulatory Project Manager

INDUSTRY	Title
Michael Ashburn, M.D., Ph.D.	Medical Director
Theodore Stanley, M.D.	Chairman
Andrew Crockett	Director, S-Caine Clinical and Regulatory
Jonothan Hampshire	S-Caine Patch, Clinical Project Manager
Sara Hotchkiss	Technical Operations Manager
Wade Hull, M.S.	Director, Engineering
Matthew Iverson	S-Caine Peel, Clinical Project Manager
[redacted]	
[redacted]	
Lynne Pauley, M.S.	Medical Writing
[redacted]	
Martha Charney, Ph.D.	Pharmacokinetics
Todd Davies	Clinical Data Manager
[redacted]	
Julie Morrissey	Stability Coordinator
Larry Rigby, M.A., A.B.D.	President and CEO
Nicholas Burton	S-Caine Patch Regulatory
FDA	**Title**
Bob Rappaport, M.D.	Acting Division Director
Nancy Chang, M.D.	Anesthesia Team Leader
Arthur Simone, M.D.	Medical Officer
Tim McGovern, Ph.D.	Supervisory Pharmacologist
Suliman Al-Fayoumi, Ph.D.	Clinical Pharmacologist
Dale Koble, Ph.D.	Chemistry Team Leader
Kim Compton	Regulatory Project Manager

Meeting Objective: The purpose of the meeting was to provide responses to the sponsor's questions in their meeting package regarding preparation for submission of a new drug application for their product.

General Discussion:
The sponsor's questions are listed in *Italics* with the FDA responses presented at the meeting following. Pertinent discussion that took place at the meeting regarding a specific question will follow the question and FDA response.

Note: The questions were not addressed in numerical order at the meeting, but rather in discipline order: CMC, Pre-Clinical, Clinical Pharmacology, Clinical.

Question #4
Are the proposed Regulatory Specifications for the S- Caine Patch acceptable?

FDA Response

- The regulatory specifications for the drug release from the patch should be revised to include three appropriate sampling points and appropriate acceptance criteria.

- Provide a clear justification with supporting data for the acceptance criteria proposed for all specifications.

Provide impurity specifications for the drug substance and drug product in the manner suggested in the ICH guideline.

Discussion of Question 4
The sponsor inquired if a submission containing secondary statistical data requested by the Agency had been reviewed. Dr. Rappaport indicated that if the materials were not specifically identified as being for discussion at this meeting, the reviewers may not have understood that the sponsor wanted to discuss them at this time. Dr. Koble indicated he would follow-up on this matter.

Question #5
The proposed format of the stability data tables is provided in the briefing packet. Is this format acceptable?

FDA Response
Yes

Question #6 (1)
The Environmental Assessment calculations and conclusions are included in the briefing packet. Since the potential introduction concentration is far less than 1 ppb [redacted] *this product qualifies for a Tier 0 approach and categorical exclusion from preparation of an environmental assessment. Does FDA agree?*

FDA Response
Yes

Question #3
As agreed with the Agency, segment II reproductive toxicology studies on the combination of lidocaine and tetracaine will be completed and submitted to the Agency during the review of the NDA for the S-Caine patch. Segment I and III reproductive toxicology studies for tetracaine will be submitted as a Phase IV commitment. Given that no data from reproductive toxicology studies will be available at the time of NDA submission, is the language contained in the draft package insert acceptable for NDA submission?

FDA Response
- The proposed wording is generally acceptable although final wording is subject to change upon formal review of the data.
- In the absence of tetracaine data, the Pregnancy Category should be a [redacted]
- The segment II studies in 2 species should be submitted within 120 days of NDA submission.
- A Phase 4 commitment for the Segment I and III studies for tetracaine is acceptable assuming the product is approved in the first review cycle.
- It is expected that the Segment I and III studies for tetracaine will be initiated in the near future. The sponsor is requested to commit to acceptable timeframes for initiation of studies and submission of study reports.

Discussion of Question 3
As a Phase 4 commitment, the reproductive toxicology studies should be submitted within 6 months of approval. Dr. McGovern indicated that if the review of this NDA goes to a second cycle, the Division would like the Segment I and II studies prior to approval.

Question #6 (2)
Do the data outlined in the Section 5 summary (pages 52-73) appear sufficient for NDA approval?

FDA Response
- Generally yes.
- NDA submission should include the referenced reproduction toxicity studies with lidocaine along with sponsor's assessment of the adequacy of these studies according to current standards (e.g., dose selection, dose regimen).

- For the proposed Segment II combination studies in rats and rabbits, it is recommended that additional dosing arms with tetracaine and lidocaine alone are added to assist in data interpretation.

Discussion of Question #6 (2)
The sponsor stated that their product is a eutectic mixture and the data demonstrate that dosing in the segment II studies is limited by one drug over the other. Dr. McGovern stated that this is the reason for the recommendation to add additional dosing arms. Dr. McGovern stated that if the sponsor submitted a protocol, the Division could review it and discuss the specific issues with the sponsor.

Dr. McGovern stated that the sponsor should dose up to the dose-limiting exposure level in order to obtain an idea of the individual drug toxicity.

Pre-Clinical Comments (presented at the meeting)
- Safety qualification of impurities exceeding ICH recommended levels may be needed.

Question # 7
Is the proposed organization and content of Section 6 satisfactory?

FDA Response
Yes

Question # 8
ZARS believes that the regulatory requirement for a bioavailability study for the S-Caine patch should be waived because it is a topical product with an intended local site of efficacy. Does the Agency concur?

FDA Response
Based on the preliminary data provided by the sponsor, systemic exposure to lidocaine & tetracaine following S-Caine application appears to be limited. The regulatory requirement for a relative bioavailability bridging study may be waived provided the sponsor demonstrates a lack of meaningful systemic exposure across conducted studies for the S-Caine application.

Discussion of Question #8
Dr. Al-Fayoumi stated that the sponsor would need to demonstrate in all studies that there was no meaningful systemic exposure that would result in pharmacologic action. He also stated that in order to be a 505(b)(2) application, the sponsor would need to choose a reference listed drug (RLD). Normally for the portion of the application the sponsor references outside information (i.e. previous Agency findings of safety and efficacy for lidocaine and tetracaine), the sponsor would need to provide a link to demonstrate how their product and the RLD were related. Dr. Rappaport clarified such a link might be waived for this product if they can demonstrate no meaningful systemic exposure exists.

Dr. Chang inquired about two subjects that had drug levels the Division would regard as clinically meaningful. The sponsor stated that the doses were intentionally increased in those studies and they felt it unlikely such observations would be seen at normal exposure levels. Dr. Chang stated that the Division would look for evidence to support this in the NDA. If an individual might experience pharmacologically relevant systemic levels of local anesthetic under clinical conditions that might be reasonable anticipated, the Division would regard this as a safety concern, particularly if these levels occur in an unpredictable manner. Dr. Rappaport stated that such observations might be addressed in the labeling.

Question # 9
It is intended that the summary of the literature for this section would be brief since summaries for the nonclinical ADME and clinical pharmacology sections would also include metabolism and pharmacokinetics. Is this acceptable?

FDA Response
The sponsor's proposal is acceptable.

Question # 10
Other than Study SC-33-02 which will be completed as a Phase IV commitment (see Supplement 012 dated June 4, 2002), ZARS has presented protocols to the Agency for the other PK studies, and the Agency deemed them to be sufficient to support an NDA (see Supplement 006 dated April 11, 2001 and conference call minutes of June 28, 2001). ZARS considers the program to still be satisfactory for the support of the NDA. Does the Agency concur?

FDA Response
Yes [from the PK perspective]

Discussion of Question # 10
The sponsor inquired if it would be acceptable to provide interim data on this study at filing of the application, then provide the balance during the review cycle, at approximately the 6-8 month point. Dr. Rappaport reminded the sponsor that with a 10-month review clock, a submission at the 6-8 month point would eliminate much of the time the reviewers needed to review the material. He also pointed out that such a submission would necessitate an additional safety update. Therefore he strongly encouraged the sponsor to collect all of the data and submit it to the Agency by the 120-day safety update.

The issues of multiple application sites and multiple patches at the same application site were discussed, with the sponsor providing a brief outline of current studies to look at these issues. Dr. Chang stated that these issues would become important during the review of the application. If there were any subjects that have unpredictably high levels that would be an area of concern to the Agency. The sponsor stated that they felt they would have a better understanding of this issue once all of the data from the current studies was available and noted that there is typically more variability in topical products versus oral formulations.

Question #1
Is the proposed organization and content of the draft table of contents (pages 7-26) for the S-Caine patch (lidocaine 70mg and tetracine 70 mg) NDA submission satisfactory?

FDA Response

- There is no mandatory format.
- The format required for the Common Technical Document (www.ich.org) is strongly recommended for FDA purposes and required for the approval process abroad.
- There is a regulatory requirement for a comprehensive index for the entire submission that includes volume and page numbers for each item. [21CFR§314.50(b)] Your table of contents appears to satisfy that requirement.

Question #2 a.
A draft package insert has been included in the meeting briefing document on pages 27-35. Although not exhaustive (as all data have not yet been analyzed), the draft includes the general organization and content of the eventual package insert.

a.) Is the proposed general organization and content of the draft package insert satisfactory?

FDA Response

- 21CFR§201.57 requirements will possibly necessitate additional sections.
- Content of the label will be considered during the NDA review. Final wording will be decided upon at that time.

Question #2 b.
Do the controlled clinical trials (see pages 105-127) appear adequate to support the "Indications and Usage" and "Dosage and Administration" sections as listed on the draft package insert?

FDA Response

- Final determination of the adequacy of the clinical trials, controlled and uncontrolled, to support the proposed indications and dosages will occur during the NDA review.
- The trials described in the meeting package incorporate, *on superficial review*, replicated studies in the populations that would typically be required to support the indications and dosages listed in the draft label.

Question #2 c.
Is the organization of the "Clinical Studies" section acceptable to the FDA?

FDA Response

At this point, it is premature to discuss the organization of the 'Clinical Studies' section. The draft label loosely reflects some of the information routinely included in this section.

Question # 11

Is the organization of Section 8 as outlined in the draft table of contents satisfactory?

FDA Response

- The organization appears to be sufficiently detailed to allow for adequate review.
- Please refer to comments about the Common Technical Document.

Question #12

The sponsor has designed the clinical program to support the indication of the S-Caine patch as a [redacted]' The sponsor presented protocols to the Agency for the Phase III clinical program, and the Agency deemed them to be sufficient to support an NDA (see Supplement 006 dated April 11, 2001 and conference call minutes of June 28, 2001). In addition, the sponsor has provided in this briefing document individual study synopsis for each clinical trial conducted with the S-Caine patch. The sponsor considers the clinical program still to be satisfactory to support the indication as listed above. Does the Agency concur?

FDA Response

- The final decision on indication(s) will be made after full review of the individual trials and the clinical program as a whole.
- A cursory review of the types of data (to be) collected in the trials suggests that appropriate types of trials were conducted and a sufficient body of data collected (when the studies are completed) to support an NDA.
- It was not clear from the meeting package that the following types of data were collected:
  - response to repeated applications at the same site;
  - response to prolonged application time at one site (24h).

Discussion of Question # 12

Dr. Simone stated that the Division's concern deals with how the product will actually be used in practice, especially in pediatric patients in whom prolonged exposure to the patch and multiple patch site applications might be an issue. The sponsor stated that some animal studies suggested an increased exposure time could lead to skin irritation or injury so they are hesitant to perform this type of study in humans. Dr. Simone stated that the Division has consulted the dermatology experts in the Division of Dermatologic and Dental Drug Products (DDDDP), noting that further internal discussion on this issue is still needed.

Dr. Chang referred to the OGD guidance on dermatolgic products in which a 21-day protocol is the standard study we would request even for acute-use products, but noted that we would not request such a study if it would put patients at risk. Therefore, she stated that the sponsor could propose a study that met the needs of the guidance while decreasing the risk to patients. She noted that information about toxicity in animals might need to be included in the labeling.

Dr. Rappaport suggested that the Division have further internal discussion once the response form the DDDDP consult is reviewed and then respond to the sponsor on this issue. He noted that an action item would be to schedule an internal meeting to discuss this issue.

Question #13
Are the projected patient totals as presented in tables on pages 95-97 in the adult, pediatric, and geriatric age groups satisfactory?

FDA Response

The overall numbers appear satisfactory, however the breakdown within the pediatric and geriatric populations needs to be better specified.

- Geriatric trials should include a significant number of subjects 75 years of age [and older].

- Pediatric subjects should include adequate representation of neonates, infants, children and adolescents.

Question #14
Because of the similarities between many of the Phase II and Phase III clinical studies, the sponsor has proposed to include some phase II studies in the "Controlled Studies" section of the NDA under the subheading of "Controlled Studies using developmental S-Caine formulation." The sponsor has further proposed to include the Phase III controlled clinical studies in under the subheading of "Controlled studies using final S-Caine formulation." (see discussion on page 98). Is this approach acceptable?

FDA Response

- Provided appropriate bridging information (e.g.., comparative in-vitro dissolution) is submitted to support the claim that changes in the amount of excipient and sites of manufacture of the two products do not significantly affect the final product, this approach is acceptable.

- This approach should not affect the presentation of data in the integrated summaries of safety and efficacy.

Discussion of Question # 14
Dr. Koble clarified that the Agency was requesting a pharmaceutical/chemical rationale or "bridge" to explain why, or how, the product properties have not changed throughout formulation changes to the product. This is normally done under SUPAC guidelines. He noted

that the Guidances are not specific to this dosage form and the sponsor will need to justify the changes to us.

Dr. Simone stated that the Division requires data to demonstrate that the patch formulations are equivalent to one another. Dr. Rappaport indicated that if any differences were observed, it might be possible to present them in the labeling.

Question #15
Are the format and general content of the example tables for clinical studies and list of investigators, INDs and NDAs (pages 102-104) acceptable?

FDA Response

- In the table of clinical studies, inclusion of whether the patch formulation was developmental or final in the "formulation" column would be helpful.

- In the same table, a column giving a summary of safety and/or efficacy results would be very useful.

- The List of Investigators, INDs and NDAs appears to be fine as is.

Question #16
The sponsor proposes to include case report tabulations in the respective clinical reports in Section 8. Is this acceptable to the Agency?

FDA Response

- Including case report tabulations in the respective clinical reports in section 8 is acceptable provided that all studies are still integrated in the ISS.

- Placing them in the report sections as well will assist in the review process.

Question #17
The sponsor proposes to limit the inclusion of CRFs in the NDA to deaths, SAEs and withdrawals due to adverse events. Is this acceptable to the Agency?

FDA Response

This is consistent with regulatory requirements and is acceptable.

Question #18
The sponsor proposes to submit the NDA in the traditional hard copy format. In addition, for the convenience of the reviewers, the sponsor proposes to submit on CD desk copies of the clinical study reports (with raw clinical data) and desk copies of the respective section summaries. The clinical reports and section summaries will be available in Word format and the clinical data will be available in Microsoft Excel. Is this proposal satisfactory?

FDA Response

- While an electronic submission is preferred, the traditional hard copy is still acceptable. Compliance with Guidances for Industry is strongly encouraged. [www.fda.gov/cder/guidance]

- All review work is based on information as it appears in the archival copy submitted to the FDA Document Room. Desk copies may not be used for review purposes, except for labeling.

Discussion of Question # 18

Dr. Rappaport stated that the Division recommends beta testing the submission with us before officially submitting it.

Closing discussion

Dr. Simone summarized the Agency's remaining concerns:

- Repeat exposures at the same site
- Sensitization
- Prolonged exposures to the product

The sponsor stated that a repeat exposure protocol has been submitted to the Agency and noted that the prolonged exposure issue was a new one. Dr. Rappaport indicated that the Division would be flexible on this issue.

Dr. Simone stated that the term "minor dermatologic procedure" might need additional clarification in the label.

The sponsor inquired if the Agency would like to see "data shelves" prior to their submission to the ISS. Dr. Rappaport stated that if the Division had the resources to look over these materials prior to their submission, they might be useful.

Dr. Koble stated that for release rate testing specifications, a maximum and a minimum are needed. Dr. Al-Fayoumi added that typically the release rate test should demonstrate an overall release of 80-100% of total drug in the patch.

Post Meeting Comment from ODS

The sponsor is encouraged to evaluate the risk with use of the product and propose ways to manage or reduce these risks. Plans for risk management should be included in Module I of the Common Technical Document for the NDA application.

If the NDA application is not being submitted in the Common Technical Document format plans for risk management should be included in the Clinical Section.

Action Items:

1. Schedule an internal meeting to discuss the issue of dermal sensitization and the consult response from DDDDP.

2. The Agency will prepare the official minutes of the meeting and provide the sponsor with a copy.

Minutes prepared by: Kim Compton
Minutes concurred by Chair: Nancy Chang, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kimberly Compton
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