

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-717

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

13. Patent information

Included in this section are Forms FDA 3542a for the following patents.

Patent Number 5,919,479
Expires: July 28, 2015
Patent Owner ZARS, Inc.

Patent Number 6,528,086
Expires: September 28, 1019
Patent Owner ZARS, Inc.

**APPEARS THIS WAY
ON ORIGINAL**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-717

NAME OF APPLICANT / NDA HOLDER

ZARS, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)
lidocaine and tetracaine

STRENGTH(S)
lidocaine 7%, tetracaine 7%

DOSAGE FORM
Cream

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5919479

b. Issue Date of Patent
7/6/1999

c. Expiration Date of Patent
7/28/2015

d. Name of Patent Owner
ZARS, Inc.

Address (of Patent Owner)
1142 West 2320 South

City/State
Salt Lake City, UT

ZIP Code
84119

FAX Number (if available)
801-350-0909

Telephone Number
801-350-0202

E-Mail Address (if available)
prichards@zars.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
<i>Patricia J. Richards</i>	<i>28 November 2005</i>

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Patricia J. Richards, Vice President, Regulatory Affairs	
Address 1142 West 2320 South	City/State Salt Lake City, UT
ZIP Code 84119	Telephone Number (801) 350-0202
FAX Number (if available) (801) 350-0909	E-Mail Address (if available) prichards@zars.com

The public reporting burden for this collection of information has been estimated to average 9 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

1.1 ZARS, Inc. PATENT INFORMATION

Patent No. 6,528,086
Expires: September 28, 2019
Method of Use and Drug Product Patent
Patent Owner ZARS, Inc.

The undersigned declares that Patent No. 6,528,086 covers the formulation, composition, and/or method of use of S-Caine Peel. 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
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 Peel. This product is the subject of this application for which approval is being sought.

Authorized Signature



Date

11/14/03

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.

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY

NDA # 21-717

SUPPL #

HFD # 170

Trade Name

Generic Name (lidocaine and tetracaine) 7%/7% Cream

Applicant Name Zars, Inc.

Approval Date, If Known ~~June 27, 2006~~

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?

No

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# 21-623	lidocaine/tetracaine
NDA# 19-941	lidocaine/prilocaine
NDA# 21-504	lidocaine (see Orange Book for additional lidocaine products applications)

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:

Study SCP-	Procedure Type	Population
40-05	Dermal Filler Injection	Adult
41-05	Non-alative facial Laser	Adult
42-05	Pulsed dye laser therapy	Adult
43-05	Laser assisted tattoo removal	Adult

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"):

Study SCP-	Procedure Type	Population
40-05	Dermal Filler Injection	Adult
41-05	Non-alative facial Laser	Adult
42-05	Pulsed dye laser therapy	Adult
43-05	Laser assisted tattoo removal	Adult

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 # 59,801 for both investigation 1 & 2. YES ! NO
! Explain:

Investigation #2 !
!
IND # 59,801 for both investigation 3 & 4. YES ! NO
! Explain:

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

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

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Bob Rappaport
6/28/2006 04:38:18 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-717 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: November 17, 2003 Action Date: June 29, 2006

HFD 170 Trade and generic names/dosage form: TRADENAME (lidocaine and tetracaine) 7%/7% Cream

Applicant: Zars, Inc. Therapeutic Class: 3S

Indication(s) previously approved:

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

Number of indications for this application(s): 1

Indication #1: Local dermal analgesia on intact skin

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. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments:

It is only approved for adult population since efficacy was not shown in pediatric population.

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}

Pratibha Rana, MS

Regulatory Project Manager

cc: NDA 21-717
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 ##-###
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/

Parinda Jani
6/29/2006 02:56:53 PM

DEBARMENT STATEMENT

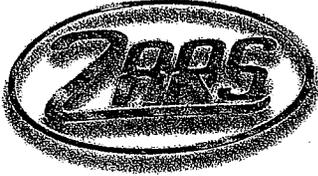
ZARS, Inc. herewith certifies that the services of any persons debarred under Section 306(a) or (b) were not and will not be used in any capacity in conjunction with this application, NDA 21-717 (S-Caine™ Peel).

Signed: Patricia J. Richards

Date: 06 Dec 05

Patricia J. Richards
Vice President, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**



DRUG DELIVERY TECHNOLOGY

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: _____

T. Andrew Crockett
T. Andrew Crockett
Director
Clinical & Regulatory Affairs

Date: Nov. 14, 2003

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

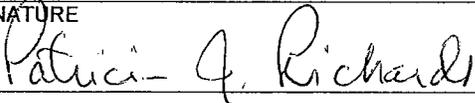
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the 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 list.	

- (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 Patricia J. Richards	TITLE Vice President, Regulatory Affairs
FIRM / ORGANIZATION ZARS, Inc.	
SIGNATURE 	DATE 11/30/05

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

1 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

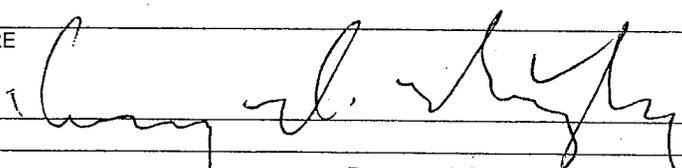
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the 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 Larry Rigby	TITLE C.E.O
FIRM / ORGANIZATION ZARS, Inc.	
SIGNATURE 	DATE 11/14/03

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

20 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE: June 28, 2006

DRUG: S-Caine (lidocaine and tetracaine) 7%/7% cream

NDA: 21-717

SPONSOR: ZARS, Inc.

INDICATION: for local dermal analgesia

ZARS Inc. submitted NDA 21-717 for S-Caine on November 17, 2003. ZARS had previously submitted an NDA for a patch formulation containing the same active ingredients; that application was eventually approved on June 23, 2005, with the trade name Synera. The Synera application was transferred to another sponsor after approval. ZARS has a contractual agreement with that sponsor regarding marketing, and maintains ownership of the patents on the Synera product. A not-approvable action was taken on the cream formulation on September 15, 2004. This action was primarily based on the fact that there were extensive data integrity concerns and ethical improprieties related to the trials which were performed in the pediatric population (See Dr. Robert Meyer's Action Memo). The sponsor submitted their response to the not-approvable letter on December 30, 2005.

The clinical studies in this response were reviewed by Mwango Kashoki, M.D. A statistical review of those studies was provided by Kate Meaker, M.S. Consultations on this application were provided by the Office of Drug Safety and the Division of Drug Marketing, Advertising and Communications.

The sponsor submitted five new clinical studies in support of the application. Four of these trials evaluated the product in adult subjects, and one evaluated S-Caine in pediatric subjects. Dr. Kashoki and Ms. Meaker have thoroughly evaluated these trials in their reviews and, as such, I will only summarize the results of the studies.

Each of the adult trials demonstrated a statistically significant treatment effect for S-Caine compared to placebo, as per the summary results presented in Dr. Kashoki's table (page 5 of her review), reproduced below:

Summary of Efficacy of S-Caine in Adults

Study	VAS Score (mean ± SD)		p-value
	S-Caine	Placebo	
SCP-40-05	24.2 ± 18.13	37.4 ± 23.52	< 0.0001
SCP-41-05	21.4 ± 18.89	38.0 ± 24.46	< 0.0001
SCP-42-05	16.4 ± 19.55	30.9 ± 17.06	0.0008
SCP-43-05	39.1 ± 25.48	58.6 ± 21.59	<0.0001

These trials employed a superficial dermatological procedure (collagen injection, pulsed dye laser therapy, facial laser resurfacing and laser-assisted tattoo removal) as the painful stimulus. A 100-mm VAS scale was used to measure the pain associated with the procedure.

The single pediatric trial failed to show any difference in efficacy between the product and placebo. This study employed a minor vascular access (venipuncture or intravenous line placement) procedure as the painful stimulus following a 30-minute treatment with study drug. The Colored Analog Scale, a continuous pain rating scale enumerated from 0 to 10, was used to measure the pain associated with the procedure. Dr. Kashoki's table (also from page 5 of her review) summarizes the results of this study and is reproduced below:

Summary of Efficacy of S-Caine in Pediatric Patients

Study	VAS Score (mean ± SD)		p-value
	S-Caine	Placebo	
SCP-46-05	1.77 ± 2.46	2.03 ± 2.34	0.64

The results of this study are consistent with the pediatric studies submitted in the original NDA. In that submission, two of the three pediatric trials failed to show a difference between S-Caine cream and placebo. The third trial did show a statistically significant treatment effect, but was not considered interpretable due to data integrity concerns and the fact that the trial was performed under conditions that were deemed unethical by the Agency.

There were no deaths or serious adverse events reported from the original or the new studies. The only common adverse events that occurred more frequently in the study drug-treated subjects compared to the placebo-treated subjects were local dermal reactions. The most commonly reported event noted across the controlled studies in the NDA resubmission was: erythema (26% in both S-Caine and placebo subjects). Other

common dermal adverse events that occurred with relatively similar frequency in both the S-Caine and placebo groups were edema (18%), echymosis (11%) and rash (13%). Across all controlled trials, the only adverse event reported more frequently in the S-Caine subjects was “application site reaction.” The safety profile as noted above is similar to what was seen in the safety database from the original application and demonstrates the expected toxicity profile for a product that provides topical local anesthetic delivery.

Discussion:

The sponsor has provided data on the efficacy and safety of S-Caine that is adequate to support an approval action for use of the product in adult patients undergoing superficial dermatological procedures. They have failed to provide adequate evidence of efficacy of their product for use in pediatric patients.

This is a section 505(b)(2) application. The application references the available literature and the previously approved Synera application. Although ZARS has obtained right-of-reference to the Synera NDA, the fact that they have depended upon the literature for approval results in this NDA falling within the realm of the 505(b)(2) section of the FD&C Act .

There are no patents listed for EMLA, the drug product identified by the sponsor as the Reference Listed Drug (RLD). ZARS has represented that it retains ownership of the patents for the Synera product; certification to those patents is not required for approval of the application.

The three year exclusivity period protecting Synera does not block approval of this 505(b)(2) application because the Synera lidocaine and tetracaine patch does not have the same conditions of approval as the S-Caine lidocaine and tetracaine cream; new clinical studies were required to support the approval of the S-Caine NDA.

Action: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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

/s/

Bob Rappaport
6/28/2006 08:10:21 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research



DIRECTOR'S DECISIONAL MEMORANDUM

Date: Wednesday, September 15, 2004
NDA: 21-717
Sponsor: ZARS, Inc.
Proprietary Name: S-Caine Peel (lidocaine 7%/tetracaine 7% cream)
Author: Robert J. Meyer, MD, Director, ODE II
on behalf of Bob Rappaport, MD, Director, DACCADP

Introduction: This is the first cycle for this NDA for a combination of lidocaine and tetracaine in an oil-in-water emulsion (or cream) formulation that one applies with a spatula, tongue depressor or gloved finger that then forms a solid, pliable membrane on the skin. The formulation contains 7% lidocaine by weight, along with 7% Tetracaine. The product is intended to provide analgesia to intact skin for the purposes of dermatologic _____ interventions (e.g., laser procedures _____). Lidocaine is approved for similar usage at concentrations comparable to that in this formulation. Although tetracaine is a compendial drug substance and has been in common use as a local and topical anesthetic, it is not approved in any NDA.

There is a closely related application (21-623) from this same sponsor called S-Caine Patch that was given an approvable action in February 2004, with the deficiencies being primarily CMC. NDA 21-623 satisfactorily addressed the issue of the combination policy with a factorial study. Therefore, by prior agreement, the Peel NDA does not address the issue of the utility of the combination per 21 CFR 300.50.

This application is being reviewed in the Division of Anesthetics, Critical Care, and Addiction Drug Products. Dr. Rappaport, the Director of that division, is not available to oversee the final stages of this action, so I am acting in his stead for this action.

Chemistry/Manufacturing and Controls:

The CMC review team (see Dr. Chiapperino's review) is recommending approval. From the CMC standpoint, this is a relatively simple dosage form and the sponsor has satisfied the data requirements concerning the drug substances, drug product, and stability. Note that the formulation changed considerably over the course of development in terms of the amount and types of excipients included, though the concentrations of the active drugs were consistent. Changes in the formulation could change bioavailability of the drugs to the site of action. However, the sponsor did provide many studies utilizing the final, to be marketed formulation.

As of September 10, 2004, all the EERs are acceptable and an overall recommendation of acceptable was entered by HFD-322.

Preclinical: Given that these are established drugs (with lidocaine in many approved products) and that the division has previously reviewed the sponsor's preclinical data package for the S-caine patch, there are few unique preclinical issues with this NDA. The reviewer (Dr. Thornton-Jones) has found the NDA acceptable. The Pharm/tox team did recommend some substantive labeling revisions which can be sent to the company along with the action letter.

Biopharmaceutics: When used as directed, there were systemic levels of lidocaine documented in adults, with the C_{max} coinciding with the time of removal. In other words, the concentration continued to increase while the membrane was on the skin, up to 2 hours. The concentrations of lidocaine seen were relatively small (highest in adults was 217 ng/mL, compared to therapeutic levels of 1.5 – 5 mcg/mL). Tetracaine was not measurable in adults, but was documented in some pediatric patients.

PD studies were done, notably study SCP-34-03 which, using a pin prick model, attempted to characterize the offset of analgesic effects of the peel once removed. There were some issues in the analysis of this trial (due to a post-hoc change in definition of return of sensation), but the data appear to indicate that analgesia increases after the peel is removed for approximately 90 – 120 minutes, then slowly decreases out beyond 4 hours or more. (see Dr. Josefberg's graphic 8.4.9.10)

Overall, there appear to be no substantive outstanding biopharmaceutics issues.

Clinical / Statistical: See Dr. Josefberg's primary Medical Officer Review, Dr. Permutt's Statistical Review and Dr. Chang's Team Leader Memo for details. The sponsor submitted 8 adult efficacy studies (one of these only in geriatric patients) and 2 pediatric studies that utilized the final formulation. A third pediatric study was a positive-control trial where there was no intent to show a difference – so while this had an efficacy assessment, the data are not useful for making inferences on efficacy.

Efficacy: The settings of the adult studies varied from "minor" skin procedures, such as laser hair removal and vascular access, to somewhat more morbidity-inducing procedures, such as laser tattoo removal and laser sclerosis of veins. The studies used a visual analogue scale of pain intensity as the primary endpoint and, for the adult trials, there was often a contralateral placebo control (the same cream/peel without any active drug). In these adult studies, 7 of 8 showed a statistically significant reduction in the VAS compared to placebo, with reductions being mostly in the range of about 15 - 20 mm out of a 100 mm scale relative to placebo. The only failed study was a vascular access "model" in adults, but the comparable study in geriatric patients showed efficacy.

In pediatrics, there were two studies of adequate design to show efficacy. It is important to point out two things regarding pediatrics with this drug. First, the PK data show a higher exposure level to the active ingredients in pediatric patients compared to adults, despite smaller application areas and shorter durations in the children. However, this may or may not predict local efficacy. Secondly, given differences in dermal and subcutaneous structure in children (thickness of the layers of adipose and dermal connective tissue, and depth and extent of blood vessels) compared to adults, an

extrapolation of efficacy and safety from adults to children does not appear to be fully warranted, despite the contention of the sponsor. Therefore, I believe at least one positive study along with pediatric specific safety data would be needed to consider approving the peel in this population. The two studies submitted used different pain-inducers, one being IV insertion and the other being medically indicated lidocaine injections. This latter trial failed with no clear support of efficacy. The IV trial showed statistical differences in the “Oucher” scale used, but the efficacy came primarily from older children (ages 7 – 17) who used a numeric scale and not from younger children (3 – 6) who used a photographic scoring system. While one might have extended an approval down to age 7 based on these data (along with appropriate caveats about increased exposure), this IV study had 43 protocol violations that turned out to be a violation of the inclusion criteria that required children to have a medical need for the IV in order to enter into the study. Apparently, the CRO site doing the study enrolled children who did not otherwise need an IV in order to speed the enrollment process. This is a clear violation of a part of the protocol written to make this study ethically acceptable and feasible.

Beyond the ethical issues, a “for cause” DSI inspection of the sponsor and select study sites was done due to there being problems in the data set originally provided to the statistical team. There appeared to be a reversal of drug and placebo in at least some of the data. This clinical inspection, besides documenting the ethical issue above, showed systemic problems with ZARS in conducting and monitoring its trials. Due to the nature and extent of these problems, DSI has recommended not using any of the current data from ZARS in support of this NDA. Among the most concerning DSI finding is that the sponsor reversed randomization at one study site based solely on the weight of medication tubes. (This apparent ability to detect drug from placebo based on tube weight raises the issue of the effectiveness of the blind, incidentally, an important issue in a study with subjective ratings). This reversal was then carried through to a second site, apparently in error. From the records that DSI audited, it is not clear if all the errors were indeed straightened out and the company apparently could not provide a convincing explanation of what happened, how it was addressed and if it was ever fully rectified.

Safety: The safety data for this NDA do not show any surprising or important toxicities. There are local effects of the peel, including erythema, blanching, edema and rash being amongst the most prominent local reactions that appeared in excess in the drug treated group. There was little indication that there were important systemic adverse events (which is not surprising, given the low lidocaine levels and negligible tetracaine levels resulting from use of the peel. There were no reports of any serious rashes leading to important consequences.

There were no serious AEs, deaths or even withdrawals due to AEs, but all the trials for this product were single application trials, so this would be expected. Overall, the safety data support that this product is mostly well tolerated and does not appear to have any concerning or surprising safety issues, especially compared to similar such products.

Financial Disclosure: There were not any significant financial considerations reported for any of the investigators and therefore, there appears to be no reason to believe that financial conflicts of interest would be of concern in this application.

Labeling: The labeling, were this product to be approved, would need substantial revisions. However, in this cycle, where the division is not recommending approval, we will not be supplying definitive labeling comments. The nomenclature for this product (the latest proposal from the sponsor being TetraPeel) has been reviewed by ODS and found to be not acceptable due to it being misleading, in that it implies it contains only tetracaine. I support this conclusion. The sponsor will need to re-propose a name.

Conclusions: The data presented by ZARS in support of this NDA on their surface appear to support a conclusion of efficacy in adults, with weaker support of efficacy in children above the age of 7 only. No data supporting efficacy below age 7 were provided. However, the positive data in children 7 years and older primarily came from study 28-02. As detailed above, approximately half of these children were not otherwise in need of IV access, but rather were knowingly entered into the trial by the CRO conducting the study in clear violation of the protocol. It is recommended by the FDA's Ethicist that data from this study not be accepted for the purposes of drug approval, given the clear breach in ethics entailed in generating the data. I concur with this recommendation. Without this study, there are insufficient data to allow for pediatric approval, and we will need to ask the sponsor to conduct a further acceptably designed and conducted efficacy study or studies in children.

The adult data appear to be more convincingly positive. However, the Division of Scientific Investigations has turned up some serious issues with data integrity with the adult studies as mentioned above. Therefore, we will not approve this drug on this cycle, instead issuing a "not approvable" action. The sponsor will be asked to either provide new data from properly performed, monitored and analyzed studies in adults or, alternatively, attempt to assure us of the data integrity of the data provided.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Robert Meyer
9/15/04 02:20:23 PM
MEDICAL OFFICER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-717	Efficacy Supplement Type SE-	Supplement Number
Drug: Tradename (lidocaine and tetracaine) 7%/7% Cream		Applicant: ZARS Inc
RPM: Pratibha Rana	HFD-170	Phone # 301-796-1277
<p>Application Type: () 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>(X) Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p style="padding-left: 20px;">EMLA® Cream (Lidocaine 2.5% and Prilocaine 2.5%)</p> <p style="padding-left: 20px;">No Reference Drug for Tetracaine</p>	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 	(X) Standard () Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 	3S	
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 		
❖ User Fee Goal Dates		
July 3, 2006		
❖ Special programs (indicate all that apply)		
() None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2		
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 	(X) Paid UF ID number 4636	
<ul style="list-style-type: none"> • User Fee waiver 	() Small business () Public health () Barrier-to-Innovation () Other (specify)	
<ul style="list-style-type: none"> • User Fee exception 	() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)	
Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 	() Yes (X) No	

<ul style="list-style-type: none"> This application is on the AIP Exception for review (Center Director's memo) OC clearance for approval 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.</p>	<input checked="" type="checkbox"/> Verified
<p>❖ Patent</p>	
<ul style="list-style-type: none"> Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input checked="" type="checkbox"/> Verified
<ul style="list-style-type: none"> Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p>
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	<p><input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	No
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	6-28-06

General Information

General Information	
Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	NA, September 15, 2004
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	DMETS: June 13, 2006 DDMAC: June 9, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	DMETS: June 13, 2006 DDMAC: June 9, 2006
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	February 6, 2002
• Pre-NDA meeting (indicate date)	July 16, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	6-28-06, 9-15-04, 9-14-04
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	6-22-06, 9-15-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	6-28-06
❖ Demographic Worksheet (NME approvals only)	
❖ Statistical review(s) (indicate date for each review)	6-7-2006, 8-18-04
❖ Biopharmaceutical review(s) (indicate date for each review)	8-30-04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	6-21-06, 9-14-04
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	6-15-06, 9-14-04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	CMC Review #1, Page 54
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	6-23-06, 6-14-06, 9-10-04
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Rana, Pratibha

From: Kashoki, Mwango
Sent: Thursday, June 29, 2006 11:53 AM
To: Currier, Carolanne
Cc: Rana, Pratibha; Jani, Parinda; Rappaport, Bob A; Hertz, Sharon H
Subject: RE: Clinical Inspection Summary for NDA 21-717

Thank you for this latest summary of the clinical inspection findings, Carolanne!

From: Currier, Carolanne
Sent: Thursday, June 29, 2006 11:50 AM
To: Kashoki, Mwango
Subject: Clinical Inspection Summary for NDA 21-717

Hi Mwango-

I just finished reviewing the last S-Caine EIR and am starting to write the Clinical Inspection Summary for DFS. I just wanted to give you a preview of what's coming:

We assigned 4 inspections for the new studies for NDA 21-717:

Terry Jones - Protocol SCP-40-05 - No problems found during the inspection. NAI Classification - all data acceptable.

Mark Taylor - Protocol 42095 and 45-05 - No problems found during the inspection of either study - NAI - all data acceptable.

Daniel Stewart - Protocol 41-05, 42-05, 45-05, 47-05 - Minor informed consent documentation and record keeping problems, none of which are of any clinical significance. VAI classification. All data acceptable.

William T. Garland - Protocol 44-05 - Protocol deviations and inaccurate record keeping problems noted. Protocol deviations included multiple persons performing pinprick tests (instead of the PI or designee as per protocol), out-of-sequence randomization for 19 subjects (was not intentional and would not affect study results), 7 subjects had pinprick readings done out of the time window allowed by the protocol, and lack of documentation of who performed all required tests and assessment (however all personnel were qualified and appropriately trained for the duties they performed). There were also a few minor administrative and transcription errors - none of clinical significance. It does not appear that, with the exception of the first protocol deviation listed above, any of the protocol deviations or inaccurate records would have affected the outcome of the study or jeopardized the validity of the data. Besides, it appears these protocol deviations were all reported in the NDA submission so you should already know about them. My only question is what affect multiple pinprickers would have had on efficacy - I suspect very little. This review has not been signed off by my supervisor yet, but I classified it as VAI and recommended that the data could be used.

In short, it appears that all data from the above studies could be used to support an approval decision.

Contact me if you have any questions. I hope to get the Summary into DFS tomorrow or Monday at the latest. Sorry for the last minute review.

Carolanne

**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
7/6/2006 09:48:24 AM
CSO

**Updated 06/28/06: NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)**

NDA # 21717 Supplement # Efficacy Supplement Type SE-

Trade Name: Tradename
Established Name: (Lidocaine and Tetracaine) 7%/7% Cream
Strengths: Lidocaine 7% Tetracaine 7% Cream

Applicant: Zars, Inc.
Agent for Applicant:

Date of Application: December 30, 2005(Resubmission)

Date of Receipt: January 3, 2006

Date clock started after UN:

Date of Filing Meeting:

Filing Date:

Action Goal Date (optional): June 27, 2006

User Fee Goal Date: July 3, 2006

Indication(s) requested:

Type of Original NDA: (b)(1) (b)(2) X
OR

Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S X P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee Status: Paid X Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO X
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES NO X
- 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
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES X NO
- Was form 356h included with an authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES X NO
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A X YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Additional comments:
- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.
Additional comments:
- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, _____ Years NO X
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it 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 this application.” Applicant may not use wording such as “To the best of my knowledge”

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y X NO
- PDUFA and Action Goal dates correct in COMIS? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND 59,801
- End-of-Phase 2 Meeting(s)? Date(s) February 6, 2002 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) July 16, 2003 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic “Content of Labeling” submitted? YES NO X
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
YES X NO
- Risk Management Plan consulted to ODS/IO? N/A X YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y X NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
N/A X YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A X YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: Filing meeting cancelled: Application filable.

BACKGROUND:

First cycle: Received date: November 17, 2003
Action date: NA, September 15, 2004
Resubmission: Received date: January 3, 2006
Due Dates: PDUFA: July 3, 2006, Action Date: June 27, 2006

ATTENDEES: NA

ASSIGNED REVIEWERS:

Discipline

Reviewer

Medical:	Mwango Kashoki
Statistical:	Kate Meaker
Pharmacology:	Dan Mellon
Chemistry:	Ali Al Hakim
Environmental Assessment (if needed):	
Biopharmaceutical:	Srikanth Nallani
Microbiology, sterility:	
DSI:	
Regulatory Project Management:	Pratibha Rana
Other Consults:	DSI, ODS- DMETS/DDMAC

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

CLINICAL FILE X REFUSE TO FILE

- Clinical site inspection needed? YES X NO
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- 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 X YES NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A FILE X REFUSE TO FILE

BIOPHARMACEUTICS FILE X REFUSE TO FILE

- Biopharm. inspection needed? YES NO X

PHARMACOLOGY	N/A <input type="checkbox"/>	FILE X	REFUSE TO FILE <input type="checkbox"/>
• GLP inspection needed?			YES <input type="checkbox"/> NO <input type="checkbox"/>
CHEMISTRY		FILE X	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?			YES X NO <input type="checkbox"/>
• Microbiology		NA X	YES <input type="checkbox"/> NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- 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.
- X No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of 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. Convey document filing issues/no filing issues to applicant by Day 74.

Pratibha Rana, MS
Regulatory Project Manager, HFD-170

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES X NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
N 19-941EMLA[®] Cream (Lidocaine 2.5% and Prilocaine 2.5%), however the application does not rely on data from, EMLA. This application relies on the Agency's findings of safety and efficacy from N 21-623, Synera (Lidocaine 70mg/Tetracaine 70mg) Patch .

Endo is the application owner for Synera

Endo has the rights to Synera

Endo owns the IND and NDA for Synera

Endo is ZARS' marketing partner, and has the right to market Synera in the US

ZARS owns the patents for Synera. Endo has license to the patents.

ZARS owns patents that were submitted in the NDA for S-Caine, and ZARS retained the right of reference to those patents.

No Reference Drug for Tetracaine

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO X

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES X NO
The pharmaceutical alternative is NDA 21-623, Synera.

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. 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 Peel is Lidocaine/Tetracaine whereas the EMLA Cream is Lidocaine/Prilocaine.

7. 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 (see 21 CFR 314.101(d)(9)). YES NO
8. 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 21 CFR 314.101(d)(9)). YES NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise YES NO

made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9).

10. Are there certifications for each of the patents listed for the listed drug(s)? YES X NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 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. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 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 as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 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).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES X NO

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

YES NO X

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

N/A X 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 X YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

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

NA X 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.

IND# _____ NO

OR

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

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES X NO

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this page is the manifestation of the electronic signature.**

/s/

Pratibha Rana
6/28/2006 03:57:55 PM
CSO

Rana, Pratibha

From: Rana, Pratibha
Sent: Thursday, June 22, 2006 5:30 PM
To: 'Patricia Richards'
Cc: Rana, Pratibha
Subject: N21-717/S-Caine/Labeling Change Request/6-22-06

Attachments: S-Caine PI to Sponsor_6_22_06 PR.doc

Patricia,

Here is the revised PI and further comments regarding labeling and the proprietary name. Please submit the changes asap. Please send me the changes via email as well.



S-Caine PI to
sponsor_6_22_06 ..

Carton and tube labeling

- Under the "contains" sub-heading: Make the phrase "and the following inactive ingredients" normal font.
- Add the sentence "Not for home use by patient." This can be added next to either "Rx only" or "For topical anesthetic use only." The sentence regarding non-home use should be in the same format as afore-mentioned instructions.

Proprietary name

- The proposed proprietary name, S-Caine, is not acceptable. Provide an alternative proprietary name for Agency review.
- Availability of an agreed-upon proprietary name is not required for action to be taken on the NDA by the PDUFA date.

Please let me know if you have any questions.

Pratibha

Pratibha Rana, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone: (301) 796-1277

13 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Pratibha Rana
6/22/2006 05:47:03 PM
CSO

Rana, Pratibha

From: Rana, Pratibha
Sent: Tuesday, June 20, 2006 7:53
To: 'Patricia Richards'
Cc: Rana, Pratibha
Subject: NDA 21-717 (S-Caine)/PI

Patricia,

Please find the attached revised PI. Please make the changes recommended by the Review Team and resubmit the revised PI as soon as possible.
Please let me know if you have any questions.

Pratibha

Pratibha Rana, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone: (301) 796-1277

**APPEARS THIS WAY
ON ORIGINAL**

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Pratibha Rana
6/20/2006 08:18:07 PM
CSO

Rana, Pratibha

From: Rana, Pratibha
Sent: Tuesday, June 20, 2006 4:04 PM
To: 'Patricia Richards'
Subject: NDA 21-717 (S-Caine)

Hello Patricia,

Please make the following changes requested by the CMC Review Team:

1. Revise the established name by keeping only "lidocaine and tetracaine" inside the parenthesis and moving "7%/7% cream" outside the parenthesis (PI, carton and tube).
2. Include the net weight of each of the active ingredients on the container/closure system (tube and carton).

Please let me know if you have any questions.

Pratibha

Pratibha Rana, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone: (301) 796-1277

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/s/

Pratibha Rana
6/20/2006 04:15:56 PM
CSO

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: June 9, 2006

To: Pratibha Rana, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

From: Michelle Safarik, PA-C, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Subject: NDA 21-717
DDMAC labeling comments for S-Caine (lidocaine and tetracaine cream 7%/7%)

Per your e-mail consult request dated June 8, 2006, DDMAC has reviewed the proposed product labeling (PI) and proposed carton and tube labeling for S-Caine, and we offer the following comments.

PI

Indications and Usage

1. For consistency with the Dosage and Administration section of the proposed PI, would it be possible to revise this section to the following: "S-Caine is indicated for use on intact skin in adults..." (emphasis added).

Warnings

1. We recommend a cross-reference to the Overdosage section of the proposed PI after the first paragraph for consistency with the Synera label.
 2. We recommend a cross-reference to the Handling and Disposal section of the proposed PI after the second paragraph for consistency with the Lidoderm label.
 3. "Even *used* S-Caine may contain a large amount of lidocaine and tetracaine" (original emphasis).
- 

4. _____ it is important to store and dispose of S-Caine out of the reach of children and pets” (emphasis added).

We recommend deletion of “ _____ ” as this minimizes the risks associated with S-Caine use. In addition, this deletion would make this statement consistent with the Synera and Lidoderm labels.

Carton Label

- 1.



Tube Label

- 1



2. For increased consumer safety, would it be possible to include information from the Handling and Disposal section of the proposed PI regarding hand washing after handling S-Caine and avoiding eye contact with the drug?

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/s/

Michelle Safarik
6/9/2006 10:21:14 AM
DDMAC REVIEWER



NDA 21-717

ZARS, Inc.
1142 W. 2320 S. Suite A
Salt Lake City, UT 84119

Attention: Patricia J. Richards
Director, Regulatory Affairs

Dear Ms. Richards:

Please refer to the meeting between representatives of your firm and FDA on February 8, 2005. The purpose of the meeting was to discuss your proposed clinical development program.

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) 827-1620.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.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

Date/Time: February 8, 2005/ 11:00 am
Location: Parklawn, Conference Room A
Application: NDA 21-717
Sponsor: ZARS, Inc.
Drug/Dosage Form/Doses: S-Caine Peel (lidocaine and tetracaine cream 7%/7%)
Indication: Topical application for local anesthetic
Type of Meeting: Type A
Meeting Chair: Rigoberto Roca M.D., Deputy Director
Minutes Recorder: Dominic Chiapperino, Ph.D., Regulatory Project Manager

Sponsor Attendees	Title
_____	Consultant to ZARS
_____	Consultant to ZARS
T. Andrew Crockett	Director of S-Caine Projects
_____	CRO Representative (_____)
Jono Hampshire	S-Caine Project Manager
Wade Hull	Director of Engineering
_____	Consultant to ZARS
Robert Lippert	Executive Vice President and Chief Operating Officer
Earl Nordbrock, Ph.D.	Senior Biostatistician
Patricia Richards	Director of Regulatory Affairs
FDA Attendees	Title
Rigoberto Roca, M.D.	Deputy Director DACCADP
Ravi Haraphanalli, Ph.D.	Team Leader, Chemistry
Tom Permutt, Ph.D.	Team Leader, Statistics
Howard Josefberg, M.D.	Clinical Reviewer
Suzanne Thornton-Jones, Ph.D.	Pharmacology/Toxicology Reviewer
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer
Carolanne Currier	Consumer Safety Officer, DSI
Pratibha Rana, M.S.	Regulatory Project Manager
Dominic Chiapperino, Ph.D.	Regulatory Project Manager

Meeting Objective(s):

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the January 20, 2005, meeting package. The Sponsor's questions are presented below in *italicized* text and in the order in which they were addressed at the meeting. Agency responses, prepared prior to the meeting and presented on slides, are **bolded**. Discussion is presented in normal text.

Question 8: Does FDA agree that ZARS may rely upon the CMC, Toxicology, PK and Phase 2 dosing data in the original NDA as outlined in the Briefing Document Overview (section 2, pages 6-8)?

FDA RESPONSE

CMC Response: We remind you of your agreement to address the following issues listed in your amendment dated Sep. 10, 2004.

- 1. To reevaluate the drug release specifications once data from multiple commercial batches during the first year of production.**
- 2. To provide the Agency with data on three validation batches demonstrating the correlation between assay homogeneity of the bulk drug product before it is packaged into _____ tubes with assay data on finished tubes to support the adequacy of assay testing only on the bulk drug product.**
- 3 To provide additional specifications if the data does not demonstrate the above correlation.**

Discussion: ZARS stated that the requested CMC information had been collected recently, and asked if it would be acceptable to submit these data in advance of the complete response. Dr. Harapanhalli stated that submission of a complete response in one package would be preferred. ZARS had no objection to CMC data submission at the time of their complete response.

Pre-Clinical Response

- Acceptable to rely on the non-clinical data submitted to the original NDA and provide the final study report for the male fertility and reproduction (Segment I) study when the NDA is resubmitted.**

Biopharmaceutics Response

- No further pharmacokinetic studies should be necessary.**

Clinical Response

- Data from the earlier Phase 2 dose-ranging studies should be acceptable**

Question 1: Is the proposed exposure in the new clinical studies summarized in Briefing Document Overview (section 2, pages 3-6) acceptable for adults?

FDA RESPONSE

- The studies proposed should provide acceptable exposure in the adult population, barring unexpected findings**

Question 2: Does FDA agree with the proposed efficacy endpoints in the adult efficacy trials outlined in the Briefing Document Overview (section 2, pages 3-4)?

FDA RESPONSE

- Yes

Question 3: Does FDA agree with the proposed efficacy endpoints in the pediatric efficacy trial outlined in the Briefing Document Overview (section 2, pages 5-6) and draft protocol SCP-46-05?

FDA RESPONSE

- **The Color Analog Scale *might* be an acceptable instrument**
- **In contrast to the Oucher Scales and their variants, the CAS has not been used widely**
- **The complete protocol should contain justification for selection of the CAS, including a discussion of the key validation studies**
 - **The briefing document contains only short instructions for administration**

Discussion: ZARS conveyed their rationale for choosing the Color Analog Scale (CAS). They believe that the more traditionally used Oucher Numeric pain scales, although well validated for use in older children, are not necessarily appropriate for the youngest of the patients that they intend to study (e.g. five-year-olds). Use of a single instrument for all pediatric subjects would be preferable to use of two separate Oucher type instruments, one for older children and a different one for the younger ones, as done previously. The (CAS) has been used in children as young as five, as well as in teenagers. They expect that the CAS will facilitate collection of meaningful pediatric efficacy data, across the entire 5 to 17 year old age range.

Samples of the actual CAS instrument were provided for the Agency meeting attendees. Drs. Josefberg and Roca indicated that the Division encouraged the use of new, well-validated instruments for pain measurement, where appropriate, and could be amenable to use of the CAS. As stated on the slide, the complete protocol should contain adequate justification for selection of the CAS, including a discussion or review of the key validation studies.

Dr. — stated that ZARS has found pediatric recruitment to be particularly time consuming. ZARS hoped for an expeditious review of the new pediatric efficacy protocol because they would not begin enrolling subjects prior to receipt of Agency concurrence on use of the CAS, and other comments. Dr. — asked how long ZARS might expect to wait after submission of the new protocol. Drs. Josefberg and Roca said that the Division would attempt to provide feedback within about thirty days. Dr. Roca also requested that the Agency be informed of the proposed study initiation dates. Ms. Richards stated that a teleconference could be arranged with Dr. McGrath, the author of the CAS, and Dr. —, ZARS' expert consultant, if the Division thought it would be helpful.

Question 4: Does FDA agree with the proposed safety exposure by pediatric age group outlined in the Briefing Document Overview (section 2, pages 5-6)?

<u>Proposed Pediatric Exposure</u>	
0 - 1 month	= 4
1 mo. - 1 yr.	= 10
1 - 2 years	= 10
2 - 12 years	= 72
12 - 17 years	= 24
Total	= 120

Proposed Pediatric Exposure

- **The two pediatric studies proposed could provide adequate exposure, in children ages two and up**
- **Additional neonatal and infant exposure data would be expected**

Discussion: Dr. Josefberg expanded on these two points.

The single pediatric efficacy trial, to be conducted in children ages five and up, could provide efficacy data adequate to support approval for use in that group. Safety data from the second pediatric study, which would include patients as young as two years of age, could potentially be reflected in the product label.

Additional neonatal and infant exposure data would be expected if ZARS intended to discuss the infant or neonatal populations in the label, even in the absence of an efficacy claim

Question 5: Does FDA agree with the proposed exposure by skin type outlined in the Briefing Document Overview (section 2, page 4)?

FDA RESPONSE

- **Proposed: “All skin types will be well represented with a minimum active exposure of 30 subjects per skin type (adult + pediatric), as agreed at EOP2 meeting”**
- **This should be acceptable**

Question 6: Will the proposed exposure in geriatrics outlined in the Briefing Document Overview (section 2, page 4) be sufficient for geriatric labeling?

FDA RESPONSE

- **Proposed: “A minimum of 100 subjects in the new trials will be 65 years or older. A minimum of 30 of these will be 75 years or older.”**
- **This should also be acceptable**

Question 7: Do the proposed clinical trials for the complete response outlined in the Briefing Document Overview appear adequate to support the proposed indication of _____

FDA RESPONSE

- **Precise label wording, including the scope of the indication, will be considered during review of the application**
- **‘Duration of anesthetic effect’ should be measured directly, not derived**
 - **12-hour assessment period, as proposed**

Discussion: Dr. _____ asked about the possibility of reporting only those adverse events considered by the investigators not to be related to, or caused by dermatological surgical procedures. While acknowledging the difficulty of distinguishing drug-related from procedure-caused events, Drs. Josefberg and Roca expressed concern that potentially valuable information would be lost with limited AE reporting.

Dr. Permutt stated that all adverse events should be reported using conventional definitions and reporting procedures. The Division would then utilize the data as appropriate. All adverse events should be assessed for causality, from the doctor’s/investigator’s perspective, as well as from the Sponsor’s.

ZARS indicated understanding of the Division’s expectations regarding AE reporting.

Question 9: Does the proposal contained in this briefing document appear adequate to address FDA’s requirement to “provide new data from properly performed, monitored and analyzed studies in adults [and children] that provide substantial evidence of effectiveness” and does the proposal support approval of NDA 21-717?

FDA RESPONSE

- **The studies proposed could, possibly provide sufficient evidence of TetraPeel efficacy and safety to permit approval for use in adults and children ages five and up**
 - **Approval would be based upon data**

ClinicalComments

- **Each protocol should be finalized prior to study initiation**
 - **Complete study entry criteria**
 - **Identification of clinical sites and investigators**

- **(with submission of all supporting documentation)**
- **Should addition of a site be necessary, the protocol amendment should be submitted in a timely manner**
- **Case Report Forms for all adverse events**

ZARS' final points for discussion:

The new clinical protocols will be provided in two separate submissions. The first will contain protocols for which ZARS hoped for expeditious review and comments. The second will contain all remaining protocols for the Agency's review.

Data from "new" studies, and from "old" studies would be presented separately, but merged data will also be presented where appropriate.

ZARS also asked if the Division would prefer to receive CRT data electronically, and if the structure and format previously used was acceptable. Dr. Josefberg stated that electronically submitted data would be preferred. The overall dataset structure employed previously would be acceptable also.

The meeting adjourned at 12:15 PM

Action Items:

1. The protocol for proposed pediatric efficacy study, *SCP-46-05*, will be submitted shortly for Agency comment.
2. ZARS will report the initiation dates of all new clinical studies as they become known.

Minutes prepared by:
Dominic Chiapperino, Ph.D.

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/s/

Dominic Chiapperino
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MEMORANDUM OF TELECONFERENCE

DATE: November 23, 2004

APPLICATION NUMBER: NDA 21-717, TetraPeel (lidocaine and tetracaine cream 7%/7%)

BETWEEN:

ZARS, Inc.

_____	Vice President of Clinical and Regulatory Affairs
_____	Consultant to ZARS
Andy Crockett	Director of S-Caine™ Projects
_____	Consultant to ZARS
_____	Consultant to ZARS
Robert Lippert	Executive Vice President and Chief Operating Officer
Patricia Richards	Director of Regulatory Affairs

AND

Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

Bob Rappaport, MD	Director
Rigoberto Roca, MD	Deputy Director
Nancy Chang, MD	Medical Officer
Howard Josefberg, MD	Medical Officer
Lisa Malandro	Project Manager

Division of Scientific Investigations (DSI)

Joe Salewski	Deputy Director
Ni Khin, MD	GCPB1 Branch Chief
Carolanne Currier	Consumer Safety Officer

SUBJECT: Response to request for teleconference dated October 19, 2004

ZARS, Inc. submitted a proposed strategy and a series of questions to the Division with a request for a teleconference to discuss avenues for addressing the issues identified in the not approvable letter dated September 15, 2004.

Dr. Josefberg stated that the proposal was acceptable, in principle. As submitted, however, much of the relevant detail is missing, and it is not clear whether and how ZARS' Quality Assurance (QA) procedures are to be audited. The division would like to see additional detailed information on the proposed format and content of _____ report.

- Several statements in the proposal refer to proprietary _____ instruments and procedures:

- “A systems-based audit of ZARS' clinical operations to determine compliance with sponsor/monitor regulatory requirements following — Work Instruction, Contracted Bioresearch Sponsor Audits”
- “Audit of the study database following — Data System Audit Work Instruction”

These descriptions are not informative. Dr. Josefberg stated that, before the Division can concur with ZARS' plan, a complete and detailed description of the planned audit procedures, and the contents proposed for the final report, should be submitted for review.

The Division requested 100% audit of all studies that contributed to efficacy findings and all sites from these studies. However, with adequate justification, it may be acceptable to forego audit of some sites from adult trials that made a negligible contribution to the total enrollment. All audit activity should be conducted by blinded auditors.

- Audit should include not only comparison of source material to CRFs, but also comparison of CRFs, CRTs and final study reports. The origin of any discrepancies uncovered should be determined. If this comparison will not be 100%, justification should be provided along with a detailed description of the methods for sampling and comparison.
- ZARS' QA procedures themselves must also be audited, especially after data lock.

The breadth and depth of the audit should be adequate to assure the Division and DSI that we can rely on ZARS' procedures for QA, and for data collection, management and analysis. The final report must contain sufficient information to document that there were no additional instances of data manipulation and that all data are complete and accurate and can be independently verified. There should be detailed investigation of ZARS' procedures for verification and documentation of treatment group assignment, and of actual drug administered. ZARS' problems with drug accountability must be examined as well.

The report should address how (and why) treatment assignments were manipulated post-hoc in Study SCP-33-02. The source of the assignment errors in SCP-33-02, and the progression of the subsequent data manipulation should be documented. Any problems or discrepancies uncovered in other trials must be traced back to their sources as well. The potential for similar errors in other studies should also be assessed.

The enrollment of 43 children (100%) in violation of protocol at Dr. Jones' clinical site should also be examined. Despite several site visits by the ZARS monitor during the course of subject accrual, enrollment continued until the trial's target 'N' was achieved.

The report should contain information about:

Documentation of qualification of auditors from — , along with documentation of QA procedures to be employed by — in the course of their audit
 Adequacy of training of study monitors and adequacy of study monitoring procedures

Finally, the Division reiterated that at least one additional, adequate and well-controlled pediatric trial would still be required.

Lisa Malandro
Regulatory Project Manager

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/s/

Lisa Malandro
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CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-717

ZARS, Inc.
1142 W. 2320 S. Suite A
Salt Lake City, UT 84119

Attention: T. Andrew Crockett
Clinical and Regulatory Affairs

Dear Mr. Crockett:

Please refer to your new drug application (NDA) dated November 14, 2003, received November 17, 2003, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for S-Caine™ Peel (lidocaine 7% and tetracaine 7% cream).

We acknowledge receipt of your submissions dated March 15, June 15, July 9, and September 7, 2004.

We also acknowledge receipt of your two submissions dated September 10, 2004. These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. There were significant protocol deviations found following the inspection of the records from three sites, along with evidence of inadequate monitoring of study sites and inadequate data management procedures that have raised significant doubts about the reliability of data provided to the Agency. These findings indicate systemic issues with study monitoring and data handling that might hold for other studies and sites as well.
2. Study 28-02 had a high number of protocol violations (43 of 83 subjects, all enrolled at a single center) involving the enrollment of pediatric subjects for whom a vascular access procedure was not indicated, despite this being a requirement of the protocol. These violations resulted in the enrollment of inappropriate subjects. This disregard for the protection of the rights, safety and welfare of the pediatric study subjects by the principal investigator for study 28-02 leads us to conclude that the resulting data cannot be used to support pediatric efficacy. The other pediatric studies submitted did not themselves provide substantial evidence of effectiveness.

3. There were inadequate quality assurance processes in place following dataset lockdown. There are discrepancies between the case report forms, case report tabulations, and the final study reports.
 - a. In the analysis of Study 33-02, the basis for the decision that placebo and S-Caine Peel were incorrectly assigned was not satisfactorily documented. Except for presumptive evidence of identity based on tube weights, there is no primary documentation to definitively determine which treatment was administered in each instance.
 - b. There is no documentation that the study monitors were properly trained to perform monitoring activities, such as clinical site pre-study evaluations, site initiation visits, routine monitoring visits, or close-out visits. The monitors failed to assure that the studies were being conducted in accordance with the protocol; e.g., the monitors failed to note the enrollment of ineligible subjects, misplacement of a subject in the wrong age group, and other protocol deviations at site #3 for protocol SCP-28-02. Because of the deficiencies found and the lack of documentation of proper training and expertise of the monitors, it is unclear if the monitoring was sufficient at any study site.
 - c. The drug accountability and handling was found to be inadequate at several sites. For instance, in site # 3 from study 28-02, two out of three Label Control Forms document that the number of approved, issued, and utilized labels exceeded the number of patient packages containing study drug. Again, it is unclear if study drug labeling, accountability and handling were adequate at any study site.

In order for your drug to be approved, you will need to:

Provide new data from properly performed, monitored and analyzed studies in adults that provide substantial evidence of effectiveness.

Alternatively, provide to the FDA clear documentation of data integrity for the studies currently contained in NDA 21-717 that sufficiently address the deficiencies enumerated above.

For the pediatric population below the age of 12 years, provide new data from properly performed, monitored and analyzed studies conducted according to acceptable standards of human subject protection.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), we strongly recommend that you request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Pratibha Rana, M.S., Regulatory Project Manager, at (301) 827-7412.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
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/

Robert Meyer
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 9/14/04

TO: Pratibha Rana, Regulatory Project Manager
Howard Josefberg, M.D., Clinical Reviewer
Division of Anesthetics, Critical Care and Addictive Drug Products, HFD-170

THROUGH: Joseph P. Salewski, Acting Chief
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

FROM: Carolanne Currier, CSO
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-717

APPLICANT: ZARS, Inc.

DRUG: S-Caine Peel (lidocaine 7%, tetracaine 7%)

CHEMICAL CLASSIFICATION: 4

THERAPEUTIC CLASSIFICATION: S

INDICATION: Induction of local dermal anesthesia

CONSULTATION REQUEST DATE: 6/2/04

PDUFA DATE: 9/15/04 (originally 9/17/04)

I. BACKGROUND:

S-Caine Peel is a topical anesthetic cream that forms a synthetic "skin" after application. The peel is intended to deaden the skin prior to painful procedures. During the review of the NDA for S-Caine Peel, it was noted that all subjects enrolled in protocol SCP-28-02 at the site of Spencer Jones, MD, were classified as protocol deviations; none of the pediatric subjects had the "vascular access" procedure required by the protocol. In addition, electronic datasets for two study sites using protocol SCP-33-02 provided by the sponsor, Zars, Inc., to HFD-170 to facilitate review, did not match the data provided in the original paper submission. Inspections were issued to evaluate the conduct of the study by Dr. Jones, and the sponsoring capabilities of ZARS, Inc.

II. INSPECTION RESULTS:

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Spencer Jones, MD	Salt Lake City	Utah	8/3/04	EIR not recd. Copy of 483 recd on 8/26/04	OAI
ZARS, Inc.	Salt Lake City	Utah	8/3/04	EIR not recd. Copy of 483 recd on 8/24/04	OAI

A. Site: Spencer Jones, MD., Principal Investigator (PI).

1. Protocol # SCP-28-02

- a. What was inspected: Dr. Jones screened 44 subjects and enrolled 43. All source data was compared to CRFs for 15 of the 43 subjects, including the primary efficacy variable (Oucher score). Other documents reviewed during the inspection included case report forms; registration forms; medical history questionnaires; drug accountability records; informed consent and assent forms for all 43 subjects; and IRB, sponsor, monitor, and general correspondence files.
- b. Limitations of inspection: none
- c. General observations/commentary: The inspection of Dr. Jones revealed that none of the pediatric subjects enrolled at the site needed or received a vascular access as required by the protocol (SCP-29-02, section 9.3.1). During the inspection, Dr. Jones stated, and confirmed by signed affidavit, that he selected subjects from a database of children and instructed a phlebotomist to puncture the skin, visually observe blood, and withdraw the needle. He also instructed the phlebotomist to administer the same amount of pain to each subject.

Dr. Jones did not follow the investigational plan (protocol) which resulted in the study drug being administered to an inappropriate patient population. Failure to follow the investigational plan (protocol) is a violation of 21 CFR 312.60. Willfully administering the drug to an inappropriate population demonstrates that Dr. Jones failed to protect the rights, safety and welfare of the subject under his care, also a violation 21 CFR 312.60.

Ethical considerations of Dr. Jones' actions are detailed in a memo dated September 11, 2004, from Sara F. Goldkind, M.D., M.A., Bioethicist, Office Pediatric Therapeutics, OC, to Nancy Chang, M.D, Team Leader, Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), CDER. These considerations include the failure to inform the reviewing IRB of modifications to the protocol, and (possible) failure to provide correct information in the informed consent and assent provided to the subjects and parents as required by 21 CFR Parts 50 and 56 ("possible" because a copy of consent and assent forms actually used in the study are not yet available for review). In addition, according to at least one FDA pediatric advisory subcommittee and the ICH Part E11 guidance regarding the ethical conduct of research in children, the use of healthy children who do not benefit from the procedure either from diagnostic or treatment purposes is a violation of the general ethical consensus regarding pediatric research. Dr. Goldkind recommends the unethically derived data acquired because of the protocol violation should not be used to support the approval of the NDA.

Additional problems were found during the inspection of Dr. Jones' study. The inspection revealed several minor protocol deviations, such as one subject was inadvertently placed in the wrong age group, 3 subjects were not assigned the next available randomization number, and 3 subjects were contacted early (per protocol time frame) for the follow-up assessment of delayed reactions. One subject's parent/guardian signed the wrong consent form, and one subject's medical history did not

correlate with the information on the CRF. However, none of these problems appear to have had any affect on the safety of the subject, or would have influenced the outcome of the study from an efficacy viewpoint.

B. Site: ZARS, Inc. The sponsor inspection focused on the sponsoring capabilities, data management and monitoring activities for several protocols.

1. Protocol SCP-33-02 - Sites #1 and #2 (PI names unknown)

- a. What was inspected: Case report forms, selected NDA submission pages, randomization information, electronic datasets, data processing forms, and data entry forms were reviewed during the inspection. Case report forms were reviewed in detail for 5 of 30 subjects enrolled at site #1, and 5 of 25 subjects enrolled at site #2. The firm's SOPs were also reviewed to determine if ZARS followed their SOPs for data management procedures.
- b. Limitations of inspection: none
- c. General observations/commentary: The inspection revealed that the sponsoring and monitoring activities performed by ZARS were inadequate. Protocol SCP-33-02 required that the active treatment be used on one arm and placebo on the other; the arm receiving active treatment to be determined by a randomization assignment code. After reviewing pre- and post-recorded weights of the tubes of treatment and placebo, the firm decided that the original randomization assignments for subject in site#1 were reversed (i.e., subjects marked "B" in one arm, which represented the use of placebo, should have been marked "A," which represented the use of the treatment, and vice versa). In an attempt to correct the mistake, the firm switched the treatment/placebo assignments (and the corresponding pain scores), but mistakenly switched the assignments in BOTH sites #1 and #2. At some point the assignments for site #2 were switched again. It appears the majority of the assignments and scores, originally submitted to the NDA in submission 65-158, were reversed for submission 65-221, remained the same for the first electronic dataset submission of 11/14/03, but then were reversed again for the dataset provided 3/15/04. Further review revealed that the assignments for subject #21, site #2, was still incorrect, and the subject's results were switched again. When ZARS was asked to explain the reasons for the various reversals, they were not able to conclusively explain what happened and how it was (if ever) straightened out. Please also note that the original determination of inaccurate randomization was based on differing weights of product in the tubes of drug and placebo. It is possible that these differing weights could have been detected, and the blind broken.

2. Protocol SCP-28-02 - Site #1: PI = Bari Cunningham, MD; Site #2: PI = Julia Finkel, MD; Site #3 = Spencer Jones, MD (inspected as PI, see above).

- a. What was inspected: The 3 sites enrolled 29, 11, and 43 subjects, respectively. Monitoring records, drug accountability records, 1572s and CVs for all PIs and sub-investigators, IRB approval forms, and a review of investigator's brochures were reviewed for all three sites. In addition, an in-depth review of monitoring procedures and informed consents was performed for Dr. Jones' site.
- b. Limitations of inspection: none
- c. General observations/commentary: The inspection revealed that the sponsoring and monitoring activities performed by ZARS were inadequate. There was no documentation that monitors were trained to perform the monitoring activities such as clinical site pre-study evaluations, site initiation visits, routine monitoring visits, or close-out visits. ZARS monitors failed to assure the studies were being conducted in accordance with the protocol; for example, the monitors failed to note the enrollment of ineligible subjects, the mis-placement of a subject in the wrong age group, and other protocol deviations at protocol SCP-28-02 site #3 (see review of Jones study above).

ZARS monitoring reports for this study were written at the same time by two different monitors have differing information. In addition, drug accountability and handling at several sites was inadequate. ZARS applied labels to all the drug tubes used in their studies. For study site #3 (Jones), two out of three Label Control Forms document that the number of approved, issued, and used labels exceeded the number of patient packages containing the study drug. It is not known why extra labels were created, or whether this indicates that tubes were mis-labeled. Over 4,200 tubes of active S-Caine were received and accepted by visual inspection. The drug should have been accepted only after testing.

3. Protocols SCP-22-02 and SCP-26-02.

Review of inventory receipt logs and the return log sheet revealed additional drug accountability discrepancies in these protocols.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The two inspections summarized above appear to reveal two related problems with the data submitted to NDA 21-717. First, the significant protocol deviation found in the study conducted by Dr. Jones resulted in the use of inappropriate subjects and the failure to protect the rights safety and welfare of the study subjects. Second, the inadequate monitoring by ZARS failed to discover this and other problems, and the inadequate data management procedures evidenced in at least 2 other sites raises significant questions about the reliability of any data provided to FDA. Based on the apparent systemic failure of ZARS to adequately sponsor and monitor clinical trials, DSI recommends that all data submitted by ZARS not be used to support an approval decision for this NDA.

Carolanne Currier
Good Clinical Practice Branch 1
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments:

Joseph P. Salewski, Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

DISTRIBUTION:

NDA 21-717
HFD-170/Rana/Josefberg/Rapaport (through DFS)
HFD-45/Division File / Reading File
HFD-45/Program Management Staff
HFD-46/Salewski/Currier
HFD-46/GCPB1 Files: To be assigned when EIRS are received in DSI.

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? N/A 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 YES 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 submitted on form FDA 3542a? YES NO

• Exclusivity requested? YES 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
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
“*[Name of applicant] hereby certifies that it 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 this application.*” Applicant may not use wording such as “To the best of my knowledge”

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 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
YES
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: IND 59,801
- End-of-Phase 2 Meeting(s)? Date: February 6, 2002
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date: July 16, 2003
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? 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/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? N/A YES NO
NA

Clinical

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

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **YES** NO
If no, did applicant submit a complete environmental assessment?
If EA submitted, consulted to Nancy Sager (HFD-357)?
- Establishment Evaluation Request (EER) submitted to DMPQ? **YES** NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? **N/A** YES NO

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

- Name of listed drug(s) and NDA/ANDA #:
EMLA[®] Cream (Lidocaine 2.5% and Prilocaine 2.5%)
No Reference Drug for Tetracaine
- 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 Peel is Lidocaine/Tetracaine whereas the EMLA Cream is 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**
- 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**
- 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

• 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): NA

• 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.

OR IND # _____ NO

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

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 7, 2004

BACKGROUND:

This is the original 505(b) (2) application for S-Caine Peel (lidocaine 7% and tetracaine 7% cream) submitted to HFD-170. It is indicated for local dermal anesthesia on intact skin.

ATTENDEES:

Howard Josefberg, Nancy Chang, Ravi Harapanhalli, Dan Mellon, Tom Permutt, Suresh Doddapaneni, Bob Rappaport, Parinda Jani, Pratibha Rana

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Howard Josefberg
Secondary Medical:	
Statistical:	Tom Permutt
Pharmacology:	Dan Mellon
Statistical Pharmacology:	
Chemistry:	Dominic Chiapperino
Environmental Assessment (if needed):	
Biopharmaceutical:	Srikanth Nallani
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Pratibha Rana
Other Consults:	ODS/DMETS, DDMAC

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

CLINICAL FILE REFUSE TO FILE

- Clinical site inspection needed: YES NO
- 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? YES NO N/A

CLINICAL MICROBIOLOGY NA FILE _____ REFUSE TO FILE _____

STATISTICS FILE X REFUSE TO FILE _____

BIOPHARMACEUTICS FILE X REFUSE TO FILE _____

- Biopharm. inspection needed: NO

PHARMACOLOGY NA _____ FILE X REFUSE TO FILE _____

- GLP inspection needed: NO

CHEMISTRY FILE X REFUSE TO FILE _____

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

ELECTRONIC SUBMISSION:
Any comments:

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.

X No filing issues have been identified.

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

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.

Pratibha Rana, M.S.

Regulatory Project Manager, HFD-170

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this page is the manifestation of the electronic signature.**

/s/

Pratibha Rana
9/1/04 04:16:10 PM
CSO



NDA 21-717

DISCIPLINE REVIEW LETTER

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

Attention: T. Andrew Crockett
Clinical and Regulatory Affairs

Dear Mr. Crockett:

Please refer to your November 14, 2003 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for S-Caine Peel (Lidocaine/Tetracaine).

We also refer to your submission dated March 15, 2004.

The Division of Medication Errors and Technical Support (DMETS) have completed the review of the proposed proprietary name, Tetrapeel, and have identified the following deficiencies.

In the review of the container labels, carton and insert labeling of TetraPeel, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. The following comments pertain to the immediate container label.
 - a. It is not clear whether you are planning to present the proprietary name with the same print color, size, and font as the current presentation of the word "Tradename". Ensure that the established name appears with at least ½ the prominence of the proprietary name based upon print size, color and font.
 - b. The established name should be presented as "Lidocaine and Tetracaine Cream" and the product strength, 7%/7%, should appear directly below or adjacent to the established name.
 - c. DMETS recommends that the net quantity statement, "Net Wt. 30g", be relocated to appear on the principal display panel. However, please ensure that the net quantity statement is not relocated in close proximity and has less prominence than the statement of product strength.
 - d. DMETS recommends increasing the prominence of the route of administration statement and relocating the statement to the principal display panel.

- e. DMETS suggests that the “Rx only” statement should be relocated to the principal display panel.
 - f. DMETS recommends increasing the prominence of the storage condition statement.
2. Comments 1.a, 1.b, 1.e, and 1.f, also apply to the carton labeling.
3. The following comments pertain to the package insert.
 - a. Comments 1.a and 1.b, also apply to the package insert.
 - b. The “Dosage and Administration” section states that _____ . Also all terminal zeros should be deleted when expressing a product strength or quantity. For example, the designation “1.0 g” should be changed to read “1 g”. Please revise.
 - c. In the “Handling and Disposal” section, DMETS recommends increasing the prominence of the immediate disposal statement. Also include acceptable methods of disposal (i.e., disposal of the used peel in a toilet).
4. Although DMETS has no concerns relating to look-alike and/or sound-alike confusion with the proprietary name TetraPeel, DMETS believes the name TetraPeel is misleading to patients and healthcare professionals since the name implies that the product only contains the anesthetic agent tetracaine, and thus does not recommend the use of the name. DMETS believes the safest use of this product may be best managed under the same proprietary name as NDA 21-623, S-Caine™ Patch (lidocaine and tetracaine topical patch) 70 mg/70 mg.
5. The Division of Drug Marketing, Advertising, and Communication (DDMAC) finds the proprietary name TetraPeel acceptable from a promotional perspective. However, DDMAC the name “TetraPeel” alludes to a single active ingredient (tetracaine) as opposed to a combination product of tetracaine and lidocaine.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Pratibha Rana, Regulatory Project Manager, at (301) 827-7412.

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
8/31/04 10:32:54 AM

Rana, Pratibha

From: Rana, Pratibha
Sent: Monday, March 01, 2004 11:31 AM
To:
Subject: S-Caine Peel NDA 21-717 comments

Dear Andrew,

I have attached the comments from the statistics reviewer. Please let me know if you have any questions.

1. For study 33 the electronic data set main.xpt has the treatment groups reversed as compared to the paper submission. That is, the placebo appears to be significantly better than the S-Caine peel. Please verify which is correct.

2. We are not sure we understand the description of "repeated measures analysis of variance" used for the primary analysis in several studies. In study 22 the p-value given is the same as we calculate with a within-subject "period" effect (location, variable SDSITE2) in addition to the treatment effect. Is this the method that was used?

Pratibha

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

**APPEARS THIS WAY
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/s/

Pratibha Rana
3/1/04 11:39:57 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-717

ZARS, Inc.
1142 W. 2320 S. Suite A
Salt Lake City, UT 84119

Attention: T. Andrew Crockett
Director, Clinical & Regulatory

Dear Mr. Crockett:

Please refer to your November 14, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for S-Caine Peel (lidocaine 7% and tetracaine 7%).

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 January 16, 2004, in accordance with 21 CFR 314.101(a).

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 request that you submit the following information:

1. Provide method development data for the *in vitro* method for determination of drug release for S-Caine anesthetic peel provided in report # 0201250.

(The following comments were forwarded to you via email on January 9, 2004.)

2. **Coding/categorizing**
Many of your summary tables use categories that are not clearly traceable back to your data tables. You must specify how you map your verbatim data to the categories used for your analyses. Any summary or analysis presented for FDA review should be replicable using the NDA data. Including the category values in the data tables along with the verbatim values (side-by-side if possible) is the preferred way of doing this.

For example, the SCP-09-00 study report (Volume 44, Table 11.3) analyzes efficacy data by five categories for "Location of Application Site" (Head/Face/Neck, Back, Chest/Abdomen, Hip/Leg, Arm/Hand/Shoulder)

Variable "SDSITE" contains 37 unique values, however, in data file "main" for SCP-09-00. Likewise, the SCP-26-02 data file "main.xpt" contain 31 unique values for variable SDSITE, and the SCP-21-02 files contain 29 unique values for SDSITE. Table 12.1 - Extent of Exposure (in both study reports) utilizes five, and four categories, respectively.

Many variables representing numeric values (used in your calculations and analyses) are coded as alphanumeric, as are values representing times (i.e. in SCP-09-00 SDAREA area of treatment in cm², and SDACTDUR duration of treatment in hours and minutes, are both coded alphanumerically). Appropriate numeric and time formats should be used. Dates should also be coded in date format where possible.

3. **Integrated summaries**

Safety and efficacy summary tables, as in Volume 36, should also be readily reproducible from your data as submitted. An integrated listing of adverse events is necessary, at a minimum. The format used for your integrated S-Caine files (all_main.xpt and all_ae.xpt) would be acceptable.

If you have any questions, call Pratibha Rana, Regulatory Project Manager, at (301) 827-7431.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Division 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/

Bob Rappaport
1/30/04 12:51:01 PM

Rana, Pratibha

From: Rana, Pratibha
Sent: Friday, January 09, 2004 3:29 PM
To:
Subject: S-Caine Peel NDA 21-717 clinical comments

Dear Andrew,

I have attached comments from the clinical reviewer. Please let me know if you have any questions.
Pratibha

Coding/categorizing

Many of your summary tables use categories that are not clearly traceable back to your data tables. You must specify how you map your verbatim data to the categories used for your analyses. Any summary or analysis presented for FDA review should be replicable using the NDA data. Including the category values in the data tables along with the verbatim values (side-by-side if possible) is the preferred way of doing this.

For example, the SCP-09-00 study report (Volume 44, Table 11.3) analyzes efficacy data by five categories for "Location of Application Site"

(Head/Face/Neck, Back, Chest/Abdomen, Hip/Leg, Arm/Hand/Shoulder)

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Many variables representing numeric values (used in your calculations and analyses) are coded as alphanumeric, as are values representing times (i.e. in SCP-09-00 SDAREA area of treatment in cm², and SDACTDUR duration of treatment in hours and minutes, are both coded alphanumerically). Appropriate numeric and time formats should be used. Dates should also be coded in date format where possible.

Integrated summaries

Safety and efficacy summary tables, as in Volume 36, should also be readily reproducible from your data as submitted. An integrated listing of adverse events is necessary, at a minimum. The format used for your integrated S-Caine files (all_main.xpt and all_ae.xpt) would be acceptable.

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

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/s/

Pratibha Rana
3/1/04 11:43:41 AM
CSO

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. 1142 W. 2320 S. Suite A Salt Lake City, UT 84119		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NO21-717	
2. TELEPHONE NUMBER (Include Area Code) (801) 350-0202		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> 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: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: 21-717 (APPLICATION NO. CONTAINING THE DATA).	
3. PRODUCT NAME S-Caine Peel (lidocaine 7% and tetracaine 7% cream)		6. USER FEE I.D. NUMBER 4636	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) <input type="checkbox"/> 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.) <input type="checkbox"/> 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.) <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO (See item 8, reverse side if answered YES)			
<p>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:</p> <p>Department of Health and Human Services Food and Drug Administration 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. Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 CBER, HFM-99 and Rockville, MD 20852 1401 Rockville Pike Rockville, MD 20852-1448</p>			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE Director, Clinical & Regulatory Affairs	DATE 11/14/03