CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-029

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-029

NAME OF APPLICANT / NDA HOLDER
Hisamitsu Pharmaceutical Co., 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)
SALONPAS (proposed)

ACTIVE INGREDIENT(S)	STRENGTH(S)
Methyl Salicylate	10%
L-Menthol	3%

b(4)

DOSAGE FORM
Topical Patch

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 submit 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 Not Applicable	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*
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 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 proposed 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
Yoshinobu Higashi	May 18, 2006

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.

☑ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Yoshinobu Higashi	
Address 300 Campus Drive Suite 220	City/State Florham Park, NJ
ZIP Code 07932	Telephone Number (973) 765-0122
FAX Number *(if available)* (973) 765-0199	E-Mail Address *(if available)* higashi@hisamitsupharm.com

Appears This Way
On Original

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Hisamitsu Pharmaceutical Co., Inc.
408 Tashiro Daikan-machi, Tosu
Saga 841-0017 Japan

PATENT CERTIFICATION
PARAGRAPH I CERTIFICATION

In accordance with 21 C.F.R. § 314.50 (i)(1)(A)(*I*), Hisamitsu Pharmaceutical Co., Inc. hereby certifies that, based upon its comprehensive review, it is not aware of any evidence that any patent information has been submitted to the U.S. Food and Drug Administration claiming the drug, drug product, or method of use that is the subject of this application.

Kenichi Furuta
Deputy General Manager of R&D Division
Hisamitsu Pharmaceutical Co., Inc.

24. Jan. '06
Date

Contact Information in USA:
Hisamitsu Pharmaceutical Co., Inc.
New Jersey Office
300 Campus Drive, Suite 220
Florham Park, NJ 07932 USA
TEL: 973-765-0122
FAX: 973-765-0199

EXCLUSIVITY SUMMARY

NDA # 22-029 SUPPL # HFD # 560

Trade Name Salonpas b(4)

Generic Name 10% methyl salicylate & 3% l-menthol/topical patch

Applicant Name Hisamitsu Pharmaceutical Co., Inc.

Approval Date, If Known

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.

n/a

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:

n/a

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years

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?

n/a

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).

n/a

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).

There are several approved applications for drugs containing the salicylate active moiety. Three examples follow:

NDA# 11-695	Phenyl Aminosalicylate
NDA# 50-719	Bismuth Subsalicylate; Metronidazole; Tetracycline Hydrochloride
NDA# 80-947	Aminosalicylate Sodium

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 FS-67-E02: a randomized, double-blind, placebo-controlled, parallel, single-dose study of the safety and efficacy of the FS-67 patch (10% methyl salicylate and 3% l-menthol) for treating muscle strain at 15 centers in the United States.

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 FS-67-E02: a randomized, double-blind, placebo-controlled, parallel, single-dose study of the safety and efficacy of the FS-67 patch (10% methyl salicylate and 3% l-menthol) for treating muscle strain at 15 centers in the United States.

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 # 62,735 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

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

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

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

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

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Geri Smith
Title: Project Manager
Date: 09-January-08

Name of Office/Division Director signing form: Joel Schiffenbauer, M.D.
Title: Deputy Director

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

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

/s/

Joel Schiffenbauer
1/9/2008 12:42:37 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-029 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: 26-Jul-07 **PDUFA Goal Date:** 20-Feb-08

HFD 560

Trade and generic names/dosage form: SALONPAS Pain Relief Patch, 10% methyl salicylate & 3% *l*-menthol / topical patch

Applicant: Hisamitsu Pharmaceutical Co., Inc. **Therapeutic Class:** Analgesic

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- X Yes. Please proceed to the next question.
- ☐ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** _____

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s): 1

Indication #1: temporary relief of mild to moderate aches & pains of muscles & joints associated with: arthritis, simple backache, strains, bruises and sprains

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- X No. Please proceed to the next question.

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

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: X Partial Waiver X Deferred ____ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min____	**kg____**	**mo.____**	**yr. 0____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr. 3____**	**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**
- **X 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 (fill in applicable criteria below):

Min ____	**kg____**	**mo.____**	**yr. 3____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr. 17____**	**Tanner Stage____**

Reason(s) for deferral:

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

Other:_____

Date studies are due (mm/dd/yy): 20-Feb-12

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 (fill in applicable criteria below):

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Geraldine Smith
2/20/2008 02:13:29 PM

Hisamitsu Pharmaceutical Co., Inc.
408 Tashiro Daikan-machi, Tosu
Saga 841-0017 Japan

DEBARMENT CERTIFICATION

Hisamitsu Pharmaceutical Co., Inc. 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.

Kenichi Furuta
Deputy General Manager of R&D Division
Hisamitsu Pharmaceutical Co., Inc.

24. Jan. '06
Date

Contact Information in USA:
Hisamitsu Pharmaceutical Co., Inc.
New Jersey Office
300 Campus Drive, Suite 220
Florham Park, NJ 07932 USA
TEL: 973-765-0122
FAX: 973-765-0199

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

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	
[redacted]	[redacted]
[redacted]	b(6)

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NAME	TITLE
KENICHI FURUTA	DEPUTY GENERAL MANAGER OF RESEARCH AND DEVELOPMENT DIVISION
FIRM/ORGANIZATION	
HISAMITSU PHARMACEUTICAL CO., INC.	
SIGNATURE	DATE
[signature]	23. Jan. '06

Paperwork Reduction Act Statement

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

FORM FDA 3454 (2/03)

Created by: PSC Media Arts (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

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.

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Clinical Investigators

b(6)

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Clinical Investigators	
[redacted]	[redacted]
[redacted]	[redacted] b(6)
[redacted]	

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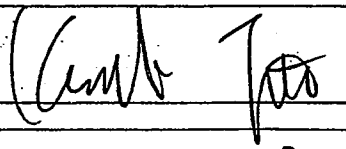
SIGNATURE 	DATE 23. Jan. '06

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Clinical Investigators	
[redacted]	[redacted]
[redacted]	[redacted]

b(6)

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FORM FDA 3454 (2/03)

Created by: PSC Media Arts (301) 443-1090 EF

OTC Drug Labeling Review for Salonpas Patch

Division of Nonprescription Regulation Development • Office of Nonprescription Products
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATE:	February 15, 2008 February 20, 2008	**RECEIVED DATE:**	February 15, 2008 February 20, 2008
REVIEW DATE:		February 20, 2008	
NDA/SUBMISSION TYPE:		NDA 22-029/Amendment-029 NDA 22-029/Amendment-032	
SPONSOR:		Cheryl D. Blume, Ph.D. U.S. contact Hisamitsu Pharmaceutical Co., Inc 813-963-3062	
DRUG PRODUCT(S):		Salonpas Patch	
ACTIVE INGREDIENT:		menthol, 3% methyl salicylate, 10%	
PHARMACOLOGICAL CATEGORY:		topical analgesic	
LABELING SUBMITTED:		February 15, 2008 submission: 1. [redacted] " • 5- and 15- patch carton labels • 5-patch pouch label 2. [redacted] "Salonpas Arthritis Pain" • 5- and 15- patch carton labels • 5-patch pouch label [redacted] February 20, 2008 submission: "Salonpas Pain Relief Patch" • 5- and 15- patch carton labels • 5-patch pouch label	b(4)
REVIEWER:		Reynold Tan	
TEAM LEADER:		Matthew Holman	

Background:

The sponsor submitted revised labeling after we requested revisions to labeling in NDA 22-029/Amendment 027, which the sponsor submitted February 11, 2008. We communicated these revisions to the sponsor on February 14, 2008.

The sponsor sent revised labeling on February 15, 2008, incorporating revisions that we requested on February 14. In addition to making revisions to the labels previously submitted, the sponsor included pouch labels which have not been previously submitted to us.

Immediately after receiving the revised labeling on February 19, we requested that the sponsor add "Pain" to the proposed trade name to specify the type of relief provided by the product.

b(4)

The sponsor committed to adding "Pain" to the trade name in a letter dated February 19, 2008. On February 20, the sponsor submitted NDA 22-029/Amendment 032 with revised labeling for that included "Pain" in the tradename.

Reviewer's Comments:

The February 15 labeling includes the following revisions that were made to the labeling submitted on February 11:

- All appearances of the phrase ' Patch" are changed to "FDA Approved Non Prescription Pain Relieving Patch."

b(4)

- All appearances of the phrase are removed.
- The phrase is revised to "Effectiveness confirmed in clinical trial" on principal display panels.
- The names and concentrations of the active ingredients, "menthol 3%, methyl salicylate 10%," are added to the statement of identity "pain relieving patch".
- The statement "Do not use more than one Salonpas patch at a time. See directions" on principal display panels and pouches is bolded to appear more prominent.
- The revised warning reads, "Keep out of reach of children. If put in mouth, get medical help or contact a Poison Control Center right away. Package not child resistant."
- In the "Stop use and ask a doctor if" section, the statement ' is revised by replacing ' with "last".
- In the "Directions" section, the statement is revised to "apply one patch to the affected area and leave in place for up to 8 to 12 hours". The statement " is revised to "if pain lasts after using the first patch, a second patch may be applied for up to another 8 to 12 hours."

b(4)

- In the "Directions" and "Other information" sections, all capitalization at the beginning of each statement is removed.

These revisions comply with our request for revisions to labeling communicated to the sponsor on February 14, 2008. Therefore, these revisions are acceptable.

The February 20 labeling revises the labeling submitted on February 15 by changing the trade name ' [redacted] to "Salonpas Pain Relief Patch." The "Salonpas Pain Relief Patch" trade name [redacted] on the 5-count and 15-count carton labels and the 5-count pouch label for the "Salonpas Pain Relief Patch" product. These revisions are acceptable. b(4)

Reviewer's Recommendation:

Send an approval letter for Salonpas Pain Relief Patch and inform the sponsor that the final printed labeling (FPL) must be identical to the enclosed labeling (Salonpas Pain Relief Patch 5- and 15-count carton and 5-count pouch labels submitted on February 20, 2008, and Salonpas Arthritis Pain 5- and 15-count carton and 5-count pouch labels submitted on February 15, 2008), and must be in the "Drug Facts" format (21 CFR 201.66).

2 Page(s) Withheld

_____ Trade Secret / Confidential

8 Draft Labeling

_____ Deliberative Process

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

/s/

Reynold Tan
2/20/2008 02:50:46 PM
INTERDISCIPLINARY

Matthew Holman
2/20/2008 02:57:02 PM
INTERDISCIPLINARY

21016

Smith, Geri

From: Schiffenbauer, Joel
Sent: Monday, December 18, 2006 8:25 AM
To: Jacobson-Kram, David
Cc: Leonard Segal, Andrea
Subject: RE: salonpas

David,

Many thanks for your response. OTC labels do not have pregnancy categories. Prilosec which is also a pregnancy category C, says to ask a physician if pregnant or breastfeeding. I anticipate that something similar will be on the Salonpas label.

Joel

From: Jacobson-Kram, David
Sent: Monday, December 18, 2006 8:22 AM
To: Schiffenbauer, Joel
Subject: RE: salonpas

Joel,
I think it is reasonable to conclude that there is sufficient clinical experience to obviate the need for reprotox studies. Are OTC products labeled with pregnancy categories?
David

From: Schiffenbauer, Joel
Sent: Monday, December 18, 2006 8:16 AM
To: Jacobson-Kram, David
Cc: Leonard Segal, Andrea
Subject: FW: salonpas

Dr. Jacobson-Kram,

I have a followup question for you in regards to the Salonpas product that we had e-mailed about previously. The issue concerns the recommendation for additional repro-tox studies as a phase 4 commitment. Since we already know that this is pregnancy category C, I am not clear as to what additional information will be gained by these studies and if the studies should be performed, why not pre-approval (the product will not be approved this cycle anyway because of a need for additional clinical data). This situation seems analagous to me to our discussions in regards to dermal carc studies.

Please see the e-mails below for additional explanations.

I appreciate your time. Thanks.

Joel Schiffenbauer

From: Mellon, Dan
Sent: Friday, December 15, 2006 1:00 PM
To: Schiffenbauer, Joel
Subject: RE: salonpas

Joel,

Good question. The nonclinical studies tested methyl salicylate. So the findings we have may be due to methyl salicylate or they may be due to the metabolite or both. Although I will not claim to be an expert on NSAIDS after only 1 year of experience, I can tell you that diclofenac studies in the literature have reported similar delays in ossification and therefore these changes may be class related.

Does that help?

Dan
PharmTox Supervisor
DAARP
301-796-1256

From: Schiffenbauer, Joel
Sent: Friday, December 15, 2006 12:53 PM
To: Mellon, Dan
Subject: RE: salonpas

Dan,

Thanks for the response. Just to further clarify the last point about the issue of the methyl salicylate specifically. Is the concern about the parenat compound because we do have considerable experience with the metabolites since like aspirin they are converted to salicylic acid.

Joel

From: Mellon, Dan
Sent: Friday, December 15, 2006 12:47 PM
To: Schiffenbauer, Joel; Hayes, Belinda
Cc: Leonard Segal, Andrea; Hastings, Kenneth L; Harrouk, Wafa; Mellon, Dan
Subject: RE: salonpas

Joel,

BeLinda is on leave today, but will be in on Monday. In the interim, I may be able to clarify for you. We did say approvable on purpose, since the sponsor would have to agree to a Phase 4 commitment or the medical officer would have to conclude that adequate human data exists to characterize the reproductive toxicity clinically. As is, we are not able to provide any solid information regarding the exposure margins for these findings based on the lack of a clear NOAEL value and the lack of toxicokinetic data in the animal studies. Further, it is my understanding that the human PK studies, completed [redacted] are not acceptable. As such, until we get these data as well we can not provide any clear exposure comparisons.

b(4)

I recognize that exposure multiples are not listed on an OTC Label, and that if this were a Rx drug product the Pregnancy Category would be a C regardless of the outcome in the absence of human data. However, if this were an Rx product, I would not be able to write a label that would include any exposure margins and would have to state that there was no clear NOAEL value. In reality, it may be that there is a very large exposure margin due to the systemic exposure in the clinical setting should be far lower than the exposure tested nonclinically via the SC route of administration. If I were the company, I would rather put a huge exposure margin rather than state that there is not NOAEL and we don't know how the nonclinical studies compare to the human exposure. I do believe the data should be requested, since technically this will be the first NDA approved for these two drugs. Should you wish to approve this product this cycle, I could understand that the information could be submitted in Phase 4 if the label will likely not change, but if the product is not going to be approved this cycle, we can not defer the request as a Phase 4 since they would not be in Phase 4.

I am not certain how your Office deals with OTC labeling for a Pregnancy Category C - as such we added the wording your Office published for ibuprofen. I defer to your Office regarding how your labeling will be handled, as I have no experience with OTC labels.

As we discussed on the phone the other day regarding the dermal carcinogenicity data, if you feel that there are

adequate clinical data to convince you that there are no concerns with this product, you certainly may conclude that the studies are not necessary. As there is obviously a clinical assessment involved in such a decision, BeLinda and I felt obligated to state approvable rather than may be approved.

Please let me know if you have any questions. I will be happy to discuss this issue and any other with your team.

R. Daniel Mellon, Ph.D.
Pharmacology Toxicology Supervisor
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II, Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 3172
Silver Spring, MD 20933-0002

Email: Dan.Mellon@fda.hhs.gov
Phone: 301-976-1256

From: Schiffenbauer, Joel
Sent: Friday, December 15, 2006 12:04 PM
To: Hayes, Belinda
Cc: Mellon, Dan; Leonard Segal, Andrea
Subject: salonpas

Belinda,

I have 2 questions about your salonpas review. First, did you mean to say the product is approvable? The reason I ask is that if the repro studies are a phase 4 commitment, then the product could be approved this cycle.

Second, could you explain your thinking about asking for the additional repro studies. It seems to me, that analagous to the issue about dermal carc studies, we would not need additioinal repro studies, because of the history of use of methyl salicylate and the fact that we would label with pregnancy category C anyway. Are you concerned about the methyl salicylate specifically, because for the metabolites we must have a lot if info?

Thanks for your help.

Joel Schiffenbauer

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

/s/

Geraldine Smith
2/20/2008 02:17:29 PM
CSO

2/14/8

OTC Drug Labeling Review for Salonpas Patch

Division of Nonprescription Regulation Development • Office of Nonprescription Products
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATE:	February 11, 2008	**RECEIVED DATE:**	February 11, 2008
REVIEW DATE:		February 13, 2008	
NDA/SUBMISSION TYPE:		NDA 22-029/Amendment 027	
SPONSOR:		Yoshinobu Higashi Manager International Development Hisamitsu Pharmaceutical Co., Inc 973-765-0122	
DRUG PRODUCT(S):		Salonpas Patch	
ACTIVE INGREDIENT:		menthol, 3% methyl salicylate, 10%	
PHARMACOLOGICAL CATEGORY:		topical analgesic	
LABELING SUBMITTED:		Principal display panels and proposed Drug Facts text for the 2 proposed trade names: 1. [redacted] (5- and 15- patches) 2. Salonpas Arthritis Pain (5- and 15- patches)	b(4)
REVIEWER:		Reynold Tan	
TEAM LEADER:		Matthew Holman	

Background:

We sent the sponsor labeling revisions on January 16, 2008. The sponsor made many but not all of the revisions that we requested and submitted revised draft labeling on January 23, 2008. Based on this labeling, we sent labeling revisions to the sponsor in an email on February 7, 2008. Recommendations for revisions to the principal display panel were listed while revisions to Drug Facts were included in a mock Drug Facts label. We did not file a formal labeling review for the January 23, 2008 labeling.

The sponsor revised the labeling based on our February 7 e-mail and submitted revised labeling on February 11, 2008. This labeling review concerns the draft labeling submitted on February 11. Only minor labeling revisions are being requested, because the sponsor has already incorporated all of the major revisions we requested on February 7. This labeling review includes the previously requested revisions in order to record these revisions in a formal labeling review. In Reviewer's Comments, those previously requested revisions that have been incorporated in the February 11 labeling are noted. Those revisions being requested for the first time are noted in Reviewer's Recommendations.

Reviewer's Comments:

Until recently, we had not considered the need for labeling to include warnings for increased gastrointestinal bleeding and cardiovascular risk associated with NSAIDs. We have required class labeling that addresses these risks for oral prescription and OTC NSAIDs as well as topical prescription NSAIDs. We discussed these warnings in numerous meetings between the Office of Nonprescription Products and the Division of Anesthesia, Analgesia, & Rheumatology Products. The systemic levels of methyl salicylate for this topical product are 2-3 orders lower than those for oral NSAID products. However, the decision has been to require the stomach bleeding and cardiovascular risk warnings on this product to be consistent with other NSAID products, in particular, the prescription topical NSAID products.

We informed the sponsor that these warnings would be required in our February 7, 2008 communication. This communication also included other minor labeling revisions. It should be noted that the stomach bleeding and cardiovascular warnings were modified slightly because the risks associated with this product are believed to be significantly lower than those for oral NSAIDs.

Principal Display Panel

1. The sponsor proposes two trade names: "Salonpas Arthritis Pain" and [redacted] In their January 23, 2008 labeling, the sponsor proposed the two trade names: "Salonpas Arthritis Pain" and [redacted]

b(4)

We find the trade names "Salonpas Arthritis Pain" and [redacted] acceptable. However, we continue to recommend against use of multiple trade names because of our safety concern that consumers who do not realize that the differently named products are the same product may use these products simultaneously resulting in overuse. In our February 7 communication, we requested that the [redacted] trade name not be used because this trade name misleadingly suggests that the product [redacted] "Salonpas Arthritis Pain" trade name or other patch products. This trade name is also misleading because the product [redacted] than other Salonpas products or other pain-relieving patch products.

We told the sponsor the trade name [redacted] was acceptable in our December 27, 2006, approvable letter.

b(4)

2. The phrase [redacted] appears on a graphic. We had recommended removal of the phrases [redacted] in our January 16 communication with the sponsor. We explained that these phrases are subjective and ambiguous and do not provide the consumer with any meaningful information.

[redacted]

b(4)

3. The phrase [redacted] is removed. The phrases [redacted] remain. We had recommended removal of the phrases " [redacted] for reasons stated in our January 16 communication. The sponsor responded that the phrase [redacted] should be allowed because they had a registered trademark for this phrase for use on topical drug products. We responded that consumers could interpret this phrase in a number of different ways and having a registered trademark for the phrase does not affect consumer comprehension of the phrase. We also requested the phrase [redacted] be revised to change the identification of the product as a "Medicated Pain Relief Patch" to be consistent with a proper statement of identity

b(4)

The phrase ' [redacted] ' should be changed to "FDA Approved Non Prescription Pain Relieving Patch" to be consistent with the acceptable statement of identity. The word [redacted] should be removed from the phrase " [redacted] Effectiveness confirmed in clinical trial" because this product is [redacted] for certain individuals.

b(4)

4. The sponsor changed the statement of identity [redacted] to "pain relieving patch." In our February 7 communication, we recommended changing the [redacted] statement of identity because, according to 21 CFR 201.61, a proper statement of identity should state the product's intended pharmacological action "in terms that are meaningful to the layman" (e.g., "topical analgesic patch," "pain relieving patch"). The sponsor had proposed [redacted] to distinguish the product from magnetic heat patches.

   This change is acceptable. However, adding the names of the active ingredients and their concentrations (i.e., menthol 3%, methyl salicylate 10%) provides useful information. This information is not required to appear by regulation but could be helpful to the consumer.

5. The statement "Do not use more than one Salonpas patch at a time. See directions" appears at the bottom of the principal display panel.

   This statement should be made to appear more prominent (e.g., by bolding, increasing the type size, or enclosing in a banner).

Drug Facts

All the following label revisions to Drug Facts (#6 through #10) were communicated to the sponsor on February 7, 2008, except the revisions noted by italic text:

6. The following label revisions address the increased risk of stomach bleeding and cardiovascular adverse effects associated with NSAIDs. These revisions must be made for consistency with the labeling approved for oral NSAIDs. These revisions are slightly different than oral NSAIDs in order to reduce redundancy in labeling and suggest that risks are lower for this product than oral NSAIDs.

"Active ingredients" section

- Add "(NSAID*)" after "methyl salicylate 10%" and, immediately below, add "*nonsteroidal anti-inflammatory drug".

Warnings section

- Add a warning that reads, "**Stomach bleeding warning**: This product contains an NSAID, which may cause stomach bleeding. The chance is small but higher if you: • are age 60 or older • have had stomach ulcers or bleeding problems • take a blood thinning (anticoagulant) or steroid drug • take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others] • have 3 or more alcoholic drinks every day while using this product • take more or for a longer time than directed".

Warnings: "Do not use" section

- Add the statement "right before or after heart surgery".

Warnings: "Ask a doctor before use if" section

- Add an "Ask a doctor before use if" heading and the following statements: "• the stomach bleeding warning applies to you • you have high blood pressure, heart disease, or kidney disease • you are taking a diuretic".

Warnings: "When using this product" section

- Add the statement "the risk of heart attack or stroke may increase if you use more than directed or for longer than directed".

Warnings: "Stop use and ask a doctor if" section

- As the first bulleted statement, add the statement "you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding."
- Add the statement "stomach pain or upset gets worse or lasts".

7. [redacted] b(4)

8. The following labeling revisions must be made to improve the clarity of proposed warnings statements:

Warnings: "Do not use" section

-
- [redacted] b(4)

- Revise the statement
  to "when sweating (such as from exercise or heat)" because increased absorption through the skin under these conditions could raise systemic salicylate levels to unsafe levels.

Warnings: "Ask a doctor before use if" section

- Add the statement "• you are allergic to topical products"

Warnings: "Ask a doctor or pharmacist before use" section

- Remove the heading and all bulleted statements. The statements now appear in the "Ask a doctor before use if" section.

Warnings: "When using this product" section

-
- Revise the statement b(4)
  to "wash hands after applying or removing patch. Avoid contact with eyes. If eye contact occurs, rinse thoroughly with water."

Warnings: "Stop use and ask a doctor if" section

- Remove from the statement "rash, itching, or skin irritation develops".

b(4)

Warnings: Pregnancy/breast-feeding section

- Revise the warning to read: "**If pregnant or breast-feeding**, ask a doctor before use during the first 6 months of pregnancy. Do not use during the last 3 months of pregnancy because it may cause problems in the unborn child or complications during delivery."

Warnings: Keep out of reach of children section

- *This warning should be revised to read: "**Keep out of reach of children**. If put in mouth, get medical help or contact a Poison Control Center right away. Package not child resistant."*

9. The following labeling revisions must be made to improve the clarity of proposed statements in the "Directions" section:

- *Revise the statement '*
  ' to "apply one patch to the affected area and leave in place for up to 8 to 12 hours".
  Revise the statement ' b(4)
  to "If pain lasts after using the first patch, a second patch may be applied for up to another 8 to 12 hours." These revised directions are more consistent with the time course of pain relief shown by the study data.
- Revise the stated age groups to read: "Adults 18 years and older" and "Children under 18 years of age".
-

b(4)

- Revise the statement " to "do not use for more than 3 days in a row".

4 Page(s) Withheld

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X Draft Labeling

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/s/

Reynold Tan
2/14/2008 01:49:27 PM
INTERDISCIPLINARY

Matthew Holman
2/14/2008 03:42:42 PM
INTERDISCIPLINARY

Smith, Geri

From: Smith, Geri
Sent: Tuesday, February 19, 2008 11:45 AM
To: 'Mikel Alberdi'; 'Cheryl Blume'
Subject: NDA 22-029 / Salonpas / comments regarding latest labeling submission

Importance: High

Hello,

We have reviewed your 02-15-08 labeling submission, and have the following comments:

1. Because the tradename is vague regarding the type of relief, please add "Pain" to the tradename so that it reads "Salonpas Pain Relief Patch."

b(4)

Please submit a letter regarding the above points (i.e., committing to add "Pain" to this tradename and withdrawing the sample sizes). Please do not resubmit revised labeling at this time.

Thanks,
Geri

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/s/

Geraldine Smith
2/19/2008 01:13:20 PM
CSO

0/14/08

Smith, Geri

From: Smith, Geri
Sent: Thursday, February 14, 2008 11:20 AM
To: 'Cheryl Blume'; 'Mikel Alberdi'
Subject: NDA 22-029 labeling comments

Importance: High

Hi Cheryl and Mikel,

We reviewed the label you submitted on February 11th, and have the additional labeling comments listed below. Please note that we have changed the dosing directions to say one patch every 8-12 hours up to 2 patches per day for 3 days. This change is to allow for the potential treatment of pain for a full 24 hour period and we believe is consistent with the data provided. It is also consistent with other analgesics which provide a range of time (e.g., ibuprofen - 1-2 tablets every 4-6 hours) to allow individuals to titrate their treatment to their pain.

1. Change the phrase [redacted] to "FDA Approved Non Prescription Pain Relieving Patch" to be consistent with the statement of identity. b(4)

2. In the "Stop use and ask a doctor if" section, revise the statement [redacted] by replacing [redacted] with "last".

3. In the "Directions" section, revise the statement [redacted] to "apply one patch to the affected area and leave in place for up to 8 to 12 hours". Revise the statement [redacted] to "if pain lasts after using the first patch, a second patch may be applied for up to another 8 to 12 hours."

4. In the "Directions" and "Other information" sections, remove capitalization at the beginning of each statement. b(4)

5. Remove the phrase [redacted] from the principal display panel. The phrase can be misleading [redacted]

6. [redacted]

7. Add the names of the active ingredients and their concentrations (i.e., menthol 3%, methyl salicylate 10%) to the statement of identity (i.e., adjacent to "pain relieving patch") on the principal display panel.

8. Make the statement "Do not use more than one Salonpas patch at a time. See directions" at the bottom of the principal display panel appear more prominent (e.g., by bolding, increasing the type size, or enclosing in a banner).

9. Revise the [redacted] warning to read, "Keep out of reach of children. If put in mouth, get medical help or contact a Poison Control Center right away. Package not child resistant." b(4)

Also, submit the labeling format information (i.e., font, type size for all text, hairlines, barlines, bullets, leading) so that we can evaluate compliance with the format requirements in 21 CFR 201.66(d).

Please resubmit a revised copy of the labeling to me, including updated pouch labeling.

Thanks,

Geri

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/s/

Geraldine Smith
2/14/2008 11:36:28 AM
CSO

a|14|8

Smith, Geri

From: Smith, Geri
Sent: Monday, February 11, 2008 3:15 PM
To: 'Mikel Alberdi'; 'Cheryl Blume'
Subject: RE: NDA 22-029 / Salonpas / comments regarding revised Pediatric Plan

Importance: High

Hello,
I believe that we will not have further comments regarding your January 31, 2008 revised pediatric plan. Please submit a revised plan, responding to these comments.
Thanks,
Geri

From: Smith, Geri
Sent: Monday, February 11, 2008 12:56 PM
To: 'Mikel Alberdi'; 'Cheryl Blume'
Subject: NDA 22-029 / Salonpas / comments regarding revised Pediatric Plan
Importance: High

Hello,

We have the following pharmacokinetic comments regarding the portion of your revised Pediatric Plan:

1. The age distribution of patients should be even among the age range studied.

2. In addition to determining plasma levels of salicylic acid, determine plasma levels of methyl salicylate and menthol.

3. Collect one additional sample at 12 hours after #6 patch application to capture the elimination phase.

4. In lieu of a traditional PK approach, you may choose to adopt the population pharmacokinetic approach to overcome some of the limitations related to number and volume of blood samples that are necessary to accurately characterize the pharmacokinetics of all three analytes (i.e., salicylic acid, methyl salicylate, and menthol). If the population PK approach is taken, you will have to appropriately adjust the number of patients commensurate with the number of blood samples that will be drawn from each patient. Sampling times should be dispersed throughout the concentration time profile.

We will provide any remaining comments on the plan to you hopefully today or tomorrow.

Also, do you have an estimate of when you will be submitting revised labeling? This will help me know how to schedule our team resources.

Thanks,
Geri

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/s/

Geraldine Smith
2/14/2008 11:32:47 AM
CSO

2/7/8

Smith, Geri

From: Smith, Geri
Sent: Thursday, February 07, 2008 2:16 PM
To: 'Cheryl Blume'; 'Mikel Alberdi'
Subject: NDA 22-029 / Salonpas / Labeling comments

Importance: High

Attachments: 020708 label to SP.pdf

Hello Cheryl and Mikel,

We have reviewed your submission of revised labeling dated January 23, 2008 and have the following comments regarding the carton labels:

1. Remove [redacted] from the [redacted] trade name. This trade name misleadingly suggests [redacted] than the identical product under the "Salonpas Arthritis Pain" trade name. This trade name is also misleading because the product [redacted] than other Salonpas products or other pain-relieving patch products. The phrase [redacted] is not acceptable. b(4)

2. Remove the phrase '[redacted]' This phrase is unclear and misleading. Having a registered trademark for the phrase does not affect consumer comprehension of the phrase.

3. Revise the [redacted] statement of identity. According to 21 CFR 201.61, a proper statement of identity should state the product's intended pharmacological action "in terms that are meaningful to the layman" (e.g., "topical analgesic patch," "pain relieving patch"). b(4)

We have incorporated several edits into the attached Drug Facts label, as discussed during our teleconference this afternoon.

As we continue to review this NDA, we may develop additional comments.

Please submit revised labeling as soon as possible for our review.

Thanks,

Geri

020708 label to SP.pdf (59 KB)...

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6 Draft Labeling

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/s/

Geraldine Smith
2/7/2008 02:22:20 PM
CSO

1/25/8

MEMORANDUM OF TELECONFERENCE

DATE: January 24, 2008

APPLICATION: NDA 22-029

SPONSOR: Hisamitsu Pharmaceutical Co., Inc.

DRUG: Salonpas [redacted] b(4)

INDICATION: Temporary relief of mild to moderate aches and pains of muscles and joints associated with: arthritis, simple backache, strains, bruises and sprains

BETWEEN the following representatives of Hisamitsu Pharmaceutical Co., Inc. ("Hisamitsu" or the "Sponsor"):

Cheryl Blume, Pharmaceutical Development Group, Inc.
Mikel Alberdi, Pharmaceutical Development Group, Inc.
Kenichi Furuta, Hisamitsu
Yoshinobu Higashi, Hisamitsu
[redacted] b(4)

AND the following staff of the Division of Nonprescription Clinical Evaluation (the "Division"):

Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Clinical Team Leader
Joseph Porres, M.D., Medical Officer
Geri Smith, Regulatory Project Manager

SUMMARY OF TELECONFERENCE:

The Division requested this teleconference to provide the Sponsor with feedback from the Pediatric Review Committee (PeRC) regarding the Sponsor's January 11, 2008 Pediatric Plan.

The Division informed the Sponsor that PeRC had reviewed the Sponsor's Pediatric Plan, request for a waiver of studies in children 3 years old and younger, and request for a deferral of studies in children 4-17 years old. PeRC considers waiving studies of Salonpas in children younger than 3 years old to be acceptable. PeRC considers deferring studies of Salonpas in children 3-17 years old, with studies conducted first in adolescents 13-17 years old, to be acceptable.

PeRC expressed the following with regard to the Sponsor's Pediatric Plan:

[redacted]

b(4)

b(4)

The Division clarified that the Sponsor could collect safety, efficacy, and PK information in one study or in separate efficacy/PK and safety/PK studies.

The Sponsor inquired as to how to proceed with studies in the younger age group (i.e., 3-12 year olds) if safety concerns are identified through studying adolescents (i.e., 13-17 year olds). The Division advised the Sponsor to confer with the Division should safety concerns arise while studying Salonpas in adolescents.

b(4)

The Division reminded the Sponsor that their Pediatric Plan is missing critical information. For the Pediatric Plan to be complete, the Sponsor must specify the number of pediatric subjects to be studied and submit a timeline within which all final study reports will be submitted to the FDA.

The Division encouraged the Sponsor to submit their revised Pediatric Plan as soon as possible.

Geri Smith
Regulatory Project Manager

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/s/

Geraldine Smith
1/29/2008 01:41:05 PM
CSO

1/25/8

Smith, Geri

Subject: FW: 505(b)(2) NDA 22-029 / Salonpas

From: Colangelo, Kim M
Sent: Thursday, January 24, 2008 1:35 PM
To: Smith, Geri
Cc: Duvall Miller, Beth A; Christl, Leah A
Subject: RE: 505(b)(2) NDA 22-029 / Salonpas

Hi Geri,

You can DFS your (revised) filing review for this application, and are cleared from a (b)(2) perspective to take action. It appears that the actives have been approved in other applications too old to be listed in the Orange Book, so it isn't likely that they will get the NCE exclusivity that they are seeking.

Have fun!
Kim

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs, CDER, FDA
301-796-0700 (OND IO main)
301-796-0140 (direct)
301-796-9856 (facsimile)
Kim.Colangelo@fda.hhs.gov

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/s/

Geraldine Smith
1/25/2008 02:28:20 PM
CSO

MEMORANDUM OF TELECONFERENCE

DATE: January 07, 2008

APPLICATION: NDA 22-029

SPONSOR: Hisamitsu Pharmaceutical Co., Inc.

DRUG: Salonpas b(4)

INDICATION: Temporary relief of mild to moderate aches & pains of muscles & joints associated with: arthritis, simple backache, strains, bruises and sprains

BETWEEN the following representatives of Hisamitsu Pharmaceutical Co., Inc. ("Hisamitsu" or the "Sponsor"):

Cheryl Blume, Pharmaceutical Development Group, Inc.
Kenichi Furuta, Hisamitsu
Yoshinobu Higashi, Hisamitsu b(4)

AND the following staff of the Division of Nonprescription Clinical Evaluation:

Joel Schiffenbauer, M.D., Deputy Director
Daiva Shetty, M.D., Clinical Team Leader
Joseph Porres, M.D., Medical Officer
Geri Smith, Regulatory Project Manager

SUMMARY OF TELECONFERENCE:

The Division requested this teleconference to inform the sponsor how the Pediatric Research Equity Act (PREA) applies to this NDA, based on recent requests from the Pediatric and Maternal Health staff.

The Division acknowledged the Sponsor's request for a full waiver of pediatric studies, and informed the Sponsor that we will likely grant a waiver only for studies in children 0-3 years old. Because of this, we explained that the Sponsor must submit a Pediatric Plan outlining their intent to conduct studies in children 3-17 years old, unless the Sponsor objects to studying the drug in children within this age range. If the Sponsor should object, they must submit their rationale to support a waiver of studies in children older than 3 years of age.

The Division outlined the information that a Pediatric Plan must contain, and referred the Sponsor to the *Guidance for Industry: How to Comply with the Pediatric Research Equity Act* dated September 2005 for additional detail. We explained that the information the Sponsor submits will be reviewed by the Pediatric Review Committee (PeRC) as required by law prior to the Division taking an action on this NDA. As such, if this information is not submitted so that it can be reviewed by both the Division and PeRC prior to the PDUFA goal date for this NDA (i.e., February 20, 2008), or if an inadequate plan is submitted, it is unlikely that we will be able to take a favorable

action on the application by that date.

The Sponsor inquired as to whether they would be eligible for 6 months of pediatric exclusivity for conducting studies in pediatrics. We responded that studies conducted under PREA (in the absence of a Written Request from FDA) are not eligible for pediatric exclusivity.

Geri Smith
Regulatory Project Manager

Attachment: January 07, 2008 email from Geri Smith to Sponsor listing the required elements of a Pediatric Plan.

Smith, Geri

From: Smith, Geri
Sent: Monday, January 07, 2008 12:55 PM
To: 'Cheryl Blume'
Subject: Information promised during our teleconference today
Importance: High

Hello Cheryl,

Here is the link to the *Guidance for Industry: How to Comply with the Pediatric Research Equity Act* that we referenced during our teleconference today. Among other things, it discusses the Pediatric Plan requirements and the Pediatric Assessment requirements. The discussion of the Pediatric Assessment requirements will further address the question Hisamitsu asked today regarding whether the pediatric plan should include studies of both efficacy and safety.
http://www.fda.gov/cder/guidance/6215dft.pdf

Here is a list of the minimal information about your Pediatric Plan that we are required to present to the Pediatric Review Committee. Please ensure that all of this is included in the plan.

Application #
Drug Name

Drug information:
Route of administration
Formulation
Dosage
Regimen

Types of studies/Study Design

Age group and population in which study will be performed

Number of patients to be studied or power of study to be achieved

Entry criteria (inclusion/exclusion criteria)

Clinical endpoints

Timing of assessments

Statistical information (statistical analyses of the data to be performed)

Timeframe for submitting reports of the studies

Comments on drug safety

Please note that it is my understanding that the final study reports and Pediatric Assessment would have to be submitted to FDA within 3 years of approval of the NDA. I'm in the process of confirming that now.

If you are able to submit the plan by the end of this week, I think that will go a long way in helping to expedite this process. Please email me an electronic copy of your official submission, if possible, so

that we can begin reviewing it as soon as possible.

Thanks,
Geri

From: Cheryl Blume [mailto:cblume@pharmdevgroup.com]
Sent: Saturday, January 05, 2008 11:29 AM
To: Smith, Geri
Cc: 'Cheryl Blume'; 'Kenichi Furuta'; 'Yoshinobu Higashi'; [redacted]
Subject: Hisamitsu Teleconference NDA#22-029

Dear Geri, b(4)

The teleconference call-in number is 800-711-9895. The access code is 7650122.

Our participants will be Kenichi Furuta, Yoshinobu Higashi, [redacted] and me.

I look forward to talking with you on Monday (01-07-08) at 11:00 AM.

Thanks,

Cheryl

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/s/

Geraldine Smith
1/16/2008 11:59:46 AM
CSO

4164

Smith, Geri

From: Smith, Geri
Sent: Wednesday, January 16, 2008 9:02 AM
To: 'Mikel Alberdi'; 'Cheryl Blume'
Subject: NDA 22-029 / Salonpas / labeling comments

Importance: High

Hello Cheryl and Mikel,

We have the following preliminary comments regarding your proposed labeling for the Salonpas patch. As we continue to review this NDA, we may develop additional comments.

1. We recommend that multiple trade names not be used for this product. Consumers who do not realize that the differently named products are the same formulation may use these products simultaneously, resulting in overuse. Please propose one trade name.

Principal Display Panel

2. Add a proper statement of identity (e.g., "topical analgesic patch," "pain relieving patch") in accordance with 21 CFR 201.61.

3. Remove the terms [redacted] " These terms are subjective, ambiguous, and do not provide the consumer with meaningful information. b(4)

4. Remove the following phrases because they are unclear and potentially misleading in suggesting unproven superiority over other similar products:

- [redacted]
- [redacted]
- [redacted]

Drug Facts

5. Revise the warning [redacted] b(4)

6. Add additional warning "**Do not use** on the face or rashes."

7. Add the bulleted statement: "**Do not use** when sweating excessively (such as from exercise or hot conditions)"

8. Add the bulleted statement: "**Do not use** any patch from a pouch that has been open for 14 or more days"

[redacted] b(4)

[redacted] b(4)

12. In the "**Stop use and ask a doctor if**" section, change the words [redacted] to "condition worsens"

b(4)

13. Revise the "**Stop use and ask a doctor if** [redacted] warning to read: "**Stop use and ask a doctor if** symptoms persist for more than 3 days"

14. Revise the "**If pregnant or breast-feeding**" warning to read: "**If pregnant or breastfeeding**, ask a health professional before use. It is especially important not to use this product during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery." See 21 CFR 201.63(a) and (e).

15. Remove the periods that appear after each of the warning statements except for those statements that constitute more than one sentence.

[redacted]

17. Under "**Directions,**" revise the statement [redacted] to read: "If pain persists 8 hours after applying the first patch, a second patch may be applied for up to another 8 hours." Add a statement that reads "Only use one patch at a time."

b(4)

18. Under "**Directions,**" change the statement "[redacted] to "Some individuals may not experience pain relief until several hours after applying the patch," and move this statement to the "**Other information**" section.

b(4)

19. List the inactive ingredients in all lowercase letters.

Please submit revised labeling incorporating all of the above comments.

Geri

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/s/

Geraldine Smith
1/16/2008 12:16:38 PM
CSO

dup's

Smith, Geri

From: Smith, Geri
Sent: Friday, January 11, 2008 8:55 AM
To: 'Mikel Alberdi'; 'Cheryl Blume'
Subject: RE: NDA 22-029 / Salonpas / Form 3542a
Importance: High

Hello Mikel and Cheryl,

Our archival copy of your June 8, 2006 submission references Form 3542a but does not include the form. Please submit this form to the NDA. It's acceptable to submit the form dated May 18, 2006 that is referenced in your June 8, 2006 submission.

Thanks,
Geri

From: Smith, Geri
Sent: Wednesday, January 09, 2008 1:28 PM
To: 'Mikel Alberdi'
Cc: 'Cheryl Blume'
Subject: RE: NDA 22-029 / Salonpas / Form 3542a

Thank you. I'll look into this and let you know if we need anything else concerning this.

Geri

From: Mikel Alberdi [mailto:malberdi@pharmdevgroup.com]
Sent: Wednesday, January 09, 2008 1:05 PM
To: Smith, Geri
Cc: 'Cheryl Blume'
Subject: RE: NDA 22-029 / Salonpas / Form 3542a

Ms. Smith,

It is a pleasure to be working with you on this NDA. Form 3542a was submitted to the NDA in Amendment A002 on 6/8/2006. I have attached a scanned copy of this Amendment for your reference. Please see pages 9-12 on this PDF.

If you require a hardcopy or any additional information, please fee free to contact us.

Thank you,

Mikel Alberdi
Pharmaceutical Development Group, Inc.
13902 N. Dale Mabry Hwy., Suite 122
Tampa, Florida 33618
(813) 963-3062
(813) 963-0972 Fax
malberdi@pharmdevgroup.com

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From: Smith, Geri [mailto:Geri.Smith@fda.hhs.gov]
Sent: Wednesday, January 09, 2008 12:51 PM
To: Cheryl Blume
Subject: NDA 22-029 / Salonpas / Form 3542a

Hi Cheryl,

Form 3542a (*Patent Information Submitted with the Filing of an NDA, Amendment, or Supplement*) is not included in the original NDA submission. Please submit this form to the NDA as soon as possible. The form is available via this link:
http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542a.pdf

Section 13 of the original NDA included a statement that Hisamitsu does not own any patents applicable to this NDA. If that is the case, then section 5 of Form 3542a should be completed.

Thanks,
Geri

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/s/

Geraldine Smith
1/11/2008 08:59:06 AM
CSO

OTC Drug Labeling Review for Salonpas Patch

Division of Nonprescription Regulation Development • Office of Nonprescription Products
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATE:	November 16, 2007	**RECEIVED DATE:**	November 19, 2007
REVIEW DATE:		January 10, 2008	
NDA/SUBMISSION TYPE:		NDA 22-029/Amendment-021	
SPONSOR:		Yoshinobu Higashi Manager International Development Hisamitsu Pharmaceutical Co., Inc 973-765-0122	
DRUG PRODUCT(S):		Salonpas [redacted]	
ACTIVE INGREDIENT:		menthol, 3% methyl salicylate, 10%	
PHARMACOLOGICAL CATEGORY:		topical analgesic	
LABELING SUBMITTED:		carton labels and 5-count pouch labels for each of 3 trade names: 1. [redacted] 2. Salonpas Arthritis Pain (15 patches) 3. [redacted] (5 patches) (Drug Facts text was also submitted separately for each of the 3 trade names)	
REVIEWER:		Reynold Tan	
TEAM LEADER:		Matthew Holman	

b(4)

Background

We sent the sponsor an Approvable Letter for this product on December 27, 2006. The Approvable Letter cited labeling deficiencies among other issues. The sponsor responded to these deficiencies by submitting revised, proposed Drug Facts labeling in NDA 22-029 Amendment A017 on July 25, 2007. We did not respond to the sponsor concerning this submission. On August 20, 2007, the sponsor resubmitted its NDA (Amendment A018). We informed the sponsor that this submission constituted a complete response. However, the sponsor did not include any labeling in this submission. Therefore, on November 13, 2007, we

requested submission of full product labeling. In response, the sponsor submitted labeling on November 16, 2007 (Amendment A021). The sponsor plans simultaneous marketing of the one patch product using three different package labels with the following three proposed trade names:

1. [redacted] b(4)
2. Salonpas Arthritis Pain
3. [redacted]

DMETS is currently reviewing these three recently proposed trade names.

Reviewer's Comments

1. The same patch product is intended to be marketed simultaneously under three different trade names [redacted] 'Salonpas Arthritis Pain', [redacted] b(4) [redacted] The Division of Medication Errors and Technical Support (DMETS) is reviewing these three trade names.

   We believe multiple trade names for the same product can cause consumer confusion. Consumers who do not realize that the differently named products are the same product may use these products simultaneously resulting in overuse. A serious safety concern with systemic exposure may not exist because directions for this product limit use to three days. Local skin irritation still exists as a minor safety concern. Although we do not have the regulatory authority to prohibit the marketing of a product under multiple trade names unless a serious safety concern is presented, we recommend that multiple trade names not be used for this product.

2. The terms "[redacted] subjective and ambiguous and do not provide the consumer with any meaningful information. These terms do not reference any standard unit of time and can be interpreted variously by consumers. Therefore, the sponsor must remove these terms from labeling. b(4)

3. In their July 14, 2006, labeling review of previously submitted labeling, DMETS recommended deleting the following phrases: [redacted] b(4)

The review states the phrase [redacted] misleadingly implies that all users of this product will be more active; the phrase '[redacted]" distracts from important statements and does not communicate any meaningful additional information; and the phrase [redacted] is unclear. This labeling submission includes the same or similar phrases: [redacted] b(4)

The sponsor must delete these phrases for the following reasons:

- [redacted] is unclear and misleading. Relief of pain does not necessarily translate into allowing greater activity. Also, the phrase may be interpreted to mean [redacted] is required for effectiveness.
- Consumers may not understand what "OTC" means in the phrase [redacted] Also, although no other OTC pain relief patch products are currently marketed under approved NDAs, OTC pain relief patch products are currently allowed marketing under the OTC monograph regulatory pathway. Therefore, this phase is misleading because it implies superiority over other pain relief patches. b(4)
- We believe the phrase '[redacted] could be misleading because it implies superiority over other pain relief patches..

Reviewer's Recommendations

I. Inform the sponsor that we recommend that multiple trade names not be used for this product. Consumers who do not realize that the differently named products are the same formulation may use these products simultaneously, resulting in overuse.

II. Inform the sponsor that it must make the following revisions to labeling for all three Salonpas products:

Principal Display Panels:

1. Add a proper statement of identity (e.g., "topical analgesic patch," "pain relieving patch") in accordance with 21 CFR 201.61.

2. Remove the terms [redacted] because these terms are subjective and ambiguous and do not provide the consumer with any meaningful information. b(4)

3. Remove the following phrases because they are unclear and potentially misleading in suggesting unproven superiority over other similar products:

   [redacted]

b(4)

Drug Facts:

4. Revise the warning [redacted] membranes or rashes" to read: "**Do not use** on the face or rashes. [redacted] b(4)

5. Add a bulleted statement that reads: "**Do not use** when sweating excessively (such as from exercise or hot conditions)".

6. Add a bulleted statement that reads: "**Do not use** any patch from a pouch that has been open for 14 or more days".

7. In the "**Ask a doctor or pharmacist before use"** section, move the words "if you are" into the heading and change the word [redacted] to "topical".

8 [redacted]

b(4)

9. In the "**Stop use and ask a doctor if**" section, make the bulleted statement [redacted] the first bulleted statement.

10. In the "**Stop use and ask a doctor if**" section, change the word [redacted] to "condition worsens".

11. Revise [redacted] warning to read: "**Stop use and ask a doctor if** symptoms [redacted] for more than 3 days". b(4)

12. Revise the "**If pregnant or breast-feeding**" warning to read: "**If pregnant or breast-feeding,** ask a health professional before use. Do not to use this product during the last 3 months of pregnancy." (see 21 CFR 201.63(a) and (e))

13. Remove the periods that appear after each of the warning statements except for those statements that constitute more than one sentence.

b(4)

[redacted]

b(4)

Add a statement that reads

16. Under "**Directions,**" change the statement

b(4)

to a statement in the "**Other information**" section that reads: "Some individuals may not experience pain relief until several hours after applying the patch."

17. List the inactive ingredients in all lowercase letters.

7 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-_____

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/s/

Reynold Tan
1/10/2008 10:50:43 AM
INTERDISCIPLINARY

Matthew Holman
1/10/2008 11:06:16 AM
INTERDISCIPLINARY

1918

Smith, Geri

From: Smith, Geri
Sent: Wednesday, January 09, 2008 12:51 PM
To: 'Cheryl Blume'
Subject: NDA 22-029 / Salonpas / Form 3542a

Hi Cheryl,

Form 3542a (*Patent Information Submitted with the Filing of an NDA, Amendment, or Supplement*) is not included in the original NDA submission. Please submit this form to the NDA as soon as possible. The form is available via this link: http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542a.pdf

Section 13 of the original NDA included a statement that Hisamitsu does not own any patents applicable to this NDA. If that is the case, then section 5 of Form 3542a should be completed.

Thanks,
Geri

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/s/

Geraldine Smith
1/9/2008 01:01:20 PM
CSO

Smith, Geri

12/21/07

From: Smith, Geri
Sent: Friday, December 21, 2007 3:27 PM
To: 'cblume@pharmdevgroup.com'
Subject: NDA 22-029 / Salonpas / request for information

Importance: High

Hello Dr. Blume,

I am the project manager now assigned to the subject NDA, as Keith Olin has transferred to another division within FDA.

We have the following request for information with regard to this NDA:

> We reference Table 8b, titled "Adverse Event Frequency in Company Database (June 2006 - March 2007)," on page 216 of Volume 4 of the initial NDA submission dated July 25, 2007. This table lists one report of ductus arteriosus stenosis foetal. Please provide details of this report.

Please submit this information as an official submission to this NDA. To expedite our review of this material, please also email me an electronic copy of the submission.

Thanks,
Geri

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/s/

Geraldine Smith
12/21/2007 03:32:06 PM
CSO

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

REQUEST FOR CONSULTATION

12-17

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447

FROM: Geri Smith, Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Room 5483; 301-796-2204; Geri.Smith@fda.hhs.gov

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12-3-07		22-029	NDA Amendment A021	11-19-07

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Salonpas patch (10% methyl salicylate, 3% menthol)	High	Topical Analgesic	02-11-08

NAME OF FIRM: Hisamitsu Pharmaceutical Co., Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Background: The sponsor submitted NDA 22-029 on 2/27/06 for approval of their Salonpas patch product as the first NDA-approved OTC topical analgesic patch product. Patch products are still being considered for inclusion in the OTC topical analgesic monograph. The sponsor proposed the following trade names in the original 2/27/06 NDA application:

- [redacted]
- [redacted]
- [redacted]

b(4)

We requested a DMETS review of these tradenames, which DMETS completed on 7/14/06. The 7/14/06 DMETS review concluded that each of the three tradenames could cause confusion between the new product and existing Salonpas products. The DMETS review concluded that the [redacted] trade names misleadingly suggested additional

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/s/

Geraldine Smith
12/4/2007 11:35:15 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-029

Pharmaceutical Developement Group
U.S. Agent for Hisamitsu Pharmaceutical Co, Inc.
Attention: Cheryl D. Blume, Ph.D.
300 Campus Dr, Suite 220
Florham Park, NJ 07932

Dear Dr. Blume:

We acknowledge receipt on August 20, 2007 of your August 17, 2007 resubmission to your new drug application for Salonpas [redacted] (1% methyl salicylate & 3% l-menthol) [redacted] b(4)

We consider this a complete, class 2 response to our December 27, 2006 action letter. Therefore, the user fee goal date is February 20, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any question, call Keith Olin, Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
10/11/2007 11:12:06 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-029

Hisamitsu Pharmaceutical Co, Inc.
Attention: Cheryl D. Blume, Ph.D.
300 Campus Dr, Suite 220
Florham Park, NJ 07932

Dear Dr. Blume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Salonpas [redacted] (1% methyl salicylate & 3% L-menthol) topical patch. b(4)

We also refer to the meeting between representatives of your firm and the FDA on February 8, 2007. The purpose of the meeting was to discuss the deficiencies and comments from the approvable letter sent to Hitsamitsu on December 27, 2006.

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 LCDR Keith Olin, Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, MD
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Drug Products
Center for Drug Evaluation and Research

Enclosure

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FOOD AND DRUG ADMINISTRATION

Meeting Date and Time:	February 8, 2007
Meeting Type:	A
Meeting Category:	NDA
Meeting Location:	FDA/White Oak 10903 New Hampshire Ave Room 1415 Silver Spring, MD 20993
Application Number:	NDA 22-029
Product Name:	Salonpas [redacted] b(4)
Received Briefing Package	January 15, 2007
Sponsor Name:	Hisamitsu Pharmaceutical Co, Inc.
Meeting Requestor:	Cheryl Blume, Ph.D. U.S. contact for Hisamitsu Pharmaceutical Co., Inc.
Meeting Chair:	Joel Schiffenbaeur, M.D., Deputy Director
Meeting Recorders:	Keith Olin, R.Ph., Regulatory Project Manager

FDA/CDER Attendees:

ONP/Division of Nonprescription Clinical Evaluation

Leah Christl, Ph.D.	Chief, Project Management Staff
Wafa Harrouk, Ph.D.	Pharmacology/Toxicology Reviewer
Andrea Leonard-Segal, M.D.	Director
Bindi Nikhar, M.D.	Medical Team Leader
Keith Olin, R.Ph.	Regulatory Project Manager
Linda Hu, M.D.	Medical Officer
Joel Schiffenbauer, M.D.	Deputy Director
Daiva Shetty, M.D.	Medical Team Leader

ONP/Division of Nonprescription Regulation Development

Matthew Holman, Ph.D.	IDS Team Leader

Division of Anesthesia, Analgesia, and Rheumatology Products

Christina Fang, M.D.	Medical Officer
Sharon Hertz, M.D.	Deputy Director

Yongman Kim, Ph.D.	Statistical Reviewer
Dionne Price, Ph.D.	Statistician Team Leader

Division of Clinical Pharmacology II

Lei K. Zhang	Senior Staff Fellow

Division of Pre-Marketing Assessment II

Terrance Ocheltree, Ph.D.	Chemist

Hisamitsu Pharmacuetical Co, Inc.

Kenichi Furuta	General Manager, International Devolvement
Dange Veerapaneni, Ph.D.	Director, Hisamitsu California Laboratories
Yoshinobu Higashi	Manager, International Development
Masahiko Tashiro	Team Leader, International Development
Takehito Kiuchi	Team Leader, International Development

Pharmaceutical Development Group, Inc.

Cheryl Blume, Ph.D.	President
Mikel Alberdi, M.P.H.	Manager, Regulatory Affairs & New Product Development

[redacted] b(4)

1.0 BACKGROUND

Hisamitsu Pharmaceutical Co, Inc. submitted a Type-A meeting request on December 28, 2006, received on December 29, 2006, to discuss the approvable letter issued to Hisamitsu on December 27, 2006. The proposed indication for this proposed product is for the temporarily relief of mild to moderate aches & pains of muscles & joints. The approvable letter addressed multiple deficiencies; including that the single patch study submitted in the NDA was not adequate to establish a dosing interval and multiple patch use in an OTC market. Also, Hisamitsu was not able to support a proper safety profile for the intended dosing schedule.

2.0 MEETING OBJECTIVE

The objective of the meeting is to discuss the deficiencies and comments from the approvable letter sent to Hitsamitsu on December 27, 2006.

3.0 DISCUSSION

Preliminary responses to the questions enclosed in the January 24, 2007 meeting package were sent to Hitsamitsu via e-mail on February 7, 2007. These questions and preliminary FDA responses are listed below.

Following introductions, the meeting agenda consisted of further discussion based on the preliminary responses from the FDA.

3.1 FDA PRELIMINARY RESPONSES

Regulatory and Clinical

1) Based on the data generated in FS-67-E02 and FDA's comments dated October 29, 2004, and April 11, 2005, Hisamitsu proposes to label SALONPAS [redacted]. Appropriately revised draft labeling is attached (Attachment 4). Hisamitsu believes this label is appropriate given the continued pain relief afforded by SALONPAS [redacted] and the self-limiting nature of the indicated pain population (see proposed label). As directed by FDA on February 24, 2005, the time to rescue was employed to assess duration. Based on the lack of requests for rescue medications, Hisamitsu has determined that [redacted] is appropriate for the indicated population. b(4)

   We request FDA's concurrence with the amended labeling and seek the Agency's agreement that no further clinical trials are required for [redacted] only. b(4)

FDA Preliminary Response:

We do not concur with the amended labeling. Your proposed re-labeling [redacted] does not result in a rational product for the conditions it will be treating, nor does it address deficiencies in the clinical data submitted in the NDA. There are no data provided to support the contention that the target OTC population will use a [redacted] The conditions noted in the Salonpas indications (pain of arthritis, backache, strains, and/or sprains), may require several days of treatment. OTC medications currently approved for these indications are labeled for multiple-dose use because the indicated conditions are likely to require more than one dose of medication for adequate treatment. Therefore, the labeling needs to specify an appropriate duration of use for each patch, a safe and effective dosing interval for repeat patches, and a total duration of use.

b(4)

Additionally, the label should enable the consumer to understand that it takes a long time for Salonpas to start to relieve pain. In the Phase 3 study there was no difference from placebo in the time to onset of analgesia (~3 hours) or to meaningful pain relief (~13 hours). This data would support labeling [redacted]

b(4)

We remind you that the October 29, 2004 meeting minutes state that the single-patch study would be acceptable as long as it demonstrated a reasonable onset and duration to support the dosing recommendations. This was not accomplished in Study E02. The October 29, 2004 minutes stated "Onset and duration are very important primary efficacy parameters in measuring single-dose effect of acute analgesia." and recommended "Extending your evaluation interval to 12 hours (or even beyond)..."

2) Does the Agency concur that no new clinical efficacy and safety data will be necessary with the new labeling directions proposed for SALONPAS [redacted]?

b(4)

FDA Preliminary Response:

We disagree. See response to question 8.1.1. At least one adequate and well-controlled clinical study will be required to provide data to support dosing instructions as well as to provide adequate safety data to address the way the product will be used.

3) If the Agency agrees that no new clinical data are necessary for this NDA, does the Agency agree that no safety data will need to be collected from a multiple-dose study?

FDA Preliminary Response:

No, we do not agree. See responses to questions 1 and 2.

4) If the Agency agrees that no new clinical data are necessary for this NDA, does the Agency also agree that no additional assessments of excess systemic salicylate exposure will be required?

FDA Preliminary Response:

Depending on the results of the proposed pharmacokinetic study, it may be necessary to add a "salicylate warning."

5) Pursuant to 21CFR314.50, Hisamitsu will include an updated safety report with the NDA Amendment addressing the comments and requests outlined in FDA's Approvable Letter dated December 27, 2006.

FDA Preliminary Response:

You will need to respond to all of the regulatory requirements for filing your NDA Amendment.

Clinical Pharmacology

6) The Agency commented in the Approvable Letter that Hisamitsu should "submit newly acquired pharmacokinetic data using adequately validated assay methods."

The [redacted] methods underwent a method technical transfer and revalidation at [redacted]. In general, the methods developed and validated [redacted] are identical (or highly similar) to the original [redacted] methods. However, [redacted] modified the [redacted] method in one significant aspect in that the employed LLOQ for salicylic acid was increased. In addition, [redacted] combined the quantification of l-menthol and methyl salicylate into one assay method. b(4)

The protocol for the new pharmacokinetic study (FS-67-15R) required by FDA in male and female subjects is provided in Attachment 5. This protocol was submitted to

Hisamitsu IND #62,735 (A043) on January 23, 2007, and Hisamitsu will initiate dosing at the end of February 2007.

Does the Agency concur that the proposed pharmacokinetic study (FS-67-15R) will be sufficient to satisfy the clinical pharmacology requirements for approval of this topical drug product?

FDA Preliminary Response:

This protocol appears acceptable.

Labeling

7) The Approvable Letter stated that the SALONPAS [redacted] trade name was not acceptable. FDA recommended that the proposed trade name be changed to SALONPAS [redacted] Hisamitsu would like to propose four additional trade names for the Agency's approval: b(4)

[redacted] b(4)

[redacted]

Does the Agency agree that these new trade names are acceptable?

FDA Preliminary Response:

The acceptability of a proposed name is a review issue and will be determined when the NDA is submitted.

The following names appear unacceptable at this time:

- [redacted] *Previously, we found the proposed tradenames* [redacted] *potentially misleading because they implied superiority to other Salonpas products. For this same reason, the name* [redacted] *is not acceptable.* b(4)
- [redacted] *This tradename does not differentiate this product from other SALONPAS products (e.g., Salonpas Patch, Salonpas Large Patch, Salonpas Hot Patch, Salonpas Gel Patch, Salonpas Gel, and Air Salonpas Spray).*

8) Hisamitsu requests the Agency's concurrence with the proposed addition of the [redacted] Warning to the Drug Facts Warnings section for our topical patch product. b(4)

FDA Preliminary Response:

We do not concur. [redacted]

b(4)

[redacted]

9) Hisamitsu requests the Agency's concurrence with the proposed [redacted] in the Drug Facts Warnings section for our topical patch product.

FDA Preliminary Response:

Your proposed label includes a warning that states [redacted]

b(4)

However, we have a draft guidance that provides an example of this type of warning. It states:

"Ask a doctor or pharmacist before use if you are taking a prescription blood thinning medicine, such as warfarin, because bleeding or bruising may occur"

10) Hisamitsu requests the Agency's guidance for the need of additional of salicylate warnings for our topical patch product.

FDA Preliminary Response:

The need for this warning and the language to be used depends on results from the pharmacokinetic study that evaluates systemic salicylate exposure. If any salicylate levels are detected, you will need salicylate warnings on your label.

11) Hisamitsu agrees to revise the label to state the patch should be discarded after 14 days after the pouch is opened.

FDA Preliminary Response:

We concur.

3.2 ADDITIONAL DISCUSSION

Hitsamitsu acknowledged the receipt of the preliminary responses from the FDA on February 7, 2006, and agreed with FDA's responses to questions 5, 8, 9, and 11.

The discussion focused on FDA's preliminary responses to questions 1, 2, and 3. FDA acknowledged that some consumers will only need one patch to treat their pain. However, analgesic products approved for OTC use are labeled for use up to 10 days to allow treatment of those individuals who require multiple doses and in whom pain lasts for longer than one day. b(4)

Hisamitsu requested clarification on how to comply with the FDA requirements and still use the information from the single-dose study. Hisamitsu stated that they are aware of the concern that the single dose study did not allow for re-dosing. Hisamitsu stated that a prolonged effect beyond the time the patch is removed could be related to a depot effect.

The FDA commented that Hisamitsu may wish to examine alternate dosing intervals such as using the patch for 4 hours and evaluating for an effect up to 12-24 hours. Hisamitsu asked if a multiple dose safety and separate single dose efficacy study showing the time to re-medication will satisfy the Agency. FDA informed Hisamitsu that they should conduct a multi-dose study to determine the dosing interval for their patch. A multi-dose study is also needed to define the safety profile as the product will be used, since the incidence of skin reactions may increase with use of more than one patch (serially). The dosing interval should reflect the safety and efficacy of their patch (i.e., balancing safety against efficacy). A multi-dose study would allow the over-the-counter (OTC) product label to inform consumers about the appropriate dosing interval and expectation of duration of relief when using the product.

Hisamitsu questioned what type of pain model they should be exploring for the efficacy study. Hisamitsu believed that it would be difficult to define the population and the duration of use in a multi-dose study because there may be multiple drop-outs due to pain relief before the end of the observation period. Hisamitsu is concerned that this may negatively affect the study outcome. FDA suggested that a study could have duration of use for 7 to 10 days with the primary endpoint at 3 days. FDA stated that there are

approaches where the improvement of pain could be separated from the drop-outs secondary to a lack of efficacy or due to adverse events.

FDA suggested finding a target population within the listed indications for this product. Hisamitsu stated that they may try to use an osteoarthritis (OA) model design for their studies. FDA stated that the duration of effect should be defined as the median time to re-medication or rescue as is used with other topical or oral pain products. FDA emphasized that in the multi-dose study Hisamitsu should collect safety data with the new dosing schedule. FDA recommended Hisamitsu submit a protocol for a multi-dose study to the FDA for review and comment before proceeding with any studies.

Hisamitsu also wanted clarification on question 7. They wanted to know if the trade name "Salonpas" would be acceptable if they remove the trade name from their other marketed OTC products. FDA informed Hitsamitsu that this would be a review issue.

In reference to questions 4 and 10, Hisamitsu acknowledged FDA's comments regarding the need for salicylate warning and stated that they understood that this would be a review issue based on the outcome of the pharmacokinetic study.

Hisamitsu sought confirmation from the FDA that successful completion of the proposed pharmacokinetic study (see question 6) was the only additional pharmacokinetic study required. The FDA agreed with this statement.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

1) Hisamitsu will propose a multi-dose study protocol and submit it to the FDA for review.

6.0 ATTACHMENTS AND HANDOUTS

None

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/s/

Joel Schiffenbauer
3/8/2007 03:25:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-029

Hisamitsu Pharmaceutical Co, Inc.
Attention: Cheryl D. Blume, Ph.D.
300 Campus Dr, Suite 220
Florham Park, NJ 07932

Dear Dr. Blume:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Salonpas ——— (15% methyl salicylate & 3% l-menthol) topical patch. b(4)

We also refer to your December 28, 2006 correspondence, received December 29, 2006, requesting a meeting to discuss the deficiencies as outlined in the approvable letter issued to you on December 27, 2006.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: February 8, 2007
Time: 10:30 to 11:30 am EST
Location: FDA/White Oak/ Building 22/Room 1417

CDER participants:

Division of Nonprescription Clinical Evaluation

Leah Christl, Ph.D.	Chief, Project Management Staff
Wafa Harrouk, Ph.D.	Pharmacology/Toxicology Reviewer
Andrea Leonard-Segal, M.D.	Director
Keith Olin, R.Ph.	Regulatory Project Manager
Steven Osborne, M.D.	Medical Officer
Joel Schiffenbauer, M.D.	Deputy Director
Daiva Shetty, M.D.	Medical Team Leader

Division of Nonprescription Regulation Development

Reynold Tan, Ph.D.	IDS Reviewer

Division of Ansethesia, Analgesia, and Rheumatology Products

Christina Fang, M.D.	Medical Officer
Sharon Hertz, M.D.	Deputy Director

Yongman Kim, Ph.D.	Statistical Reviewer
Dan Mellon, Ph.D.	Team Leader, Toxicology
Belinda Hayes, Ph.D.	Toxicologist Reviewer

Division of Clinical Pharmacology 2

Suresh Doddapaneni, Ph.D.	Team Leader, Clinical Pharmacology
Lei K. Zhang	Senior Staff Fellow

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to Keith Olin at keith.olin@fda.hhs.gov. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Keith Olin x 60962; the division secretary, x60924.

Provide the background information for this meeting (three copies to the NDA and 15 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by January 24, 2007 we may cancel or reschedule the meeting.

If you have any questions, call Keith Olin, Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
1/19/2007 04:34:41 PM

Office of Nonprescription Products - Label Review for NDA

NDA 22-029/ N-000	Salonpas
Submitted Date:	February 27, 2006
Active ingredients:	10% methyl salicylate, 3% menthol
Drug category:	external analgesic
Sponsor/Contact:	Hisamitsu Pharmaceutical Co., Inc. Cheryl D. Blume, Ph.D. 13902 North Dale Mabry Highway, Suite 122 Tampa, FL 33618 (813) 963-3062 (813) 963-0972 (FAX)
Labeling submitted:	commercial sachet – (5 patches/sachet) 5-ct. carton label – 1 sachet (5 patches/sachet) 15-ct. carton label – 3 sachets (5 patches/sachet) b(4)
Reviewer:	Reynold Tan
Review date:	December 18, 2006
Project manager:	Keith Olin

Background:

The monograph status of Salonpas [redacted] has not yet been determined. We are currently drafting the External Analgesics Final Monograph. The 2/8/83 External Analgesic Tentative Final Monograph (TFM) allows combination products containing methyl salicylate (10 to 60%) and menthol (1.25 to 16%). The allowed indication for these products is "For the temporary relief of minor aches and pains of muscles and joints" (*optional* "associated with simple backache, arthritis, strains, bruises, and sprains"). Salonpas (10% methyl salicylate and 3% menthol) meets these specifications. However, a 7/17/03 proposed rule to amend the TFM does not allow external analgesic products in patch, plaster, or poultice dosage forms. We are still considering whether to allow patch dosage forms in the External Analgesic Final Monograph. The External Analgesic TFM also requires a labeled warning statement that reads, **"Do not bandage tightly"** for products containing counterirritant-type active ingredients, such as methyl salicylate and menthol. b(4)

The sponsor previously petitioned FDA in 1988 to amend the TFM to allow marketing of products containing counterirritant-type active ingredients in patch dosage forms. The sponsor withdrew the petition in 1992, but subsequently met with FDA in 1994 to discuss clinical trial protocols testing skin irritation and percutaneous absorption. We provided recommendations on revising these protocols on several occasions before our 2003 proposed rule to exclude patch dosage form products from the External Analgesic Final Monograph. Consequently, the sponsor did not submit the results of their proposed protocols for review under the OTC monograph process, choosing instead to submit data in this new drug application.

Reviewer's Comment:

This label review will address the issue of the sponsor's proposed tradename only. FDA intends to respond to this current submission with an Approvable (AE) Letter identifying major safety and effectiveness deficiencies. Responding to these deficienciences may greatly impact labeling. Therefore, a detailed review of the labeling is premature at this point.

The sponsor proposes the following three tradenames for this product (ranked from 1st choice to 3rd choice):

b(4)

[redacted]

The tradename '[redacted]' is acceptable. The tradenames '[redacted]' [redacted] are not acceptable. FDA's Division of Medication Errors and Technical Support (DMETS) reviewed these tradenames for their potential to cause consumer confusion. We agree with the DMETS review that the modifiers [redacted] imply superiority to other marketed Salonpas products although there is no evidence of relative efficacy of the different products. Therefore, the tradenames [redacted] are potentially misleading. b(4)

Reviewer's Recommendation:

1. Inform the sponsor that it may use the tradename [redacted]." However, it cannot use the tradenames [redacted] These two tradenames suggest that the product is superior to other marketed products. Therefore, the sponsor must submit additional data for our review if it wishes to use these two tradenames. b(4)

2. Inform the sponsor that we will comment on the approvability of labeling (other than the tradename) after it meets the other deficiencies outlined in the AE letter.

5 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

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/s/

Reynold Tan
12/19/2006 10:17:26 AM
INTERDISCIPLINARY

Matthew Holman
12/19/2006 11:43:18 AM
INTERDISCIPLINARY

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Grace Carmouze, Lead Project Management Officer Pediatric and Maternal Health Staff Office of New Drugs	Keith Olin, RPM Division of Nonprescription Clinical Evaluation (DNCE) Office on Nonprescription Products 301-796-0962

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/03/06		22-029	N	02/27/06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Salonpas b(4)	Standard		11/30/06

NAME OF FIRM: Hisamitsu Pharmaceuticals, Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Hisamitsu Pharmaceuticals, Inc has submitted an new NDA 505(b)(2) for Salonpas b(4) (10% methyl salicyclate and 3% L-menthol) topical patch. Salonpas b(4) patch is used for the temporarily relief of mild to moderate aches & pains of muscles & joints associated with: arthritis, simple, backache, strains, bruises and sprains. The original NDA submission (February 27, 2006) Hisamitsu Pharm. requested a pediatric waiver for the pedriatric ages groups citing 21 CFR 314.55(c)(2). On January 10, 2003, the FDA advised Hisamitsu that pediatric studies could be deferred (IND 62735). Please advise DNCE on whether NDA 22-029 for Salonpas b(4) 1) should be used in the pediatric population as an over-the-counter product for certain age groups 2) what type of studies should be conducted by the sponsor as a postmarketing commitment 3) or should the agency grant the full waiver.

The PDUFA goal date for this NDA is December 27, 2006. We plan to sign off on this action on December 15,

2006.	
SIGNATURE OF REQUESTOR Keith Olin, Regulatory Project Manager	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Keith Olin
10/11/2006 04:45:59 PM

DSI CONSULT: Request for Clinical Inspections

Date: October 2, 200

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

From: LCDR Keith Olin, Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
301-796-0962

Subject: **Request for Clinical Site Inspections**
NDA 22-029
Hisamitsu Pharmaceuticals Co, Inc
Drug: Salonpas [redacted] (10% methyl salicyclate and 3% L-menthol) topical patch

b(4)

Protocol/Site Identification:

The following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority. We are requesting that a total of 3 sites be inspected. They are the first two sites listed below and the choice of one site from the last three sites listed. There are no specific violations or concerns for any of these sites at this time.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Radiant Research Foundation, Inc. 8122 Datapoint Drive, Suite 1010 San Antonio, TX 78229 Phone # 210-614-7493 Investigator name: William Jennings, MD	FS-67-E02	23 patients enrolled and 9 protocol violations.	Temporarily relieves mild to moderate aches & pains

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Radiant Research 8527 Village Drive, # 207 San Antonio, TX 78217 Phone: 210-946-1581 Fax: 210-946-1584 Investigator name: Francis Burch, MD	FS-67-E02	16 patients enrolled and 1 protocol violation.	Temporarily relieves mild to moderate aches & pains
Radiant Research 550 Peachtree Street, Suite 1700 Atlanta, GA 30308 Phone: 770-745-1404 Fax: 770-944-2154 Inspector name: Robert Kaufman, MD	FS-67-E02	24 patients enrolled And 1 protocol violation	Temporarily relieves mild to moderate aches & pains
Radiant Research 552-A Memorial Drive Extension Greer, Sc 29651 Phone:864-877-9239 Fax: 864-968-0149 Inspector Name: Travis Ellison, MD	FS-67-E02	24 patients enrolled And 1 protocol violation	Temporarily relieves mild to moderate aches & pains
Lifespan Research Foundation, Inc. 13322 SW 128th Street Miami, FL 33186 Phone: 210-614-7493 Fax: 210-614-4524 Inspector Name: Clara Garcia, MD	FS-67-E02	24 patients enrolled And 1 protocol violation	Temporarily relieves mild to moderate aches & pains

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) November 22, 2006. We intend to issue an action letter on this application by (division action goal date) December 15, 2006. The PDUFA due date for this application is December 27, 2006.

Should you require any additional information, please contact LCDR Keith Olin.

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/s/

Keith Olin

10/2/2006 05:03:52 PM

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

REQUEST FOR CONSULTATION

912916

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Division of Dermatology and Dental Products Attn: Mary Jean Kozma-Fornaro Chief, Project Management Staff	Division of Nonprescription Clinical Evaluation Keith Olin, Project Manager 301-796-0962

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
09/28/06		22-029	NDA	02/27/06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Salonpas [redacted] b(4)	High		11/27/06

NAME OF FIRM: Hisamitsu Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review the dermal safety studies and the irritation potential of the SALONPAS patch (NDA 22-029), and advise whether the safety data supports the dosing proposed by Hisamitsu. The PDUFA goal date is 12/27/06.

Please see attached document.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Consult Request to Division of Dermatology

Background:

Hisamitsu has submitted NDA 22-029 in support of a marketing application for SALONPAS [redacted] patch (10% Methyl Salicylate and 3% l-Menthol) for use by adults [redacted] for the indication of temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains. b(4)

The proposed directions for dosing [redacted] b(4)

[redacted] Regarding the use in women who are pregnant or breast feeding, [redacted] the recommendation is to ask a doctor.

In support of product efficacy, the sponsor has submitted results of a pilot study and a Phase 3 trial, both conducted with a single 8-Hour dose.

Hisamitsu has evaluated the safety of the FS-67 topical patch in 766 subjects, of which 256 participated in a pilot and in a Phase 3 safety and efficacy trials, and 510 participated in pharmacokinetic and dermal safety studies, as follows:

	Protocol #	Objective	Design	Number of subjects Enrolled/completed	Treatments
1	FS-67-E01	Safety & efficacy on muscle strain	Randomized double blind placebo-controlled	12/12 males 15/9 males	FS-67-A, 8 hours
2	FS-67-E02	Safety & efficacy on muscle strain	Randomized double blind placebo-controlled	50/55 males 54/49 females	FS-67-A, 8 hours
3	FS-67-03-M	pk	Open label, Randomized 3-way crossover	33/33 healthy males	FS-67-A 10% methyl salicylate ointment 60% methyl salicylate ointment
4	FS-67-03-L	pk	Open label, Randomized 3-way crossover Single dose	40/37 healthy males	FS-67-A 1.25% l-menthol ointment 16% l-menthol ointment
5	FS-67-14-PI	pk	Open label, Randomized 3-way crossover Single dose	18/18 healthy males	FS-67-A FS-67-M (10% methyl salicylate) FS-67-L (3% menthol)
6	FS-67-15	pk	Open label, Single period Single dose	18/18 healthy females	FS-67-A
7	FS-67-121	pk	Open label Single period, Single dose	22/22 healthy males	FS-67-A
8	FS-67-122	pk	Open label Multiple dose	19/17 healthy males	FS-67-A
9	FS-67-01 Vol. 95	Cumulative Irritation	double blind placebo-controlled	10/10 males 26/26 females	FS-67-A FS-67-C placebo
10	FS-67-011 Vol. 96	21-Day Cumulative Irritation	double blind placebo-controlled	10/10 males 28/28 females	FS-67-A FS-67-C placebo
11	FS-67-02 Vol. 97, 98	Repeated Insult Patch Test	double blind placebo-controlled	70 males 156 females	FS-67-A FS-67-C placebo
12	FS-67-10 Vol. 99	Phototoxicity	double blind placebo-controlled	8/8 males 20/20 females	FS-67-A FS-67-C placebo

13	FS-67-11 Vol. 100	Photoallergy	double blind placebo-controlled	8/8 males 24/24 females	FS-67-A FS-67-C placebo

There were no serious adverse events reported in the Phase 1 and Phase 2 studies.

There were several adverse events in the Phase 3 (EO-2) trial leading to study discontinuation: Subject #2 was dropped after 4 doses (2 patches each) due to ringing in the ears. Subject #14 was dropped after 6 doses (2 patches each) due to the development of rash and itching requiring Benadryl for several days. This subject also developed tinnitus on day-1. An additional 4 subjects (7, 8, 11, and 15) were dropped from the study because of headache, dizziness, weakness, nausea and/or vomiting.

No sensitization, phototoxicity, photosensitization have been reported.

In study FS-67-01, a topical safety study, 5 of 29 subjects developed strong irritation scores and the patches were discontinued; one of these was with placebo (14). The reactions were self limiting and began to resolve without treatment.

Study FS-67-011, a 21-Day Cumulative Irritation Study, was conducted at the request of the Agency to assess irritation under maximum use. The study shows a clear correlation between the number of patch applications and the number of subjects developing irritation. One subject (#37) began to experience strong erythema by the third day of continuous wear and five additional subjects (#1, 6, 15, 16, and 17) experienced strong erythema by the fifth day of continuous wear that required discontinuation. Strong irritation reactions reached 23% by the sixth day, progressed incrementally reaching 82% of the test population by the final application. The test patch produced severe erythema, petechial erosions, fissures, glazing, peeling, or scabbing in 27 subjects prior to the 15th application that required discontinuation of the patches. Seven subjects developed no irritation from the active patches and completed all 21 applications. Less than 10% of the placebo reactions required discontinuation following the fifth application. All application site reactions were self-limiting and resolved without treatment but some took up to 11 days (subject 155, study FS-67-02) to resolve in the studies were the duration of the reaction was reported. If the rate of reaction is calculated for subjects who developed any of the following: grade ≥2, marked glazing, cracking, fissuring, petechia, or required skipping application of a patch, which would normally suggest to a patient to stop treatment, the results would be as shown on the next table:

Number applications	Subjects reaching a score ≥ 2/ cracking, petechiae, fissuring, marked glazing, or required skipping patch application			
	FS-67, 34 subjects		Vehicle	
	Number of subjects	%	Number of subjects	%
2	1	2.94	1	2.94
3	3	9.82	3	9.82
4	6	17.82	6	17.82
5	11	32.67	7	20.79
6	15	44.55	11	32.67
7	20	58.50	11	32.67
8	22	65.34	16	47.52
9	27	80.19	18	52.94
10	29	86.13	18	52.94
11	30	89.10	20	58.50
12	32	94.08	20	58.50

13	32	94.08	22	65.34
14	32	94.08	22	65.34
15	32	94.08	22	65.34
16	32	94.08	22	65.34
17	32	94.08	22	65.34
18	32	94.08	22	65.34
19	33	99.01	22	65.34
21	33	99.01	22	65.34

In the pk studies with multiple dosing there were reports of local erythema reactions often lasting several days and leading to discontinuation of several subjects and to relocation of patches in other subjects, as shown in the following table:

Subject	Signs and symptoms	Outcome, days to resolution
1	Rash and pruritus	Mild, probable, 12 days
1	Application site warmth	Mild, definite
2	Tinnitus	3 days, and 17 days after discontinuation
5	Application site erythema	13 days, 12 days, 7 days
6	Application site burning	Mild, definite
8	Feeling hot, headache weakness	
9	Application site erythema	6 days
10	Application site erythema	7 days
11	Headache Dizziness, lightheaded	14 hours, Lost to follow up Therapy required
13	Application site erythema	29 days
14	Tinnitus Rash	
15	Nausea, vomiting, Dizziness, Lightheaded Application site erythema	 Therapy required 6 days
16	Application site erythema	9, 8 and 7 days
17	Application site erythema	7, 7, 6 and 6 days
19	Application site erythema	Mild, definite 5 days
20	Application site erythema	9, 13, 12, 12 and 12 days

Consult request:
Please review the dermal safety studies and the irritation potential of the SALONPAS patch, and advise whether the safety data supports the dosing proposed by Hisamitsu.

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/s/

Keith Olin

9/29/2006 04:53:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-029

INFORMATION REQUEST LETTER

Pharmaceutical Development Group, Inc.
Attention: Cheryl Blume, Ph.D.
President
13902 North Dale Mabry Highway
Suite 122
Tampa, FL 33618

Dear Dr. Blume,

Please refer to your February 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FS-67 Topical Patch (Methyl Salicylate/Menthol Topical).

We also refer to your submission dated June 9, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response, preferably before October 13, 2006, in order to continue our evaluation of your NDA.

b(4)

The Drug Master Files (DMF) used to support your NDA submission for FS-67 have been reviewed and found to be incomplete. Letters detailing the deficiencies have been faxed to the respective designated agents. They are as follows: DMF [redacted]

We acknowledge that you have agreed to include a pouch integrity test as a release specification for the commercial product. Based on additional review, please also include the specification as part of your stability commitment.

Please include residual monomers, based on the potential monomers from the excipients [redacted] and [redacted], as a specification for release of the commercial product.

b(4)

We acknowledge that you will provide placebo samples, including representative packaging by the end of September. Those samples should be sent directly to:

Terrance Ocheltree, Ph.D., R.Ph.
10903 New Hampshire Ave.
Bldg #22 Room 2487
Silver Spring, MD 20993-0002

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If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
9/26/2006 02:24:40 PM
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-029

INFORMATION REQUEST LETTER

Pharmaceutical Development Group, Inc.
Attention: Cheryl Blume, Ph.D.
President
13902 North Dale Mabry Highway
Suite 122
Tampa, FL 33618

Dear Dr. Blume:

Please refer to your February 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FS-67 Topical Patch, (Methyl Salicylate/Menthol Topical Patch).

We also refer to your submission dated June 9, 2006.

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

The Drug Master Files (DMF) used to support your NDA submission for FS-67 have been reviewed and found to be incomplete. Letters detailing the deficiencies will be issued to the respective designated agents. They are as follows: DMF [redacted] b(4)

1. Please assign an alphanumeric unique identifier to all non-compendial analytical methods and test procedures.

2. Please note that the proposed use of the novel excipients is still under review and acceptance of these excipients is pending.

3. Update the synthesis process in section 3.2.S.2.2. for methyl salicylate (Figure S.2-2), with the DMF holder, [redacted] b(4)

4. In section 3.2.S.4.2. methyl salicylate, provide chromatograms, IR spectra, and other test results for Lot Y224 and include a Certificate of Analysis.

5. Include a test for "Appearance" of the drug substance in the acceptance specification for each drug substance.

6. Add a test for ultra violet (UV) absorbing content in the acceptance specification for the backing cloth (FS-67) [redacted] or justify its absence. b(4)

7. The use of overages to account for known drug losses during manufacturing is an acceptable practice. However, a strong justification for any overage should be made. This justification should identify the cause for the loss and predict the amount loss on a scaleable factor. In your development process it was shown that the amount of overage had to be reduced by [redacted] to accommodate a 2.5 fold scale-up, [redacted]. Therefore it would be reasonable to assume that the amount of overages will have to be modified even further as the manufacturing process is scaled-up to the proposed commercial size [redacted]. Please commit to evaluating the overages during process validation and to an appropriate number of commercial batches. Also commit to reporting the outcome of this evaluation to the FDA within six months of the NDA approval date. b(4)

8. Provide a description of your in vitro release method including apparatus configuration, study conditions, sampling methods, and the resulting permeation profile to compliment the results you submitted in section 3.2.P.2.2.3.

9. Section 3.2.P.2.2.3. states that you are developing a dissolution method to use in place of the in vitro release method recommended by the FDA on July 7, 2002, during the pre-NDA meeting. Please provide an update of the progress of developing the method and make a commitment to provide an overview of the method and a summary of any relevant findings to the FDA no later than six months after the date of approval for this NDA (NDA 22-029).

10. Refer to USP <87> and <88> and provide extractable and leachable information for your backing, release liner and primary packaging material.

11. Include a pouch integrity test either as an in-process test or release specification.

12. Evaluate the potential for crystal or particle growth of *l*-menthol in the finished product upon release, in-use and storage (end of shelf life). This may be achieved by using microscopy to examine fresh (if available) and aged samples. The in-use samples [redacted] should be evaluated at the end of the proposed use period [redacted]. b(4)

13. Please provide representative samples (or placebos) of your finished drug product. If possible, include all proposed packaging.

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
8/22/2006 11:47:27 AM

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

REQUEST FOR CONSULTATION

1 of 6

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447

FROM: Keith Olin, Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
keith.olin@fda.hhs.gov

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 21, 2006		22-029	N	February 27, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Salonpas [redacted] b(4)		503 ANTI-INFLAMMATORY 5030500 MISCELLANEOUS	September 1, 2006

NAME OF FIRM: Hisamitsu Pharmaceutical Development Group, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Hisamitsu Pharmaceutical Development Group, Inc has submitted a NDA for an over-the-counter patch for the indication of temporarily relieves mild to moderate aches & pains of muscle and joint pains associated with arthritis, simple backaches, strains, bruises, and sprains. Labeling for this NDA has been submitted electronicly and can be located at \\CDSESUB1\N22029\N_000\2006-06-08 , in the EDR. Hisamitsu Pharmaceutical Development Group, Inc has sumbitted the propietary name: Salonpas [redacted] . b(4)

PDUFA DATE: December 27, 2006
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 22-029
HFD-560/Division File

HFD-560/RPM HFD-560/Reviewers and Team Leaders	
NAME AND PHONE NUMBER OF REQUESTER Keith Olin, 301-796-0962	METHOD OF DELIVERY (Check one) ☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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

/s/

Keith Olin
6/21/2006 06:04:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-029

Hisamitsu Pharmaceutical Co, Inc.
Attention: Cheryl D. Blume, Ph.D.
300 Campus Dr
Suite 220
Florham Park, NJ 07932

Dear Dr. Blume:

Please refer to your February 27, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Salonpas [redacted] (1% methyl salicylate & 3% L-menthol) Patch. b(4)

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 28, 2006, in accordance with 21 CFR 314.101(a).

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

1) Annotated specifications for the label and labeling were not submitted.

2) The patent information is not acceptable.

3) Content of labeling was not submitted in electronic format.

4) The financial disclosure form was submitted incorrectly.

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

We also request that you submit the following information:

1) Annotated specifications for the label and labeling.

2) Patent information on Form FDA 3542a.

3) Content of Labeling must be submitted electronically.

4) Financial disclosure on Form FDA 3455.

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

If you have any questions, call Keith Olin, Regulatory Project Manager, at (301) 796-0962.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/s/

Leah Christl
5/11/2006 04:07:46 PM

8/8/2

MEMORANDUM OF MEETING MINUTES

MEETING DATE: 9 July 2002

TIME: 2pm – 4pm

LOCATION: Corp S300

APPLICATION (DRUG): IND 62,735 (FS-67 Topical Patch)

TYPE OF MEETING: Pre-NDA Meeting with Pharmaceutical Development Group, Inc. (Hisamitsu)

MEETING CHAIR: Dr. James Witter

MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
1. Dr. Jonca Bull	Office Director	ODE V
2. Dr. Lee Simon	Division Director	ODE V/DAAODP, HFD-550
3. Dr. James Witter	Medical Officer Team Leader	ODE V/DAAODP, HFD-550
4. Carmen DeBellas	Chief Project Manager	ODE V/DAAODP, HFD-550
5. Dr. Josie Yang	PharmacologyTeam Leader	ODE V/DAAODP, HFD-550
6. Ms. Laura Shay	Project Manager	ODE V/OTC, HFD-560
7. Dr. Nahid Mokhtari	Interdisciplinary Scientist	ODE V/OTC, HFD-560
8. Dr. Linda Katz	Deputy Director	ODE V/OTC, HFD-560
9. Dr. Walt Ellenberg	Project Manager	ODE V/OTC, HFD-560
10. Dr. Christina Fang	Medical Reviewer	ODE V/DAAODP, HFD-550
11. Dr. Abi Adebowale	Biopharm Reviewer	DPS/DPEIII, HFD-880
12. Robert Shibuya	Pharmacology	DSI
13. Dr. Bart Ho	Chemistry Reviewer	ONDC/DNDCIII, HFD-830
14. Dr. John Smith	Chemistry Team Leader	ONDC/DNDCIII, HFD-830
15. Dr. Bonnie Dunn	Deputy Director	ONDC/DNDCIII, HFD-830
16 Ms. Jane A. Dean	Project Manager	ODE V/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Sponsor/Firm Name	Title
1. Amy Kneifel	Hisamitsu	Consultant (Regulatory)
2. Sandra Brown	Hisamitsu	Consultant (CMC)
3. Yoshinobu Higashi	Hisamitsu	Manager
4. Takehito Kiuchi	Hisamitsu	Team Leader
5. Hasatu Nakanishi	Hisamitsu	Group Leader
6. Seiji Kashiyama	Hisamitsu	Group Leader
7. Shinji Yamarato	Hisamitsu	Group Leader (CMC)
8. Masahiro Takatoni	Hisamitsu	Team Leader (CMC)
9. Takafumi Manako	Hisamitsu	Manager (CMC)
10. Ikeura Yasuhiro	Hisamitsu	Manager (CMC)

b(4)

External Attendee	Sponsor/Firm Name	Title
13. Cheryl Blume	Hisamitsu	Consultant
14. Ravi Magavi	Hisamitsu	Regulatory Affairs Manager
15. Kenich Furuta	Hisamitsu	General Manager
16. Frederick E. Reno	Hisamitsu	Consultant (Toxicology)
17. Michinori Sakai	Hisamitsu	Director (Fundamental Research Lab)

PURPOSE OF THE MEETING: Pre-NDA meeting with the FDA.

MEETING OBJECTIVES: To reach agreement on meeting NDA filing requirements before submission of application and obtain FDA response to specific questions.

QUESTIONS for DISCUSSION with FDA RESPONSE:

Sponsor Question 1:

Does FDA agree that the pharmacokinetic and skin toxicology safety trials conducted by Hisamitsu are adequate to address FDA's two safety concerns with patch products containing methyl salicylate and l-Menthol?

FDA Response to Question 1:

- *The sponsor needs to use the classic design of daily 24-hour application under occlusive dressings for 21 consecutive days in the cumulative irritation study because of the safety concern with the patch formulation. The question about whether it should be one patch per 24-hour or 1 patch per 8 hours (3 per 24 hours) will be referred to the dermatology reviewer.*
- *The adequacy of the pharmacokinetic and safety trials is ultimately a review issue.*

Post meeting addendum: *The application of one patch every 8 hours three times a day for 21 consecutive days is considered acceptable if the patch is applied to the same skin area and there is no breathing time in between the applications. The protocol should be submitted for review.*

Sponsor Question 2:

Does FDA agree that the statistical analyses completed for the pharmacokinetic and skin safety trials are appropriate?

FDA Response to Question 2:

- *Although the sponsor calculated a 97.5% Confidence Interval for the comparison of the derived AUC between treatments, this is not the preferred Agency standard. For all such comparisons the Agency prefers that the sponsor follow the general guidance regarding statistical approaches to establishing bioequivalence (i.e. based on the two one-sided tests procedure) which involves the calculation of a 90% Confidence Interval for the ratio of the averages (population geometric means) of the test and reference products. While strict bioequivalence is not the goal of these studies, the 90% Confidence Interval approach is useful for comparative purposes. The sponsor may submit results of analysis using both of the Confidence Intervals mentioned above.*
- *Statistical Analysis of Cmax needs to be included as well.*

Sponsor Question 3:

Does FDA agree with the proposed Case Report Tabulations for the pharmacokinetic and skin toxicology safety trials?

FDA Response to Question 3:

The time course of adverse event and its relationship with dosing should also be included in the Case Report Tabulation, e.g., grade 1 local reaction recorded at 1 hour after the second patch removal during the induction phase in the contact sensitization study and resolved in 5 hours without treatment. The sponsor may choose to submit the updated format for the Case Report Tabulation if requesting for reviewer's input.

Sponsor Question 4:

Does FDA agree that the completed pharmacokinetic and skin safety trials and a complete review of the clinical literature will be adequate to support the submission and approval of a 505 (b)(2) NDA for FS 67 Patches?

FDA Response to Question 4:

The foreign marketing history of the combination patch products (of the same and different concentrations, e.g., Salonpas, Icy Hot etc.) and the safety data from clinical trials, post-marketing surveillance, literature, or other sources need to be part of the submission. The safety data should be summarized in a consistent fashion for analysis of the relationship between adverse events and the level and duration of exposure.

Sponsor Question 5:

Does FDA agree that additional clinical safety or efficacy studies are not necessary?

FDA Response to Question 5:

There is a concern about the efficacy of the proposed patch product because of the difference in the way of drug application between the patch and cream/ointment products. The cream/ointment products have been massaged into the painful area to demonstrate analgesic efficacy, whereas the patch is applied directly to the painful area. The equivalence in systemic absorption alone is not considered sufficient to provide a bridge between the efficacy of these different formulations. The literature articles mentioned did not appear to address the issue. Therefore, additional clinical studies to demonstrate efficacy of the drug combination patch against placebo patch are required. The sponsor may request the 45-day special protocol assessment for a detailed and timely response when submitting the protocols.

Post meeting addendum: *Positive results should be replicated in studies of the combination patch using placebo patch as controls to demonstrate efficacy.*

Sponsor Question 6:

Will FDA agree with Hisamitsu's request for a waiver from pediatric studies?

FDA Response to Question 6:

No, the reason provided by the sponsor is not considered sufficient for a waiver. Pediatric studies are required.

Sponsor Question 7:

Hisamitsu plans on formatting the CMC section of the NDA according to the ICH Guidance M4Q. We would like the balance of the NDA will follow the usual U.S. format

and not the CTD. Is this acceptable?

FDA Response to Question 7:

Yes, this is acceptable.

Sponsor Question 8:

Does FDA agree that the proposed CMC section is adequate for NDA submission and approval?

FDA Response to Question 8:

- *The format is acceptable for submission.*
- *Approval is a review issue.*

Sponsor Question 9:

Will FDA address the specific CMC questions provided on the following page?

FDA Response to Question 9:

An additional hour was added after the 2pm meeting 7/9/02, to specifically address these questions.

Sponsor Question 10:

Does FDA agree that the proposed nonclinical toxicology databases are adequate for NDA submission and approval?

FDA Response to Question 10:

- *Yes, the FDA agrees. In addition, the NDA should include copies of all the literature references cited in Appendix 6 and a summary of the relevant findings.*
- *Approval is a review issue.*

Sponsor Question 11:

Does FDA agree that Hisamitsu's response ——— submitted 3/7/02) to FDA's 1-22-02 request for additional pharmacology/toxicology information is sufficient? b(4)

FDA Response to Question 11:

Yes, the FDA agrees.

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Sponsor Question 12:

Does FDA agree that the ongoing reproduction study data can be submitted within 120 days following NDA submission and as Phase IV commitments?

FDA Response to Question 12:

Yes, the FDA agrees. However, the Sponsor should provide a summary of the literature evidence available on the reproductive toxicity for l-menthol and methyl salicylate.

Sponsor Question 13:

Does FDA agree with the proposed OTC labeling?

FDA Response to Question 13:

- *The OTC label must be in Drug Facts format. Further specific comments will be made during the review.*
- *The summary of the label comprehension study provided in this pre-NDA submission is sparse and does not provide substantive information about how well the label was understood.*

Sponsor Question 14:

Will FDA accept and approve a 505 (b)(2) NDA submission for FS 67 topical patches?

FDA Response to Question 14:

- *The FDA will accept a 505(b)(2) application. Fileability will be determined at the 45-day fileability meeting.*
- *Approval is a review issue.*

Sponsor Question 15:

Does FDA agree with the submission of this NDA in paper format only?

FDA Response to Question 15:

- *Please refer to the following email address for information in reference to electronic submissions:* ESUB@CDER.fda.gov
- *The FDA prefers both the paper copy and the electronic version of the full reports for the non-clinical studies that have not previously been submitted with the IND. However, the paper format will be acceptable for those studies that had been submitted previously during IND stage. In addition, the FDA prefers the electronic version of the integrated summary as well as the individual study summaries for all non-clinical studies. The format should be according to the Guidance for Industry "Providing Regulatory Submissions on Electronic Format – NDAs."*

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CMC SPECIFIC QUESTIONS

I. Active Pharmaceutical Ingredients

Sponsor Question 1:

The USP monograph accepts both dl and l-Menthol. The tentative final OTC monograph for external analgesics does not distinguish between the acceptable isomeric forms. Would the agency agree that testing for the d-isomer content is not necessary based on its acceptance in both the USP and the OTC monographs?

FDA Response to Question 1:

It is agreed that testing for the d-isomer is not necessary. However, the drug substance should meet the requirement for l-menthol specified in the USP.

Sponsor Question 2:

Does the agency agree that the proposed specifications for release of methyl salicylate and l-Menthol are acceptable?

FDA Response to Question 2:

The proposed specifications for release of methyl salicylate and l-menthol appear adequate for review.

II. Excipients

Sponsor Question 3:

Does the agency agree that the proposed specifications for the non-compendial inactive ingredients are acceptable?

FDA Response to Question 3:

The proposed specifications for non-compendial inactive ingredients appear adequate for review. However, an inactive ingredient that has never been used in a US drug product would be considered as a "novel excipient."

Sponsor Question 4:

The backing cloth used in FS-67 drug product contains that have not previously been used in US marketed drug products. Hisamitsu has conducted preclinical toxicological studies of FS-67 drug product which used this backing cloth. The studies are described in the preclinical section of this pre-NDA briefing document. In addition, Hisamitsu has conducted a

b(4)

dissolution study that extracts with physiological saline and measures the contents. This information is included in the CIVIC portion of the pre-NDA section. Does the agency agree that the backing cloth is appropriate for use in FS-67 without additional studies? b(4)

FDA Response to Question 4:

The will be treated as novel excipients. Please include references to the appropriate DMFs, if applicable, or include information on the chemical names, chemical structure, etc. The safety of the contained in the backing cloth will be evaluated by the PharmTox reviewer. b(4)

III. Drug Product

Sponsor Question 5:

Hisamitsu has conducted microbial limits testing per USP chapter <61 > on new and aged samples of FS-67. No growth was found in any of the lots. A table summarizing the lots tested is included in the pre-NDA package. Full details of the study will be included in the NDA. Does the agency agree that microbial limit testing is not needed?

FDA Response to Question 5:

Deletion of the test based on results on a number of lots is insufficient justification. A scientific justification is also needed. You should provide data to demonstrate that water activity remains low throughout the manufacturing process and in the drug product.

Sponsor Question 6:

A common way to measure adhesive forces is using the ASTM probe tack test. This test is not appropriate for FS-67 due to the elasticity of the backing cloth. Alternatively, Hisamitsu plans to use the Steel Rolling ball test. A description of the test is included in the pre-NDA package. Does the agency agree that the Steel Rolling Ball test is acceptable test to measure adhesive forces?

FDA Response to Question 6:

The adhesion testing using the rolling ball test should be monitored during drug product release and stability. Moreover, in vivo adhesion tests should also be conducted.

Sponsor Question 7:

Measurement of peel forces is suggested for transdermal patches in the FDA draft stability guidance. The peel force test is designed for nonexpandable backing films. The backing cloth for FS-67 is elastic, therefore results are not conclusive. Does the agency agree that peel force testing is not appropriate for this product?

FDA Response to Question 7:

Please note that the peel force test is intended to measure the force needed to remove the release liner from the product. A revised release liner peel force study should be proposed and employed at batch release and during the stability studies.

Sponsor Question 8:

Hisamitsu plans to test for related substances in the drug product on stability only. During forced degradation studies, Hisamitsu notes that l-Menthol vaporizes rather than degrades when exposed to heat and no degradation of l-Menthol was found when exposed to acid, base, or light. Methyl Salicylate hydrolyzes when exposed to base and acid. If stability data show that the levels remain below , does the agency agree that related substance monitoring is appropriate for stability only and is unnecessary for drug product release? b(4)

FDA Response to Question 8:

Testing for impurities in the drug product should be included as one of the release and stability tests. Adequacy of the method to detect and quantitate impurities (degradants) should be demonstrated.

Sponsor Question 9:

Dissolution is listed as a suggested test for transdermal patches in the FDA draft Stability Guidance. As FS-67 is a patch that is intended to be delivered topically rather than systemically, Hisamitsu does not plan to perform the dissolution test for release or stability. Does the agency agree that dissolution is not needed?

FDA Response to Question 9:

The Agency agrees that the dissolution test is not required for release or stability. However, the sponsor should provide data on in vitro release testing using a method analogous to that described in the Guidance for Industry entitled, " Nonsterile Semisolid Dosage Forms Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation." Data obtained using human skin from living donors or cadavers would be preferable to synthetic membranes.

Sponsor Question 10:

The proposed commercial formulation for FS-67 contains a manufacturing overage. Hisamitsu has three lots made with overage on stability and will have 3 months of stability data available at the time of submission. In addition, Hisamitsu will submit 12 months b(4)

long term and 6 months accelerated data on three lots made at the commercial scale with a overage. Does the agency agree that the three lots made with a overage can be used to satisfy the primary stability batch data requirement? b(4)

FDA Response to Question 10:

The three lots made with a overage can be used to satisfy the primary stability batch data requirement. b(4)

Sponsor Question 11:

Does the agency agree that the specifications for release of FS-67 drug product are acceptable?

FDA Response to Question 11:

Appearance including dimensions, impurities (degradants) per ICH Q3B, adhesion to a substrate, release liner peel, and pouch integrity should be included in your drug product specification.

IV. Executed Batch Records

Sponsor Question 12:

In the executed batch record section of this pre-NDA package, Hisamitsu presents a table describing the lots used in the pharmacokinetic studies and the primary stability batches. There are six lots total. Three were used in the clinical studies and were made at the commercial scale with a overage. The other three are made at the commercial scale with the proposed formulation of a overage. Hisamitsu proposes to submit one executed batch record from each group. Is this proposal acceptable to the agency? b(4)

FDA Response to Question 12:

You may submit only one executed batch record, preferably a batch record from one of the primary stability batches.

Addendum to CMC specific meeting minutes:

We have consulted our Transdermal System expert, and have the following additional comments:

- ***Pouch Integrity Test:***

  The ink test as Dr. John Smith suggested is fine. Another suitable test would be measurement of tensile strength.

  It should be included either as a test (and acceptance criterion) in the drug product release or as an in-process control.

- ***Peel Force:***

  The Rolling Ball test can not be used as a substitute for the peel force test. This test is designed in the initial development stage to assure that peeling of the release liner does not present a problem. Pharmaceutical Development Group (Hasamitsu) is encouraged to develop an alternate method, if possible. These data from the peel force test should be provided in the NDA. If the range is wide, FDA will make a decision whether the range of the test is acceptable.

Minutes Preparer: Jane A. Dean, RN, MSN

Chair Concurrence: Dr. James Witter

Drafted by: J. A. Dean
Initialed by:
Final: 8/7/02

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/s/

Lee Simon
8/8/02 03:20:36 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-029 Supplement # n/a Efficacy Supplement Type SE- n/a

Proprietary Name: Salonpas
Established Name: 10% methyl salicylate & 3% *l*-menthol (FS-67 Topical Patch)
Strengths: 10% methyl salicylate & 3% *l*-menthol

Applicant: Hisamitsu Pharmaceutical Co., Inc
Agent for Applicant (if applicable): Pharmaceutical Development Group, Inc. (Cheryl D. Blume, Ph.D.)

Date of Application: February 27, 2006
Date of Receipt: February 27, 2006
Date clock started after UN: n/a
Date of Filing Meeting: April 20, 2006
Filing Date: April 28, 2006
Action Goal Date (optional): n/a User Fee Goal Date: December 27, 2006

Indication(s) requested: Temporary relief of mild to moderate aches and pains of muscle and joints associated with arthritis, simple backache, strains, bruises, and sprains.

Type of Original NDA:	(b)(1) ☐	(b)(2) ☒
AND (if applicable)		
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 or efficacy supplement is a (b)(2), complete Appendix B.

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

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

User Fee Status: Paid ☒ 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 by contacting the User Fee staff in the Office of Regulatory Policy. 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 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. 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 any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain: n/a

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  n/a 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 ☒
  If yes, explain: n/a

- If yes, has OC/DMPQ been notified of the submission? n/a YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain: n/a

- 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:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☒
   This application is: All electronic ☐ Combined paper + eNDA ☒
   This application is in: NDA format ☒ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?
   Statistical information and labeling

   Additional comments: n/a

3. This application is an eCTD NDA. YES ☐
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: n/a

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 5 Years NO ☐
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

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

NOTE: *Debarment Certification 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 . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

  Note: The original submission contains a request for a full waiver of pediatric studies and the certification required under FD&C Act section 505B(a)(4)(A). During the second cycle, the Division informed the Sponsor that a full waiver would not likely be granted. In response, the Sponsor submitted a request for a partial waiver and a deferral of the remaining pediatric studies, including the information required under FD&C Act section 505B(a)(3)(B)(i) and (ii). The Sponsor did not submit evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time (as required under FD&C Act section 505B(a)(3)(B)(iii)), however, the Sponsor did submit a pediatric plan describing its intention to conduct the studies.

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 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) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ 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? YES ☒ NO ☐
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: 62,735

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) July 9, 2002 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? n/a YES ☐ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? n/a YES ☐ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: n/a

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? n/a YES ☐ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? n/a YES ☐ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☒ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☒ NO ☐

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? n/a YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? n/a YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team? n/a YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 20, 2006

NDA #: 20-029

DRUG NAMES: Salonpas topical patch

APPLICANT: Hisamitsu Pharmaceutical Co., Inc.

BACKGROUND: This application is for Salonpas (10% methyl salicyclate & 3% *l*-menthol) topical patch for the indication of the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backaches, strains, bruises and sprains. This is a 505(b)(2) application. The Division of Nonprescription Clinical Evaluation and the Division of Anesthesia, Analgesics, and Rheumatology Products are reviewing this application and the Deputy Division Directors for both divisions will be the signatory authorities for this application under the current MaPP. The FDA met with the Sponsor for a PreNDA meeting on July 9, 2002.

ATTENDEES: see below

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Joe Porres - safety
Secondary Medical:	Christina Fang - efficacy
Statistical:	Yongman Kim
Pharmacology:	Maria Rivera, then BeLinda Hayes
Statistical Pharmacology:	
Chemistry:	Terrance Ocheltree
Environmental Assessment (if needed):	n/a
Biopharmaceutical:	Lei K. Zhang
Microbiology, sterility:	n/a
Microbiology, clinical (for antimicrobial products only):	n/a
DSI:	
Regulatory Project Management:	Keith Olin
IDS	Reynold Tan

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain: n/a

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain: n/a
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization?
  n/a YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: n/a

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

☐ The application is unsuitable for filing. Explain why:

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

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

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

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

3. ☐ 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.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Keith Olin
Regulatory Project Manager

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Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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

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

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): n/a

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☒

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☒

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval 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 ☒

   (***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**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? n/a YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? n/a YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.* n/a

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s): n/a

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☒

(***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**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? n/a YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? n/a YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

***NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s): n/a

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☒ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

No

8. 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").

n/a

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

10. Is the application for a duplicate of a listed drug whose only difference is that 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)? YES ☐ NO ☒

(See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)).

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) n/a YES ☐ NO ☐

13. 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.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s): n/a

☐ 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)]. OND will contact you to verify that this documentation was received.*

☐ 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):

☐ 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):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☒

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug* :

n/a (The application relies on published literature to support the Pharm/Tox section of the application; however, the referenced literature does not cite brand name drugs.)

Was this listed drug product(s) referenced by the applicant? (see question # 2)

n/a YES ☐ NO ☐

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

N/A ☒ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

n/a YES ☐ NO ☐

If "**Yes**," please list: n/a

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Geraldine Smith
1/24/2008 02:44:07 PM
CSO

ACTION PACKAGE CHECKLIST

Application Information			
BLA # n/a NDA # 22-029	BLA STN# n/a NDA Supplement # n/a	If NDA, Efficacy Supplement Type n/a	
Proprietary Name: SALONPAS Pain Relief Patch Established Name: 10% methyl salicylate & 3% *l*-menthol Dosage Form: topical patch		Applicant: Hisamitsu Pharmaceutical Co., Inc.	
		Division: 560	Phone # 301-796-2204

NDAs: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): n/a Provide a brief explanation of how this product is different from the listed drug. n/a ☒ If no listed drug, check here and explain: The sponsor relies on published literature to support the safety of the active ingredients in this drug. **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☒ Corrected Date: 24-Jan-08

❖ User Fee Goal Date ❖ Action Goal Date (if different)	20-Feb-08 n/a
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AE 27-Dec-06
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 3, 4

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☒ OTC drug

Other: n/a

Other comments: n/a

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)* n/a	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)* n/a	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other n/a

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic 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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-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 ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: 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 ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric 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 ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. Note: Form FDA 3542a was submitted; however, the sponsor indicates in Section 5 of the form that there are no patents relevant to this application.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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. Note: The applicant submitted a Paragraph I patent certification even though the NDA does not rely on the previous approval of any product. In the certification, the applicant did not indicate the products for which the certification was provided.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☒ No paragraph III certification Date patent will expire
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

• [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. Answer the following questions for **each** paragraph IV certification:	n/a
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (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))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	☐ Yes ☐ No
(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)? *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 section below (*Summary Reviews*).* *If "**No**," continue with question (3).*	☐ Yes ☐ No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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.*	☐ Yes ☐ No
(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)? *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 section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	☐ Yes ☐ No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) 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 (b)(2) 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 section below (*Summary Reviews*).* *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.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	Review Cycle 1: Deputy Director ONP: 27-Dec-06 Deputy Director DAARP: 27-Dec-07 Review Cycle 2: Deputy Director ONP: 20-Feb-08, 21-Feb-08 (regarding 20-Feb-08 DMETS review) Deputy Director DAARP: 20-Feb-08
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	n/a
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	n/a
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	n/a
• Original applicant-proposed labeling	n/a
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	n/a
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	n/a
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	n/a
• Original applicant-proposed labeling	n/a
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	n/a
❖ Medication Guide	

• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	n/a
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	n/a
• Original applicant-proposed labeling	n/a
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	n/a
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	n/a
• Most recent applicant-proposed labeling	Salonpas Pain Relief Patch: 20-Feb-08 Salonpas Arthritis Pain: 15-Feb-08
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 19-Oct-06, 20-Feb-08 ☐ DSRCS ☐ DDMAC ☐ SEALD ☒ Other reviews: ONP Labeling Review Cycle 1: 19-Dec-06 Review Cycle 2: 10-Jan-08, 14-Feb-08, 20-Feb-08 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	Filing Reviews: RPM: 24-Jan-08 ONP Clinical: 8-May-06 Pharm/Tox: 5-May-06 Clin/Pharm: 3-May-06 CMC: 27-Apr-06
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions) Note: included for Cycle 2 only	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	Memorandum of 07-Jan-08 teleconference (located in the "Memos to the File/Memos of Telecons" section), 07-Jan-08 email to sponsor (located in the "Outgoing Correspondence" section), and documented in the 20-Feb-08 Approval letter
• Incoming submission documenting commitment	Pediatric Plan submitted 13-Feb-08
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Review Cycle 1: 74-day letter: 11-May-06

	CMC IR letters: 22-Aug-06; 26-Sep-06 Review Cycle 2: Resubmission acknowledgement letter: 22-Oct-06 Clinical IR email: 21-Dec-07 Pediatric IR emails: 07-Jan-08, 11-Feb-08 Administrative IR emails: 09-Jan-08; 11-Jan-08
❖ Internal memoranda, telecons, email, etc.	Review Cycle 1: n/a Review Cycle 2: 16-Jan-08; 29-Jan-08
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	n/a
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 09-Jul-02
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	n/a
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	n/a
• 48-hour alert or minutes, if available	n/a
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	n/a
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	Review Cycle 1: 16-Nov-06, amended 20-Dec-06 Review Cycle 2: 3-Jan-08
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No n/a
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Review Cycle 1: 16-Nov-06 (part of CMC review) Review Cycle 2: n/a
• ☐ Review & FONSI *(indicate date of review)*	n/a
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	n/a
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	

❖ NDAs: Facilities inspections (include EER printout)	Review Cycle 1: Dates completed: 16-Nov-06; 24-Nov-06; 30-Nov-06 ☒ Acceptable ☐ Withhold recommendation Review Cycle 2: n/a
❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	n/a ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Review Cycle 1: 13-Dec-06 (includes IND review) Review Cycle 2: n/a
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	n/a
❖ Nonclinical inspection review Summary (DSI)	☒ None requested

Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	Review Cycle 1: ONP: 20-Nov-06 DAARP: 27-Nov-06 Review Cycle 2: ONP: 10-Jan-08 DAARP: 03-Jan-08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	10-Jan-08 (in clinical review)
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	Review Cycle 1: ☐ None 13-Dec-06 Division of Dermatologic and Dental Drug Products Review Cycle 2: n/a
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	Review Cycle 1: 20-Nov-06 (in clinical review) Review Cycle 2: 10-Jan-08 (in clinical review)
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	n/a
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	Review Cycle 1: 17-Nov-06; 01-Dec-06; 08-Dec-06 Review Cycle 2: n/a
• Bioequivalence Studies	n/a
• Clin Pharm Studies	n/a
❖ Statistical Review(s) *(indicate date for each review)*	☐ None Review Cycle 1: 27-Oct-06 Review Cycle 2: 02-Jan-08
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Review Cycle 1: 21-Nov-06 Review Cycle 2: 08-Jan-08

Appendix A to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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

/s/

Geraldine Smith
2/26/2008 03:32:06 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See Instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

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

HISAMITSU PHARMACEUTICAL CO INC
Yoshinobu Higashi
300 Campus Drive Suite 220
Florham Park NJ 07932
US

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

22-029

2. TELEPHONE NUMBER
973-765-0122

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

b(4)

3. PRODUCT NAME
SALONPAS (proposed) (10% Methyl Salicylate and 3% Menthol Topical Patch)

6. USER FEE I.D. NUMBER
PD3006430

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

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

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

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

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

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

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Yoshinobu Higashi	MANAGER	FEB 9, 2006

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)