CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-029

CHEMISTRY REVIEW(S)

NDA 22-029
CMC Review #2

FS-67 Topical Patch

Hisamitsu Pharmaceutical Co., Inc.

Terrance Ocheltree, Ph.D.

DIVISION OF NONPRESCRIPTION CLINICAL EVALUATION

Review of Chemistry, Manufacturing, and Controls

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b(4)

Chemistry Review Data Sheet

1. NDA 22-029

2. REVIEW #: 2

3. REVIEW DATE: 04-Jan-2008

4. REVIEWER: Terrance Ocheltree, R.Ph., Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 62-735	12-Jun-2001
CMC Review #1	14-Nov-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	27-Feb-2006
Amendment	12-Sep-2006
Amendment	12-Oct-2006
Amendment	25-Jul-2007
Amendment	17-Aug-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Hisamitsu Pharmaceutical Co., Inc.
Address:	Tashiro Daikan-machi 408, Soga Tosu, Japan 841-0017
Representative:	Cheryl Blume, Ph.D. President, Pharmaceutical Development Group 13902 North Dale Mabrey Highway, Suite 122 Tampa, FL 33618
Telephone:	(813) 963-3062

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Salonpas [redacted] b(4)

b) Non-Proprietary Name (USAN): 10% Methyl Salicylate & 3% *l*-Menthol Topical Patch

c) Code Name/#: N/A

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3, 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: OTC Analgesic
Temporary relief of mild to moderate aches and pains of muscles and joints associated with: arthritis, simple backache, strain, bruises, and sprains.

11. DOSAGE FORM: Topical Patch

12. STRENGTH/POTENCY: 10% Methyl Salicylate & 3% *l*-Menthol per system

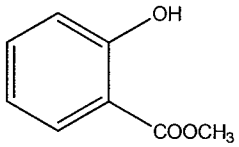
13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _____Rx __X__OTC

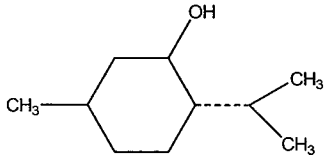
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Drug Substance 1:
Chemical Name: 2-Hydroxybenzoic acid methyl ester
USAN Name: Methyl Salicylate
Chemical Formula: $C_8H_8O_3$
Molecular Weight: 152.15
CAS Registry #: 119-36-8
Structure:



Drug Substance 2:
Chemical Name: 5-Methyl-2-(1-methylethyl)-cyclohexanol
USAN Name: *l*-Menthol
Chemical Formula: $C_{10}H_{20}O$
Molecular Weight: 156.27
CAS Registry #: 2216-51-5
Structure:



17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

Chemistry Assessment Section

b(4)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	14-Nov-2006	Terrance Ocheltree
	II			1	Adequate	14-Nov-2006	Terrance Ocheltree
	III			1	Adequate	14-Nov-2006	Terrance Ocheltree
	III			1	Adequate	14-Nov-2006	Terrance Ocheltree
	III			1	Adequate	14-Nov-2006	Sharmista Chatterjee
	IV			1	Adequate	14-Nov-2006	Sharmista Chatterjee
	IV			1	Adequate	14-Nov-2006	Sharmista Chatterjee
	IV			1	Adequate	14-Nov-2006	Sharmista Chatterjee

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62,735	Hisamitsu's IND for FS-67 Topical Patch

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	18-Dec-2006	Lloyd Payne
Pharm/Tox	Approvable	13-Dec-2006	Belinda Hayes
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMETS	N/A		
EA	Categorical exclusion claimed by applicant is acceptable	16-Nov-2006	Terrance Ocheltree
Microbiology	N/A		

The Chemistry Review for NDA 22-029

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the application is recommended for "**Approval**". The Office of Compliance has made an overall recommendation of "Acceptable" for the two drug substances and the drug product manufacturing sites based on inspection. Hisamitsu agreed to revise the label

b(4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Product

The drug product, FS-67 Topical Patch, is a non-sterile patch developed for topical application in the relief of minor aches and pains. The patch is designed to topically deliver the drug substances for local affect as opposed to typical transdermal patches that provide systemic delivery. Each patch consists of a adhesive mass containing the two drug substances and associated excipients backing cloth b(4)
. It is supplied as a 7.1 cm x 10 cm rectangular patch, containing methyl salicylate and *l*-menthol and is packaged 5 (market presentation) patches per pouch in sealed pouches.

The patch is described by the applicant as containing two drug substances, methyl salicylate and *l*-menthol, and excipients. The excipients are the backing styrene-isoprene-styrene block copolymer (SIS), polyisobutylene 1,200,00 NF and polyisobutylene NF (PIB), mineral oil, USP, synthetic aluminum silicate, and alicyclic saturated hydrocarbon resin (ASH) SIS, ASH, and the backing cloth are novel excipients. b(4)
Toxicology studies have been conducted by either the applicant or the DMF Holder to support their safe uses in the proposed drug product. Based on a review dated December 13, 2006, the Pharmacology/Toxicology Reviewer considers NDA 22-029 approvable. References are made to DMFs for all non-USP/NF compendial excipients including the backing cloth and the film. DMF references are not provided for the two PIBs, the mineral oil, since these are readily commercially available in USP/NF grades.

b(4)

The manufacturing process requires a significant overage of the two active ingredients due to The actual amount of drug substance lost during manufacturing was related to batch size. Therefore, the to-be-marketed formulation is the same formulation, as b(4) that used in the clinical studies and registration stability batches except for the amount of drug overages used to assure 100% potency. The batch size of the clinical and registration stability lots is which is of the proposed commercial batch size .

The applicant proposes an expiry period of 36 months for the market presentation stored at 25°C with excursions permitted to 15-30°C. Stability data provided in the original NDA submission to support the expiry period include 42 months at 25°C/60% RH and 6 months at 40°C/75% RH for 3 pilot scale lots packaged as 7 patches per pouch and 3 months at 25°C/60% RH and 40°C/75% RH for three additional pilot-scale batches packaged in the b(4) commercial presentation, 5 patches per pouch. No significant changes in assay or related substances have been observed for either packaging configuration, and the stability data is similar for both configurations (5 patches per pouch versus 7 patches per pouch). Therefore, the proposed 36 month expiration date is acceptable. The applicant also provided in-use stability study results to support a use period for opened pouches

The applicant acknowledged the receipt of the preliminary responses from the FDA on February 7, 2006, and agreed with FDA's request to b(4) revise the label to state the patch should be discarded after 14 days. .

2. Drug Substances

The applicant references DMFs for the two drug substances, methyl salicylate NF and *l*-menthol USP, respectively. The DMFs were prepared by the respective b(4) DMF Holders specifically for the development of this product and therefore have not been reviewed prior to this review. Initially both DMFs were found to be inadequate to support this NDA and information request letters were sent to the respective holders. Satisfactory responses were received for each of the DMFs. The DMFs are now adequate to support this NDA.

The NDA applicant, Hisamitsu, provided adequate characterization of both methyl salicylate and *l*-menthol to confirm the drug substance structures. Hisamitsu performs full acceptance testing for both drug substances including all compendial test for methyl salicylate and menthol, plus additional testing (where applicable) for assay, purity and related substances to assure the quality of the incoming drug substances. All drug substances must meet USP/NF

monograph specifications and additional acceptance criteria before use in the manufacturing of the drug product. The applicant retests the drug substances [redacted].

B. Description of How the Drug Product is Intended to be Used

FS-67 is applied to the skin by removing the [redacted] film and placing the adhesive mass in contact with the site being treated. The cloth backing is left on the adhesive mass as a protective outer layer. Once applied the patches are removed by peeling off the skin. The applicant proposes that: the patches can be left in place for [redacted] hours; only one patch be used at time per affected area; no more than two patches used per day; and the patches are not to be used for more than three consecutive days. However, actual intended use has not been determined by the medical review team. b(4)

The proposed packaging for the commercial product consists of five patches per pouch. This choice was selected by the applicant to be consistent with the directions for use and observed use during clinical studies. The applicant states that the number of patches per container is suitable for use within a short period, and is reasonable to allow full consumptions of the patches in a single pouch in the [redacted] time [redacted] designated for use after initial opening. b(4)

[redacted]

C. Basis for Approvability or Not-Approval Recommendation

The original application and subsequent amendments contain adequate information regarding the quality of the drug substance and the drug product. During the initial review period several minor issues, including the following, were resolved.

The drug substance specifications for both *l*-menthol and methyl salicylate were revised to include Appearance based on USP/NF descriptions.

The applicant committed to evaluating the percent of drug substance overages used in the manufacturing of the drug product, adjust them as necessary during the commercial validation campaign, and submitting a report of this within six months of approval.

The applicant committed to continue developing a dissolution method and submitting a final report, including method and results, within six months of approval.

The drug product specifications were revised to include a pouch integrity test according to ASTM F1140. The stability protocol was also revised to include this test at 12, 24 and 36 months.

The following issues were not resolved at the time of the first review, but have since been resolved:

GMP status recommendation by the Office of Compliance was entered into EES as "Acceptable" for the two drug substances and the drug product sites on December 18, 2006.

The Pharmacology/Toxicology review of the [redacted] novel excipients [redacted] was completed on December 13, 2006 with the recommendation of approvable. b(4)

The applicant [redacted] agreed on February 8, 2007 to revise the label to state the patch should be discarded after 14 days after the pouch is opened. b(4)

The NDA is recommended as "Approval" from a CMC perspective.

III. Administrative

A. Reviewer's Signature
DFS

B. Endorsement Block
Chemist Name/Date: Terrance Ocheltree/04-Jan-2008
Chemistry Team Leader Name/Date
Project Manager Name/Date

C. CC Block
Terrance Ocheltree
Moo-Jhong Rhee
Linda Athey
Geraldine Smith

3 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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

/s/

Terrance Ocheltree
1/3/2008 03:14:40 PM
CHEMIST

Moo-Jhong Rhee
1/3/2008 03:47:52 PM
CHEMIST
Chief, Branch III

12/20/06

Memorandum

Date: December 20, 2006

To: NDA 22-029,
Chemistry Review #1

From: Terrance Ocheltree, Ph.D.
CMC Reviewer, ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch III

Subject: Final Recommendations from the Office of Compliance and Pharm/Tox Review

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The purpose of this amendment to CMC Review #1 is to update the GMP status of the drug substances and drug product manufacturing sites and the status of the Pharm/Tox consult. The manufacturing sites were found to be Acceptable by the Office of Compliance following Pre-Approval Inspections (see Attachment 1). Pharm/Tox recommended approval of the drug product with no unresolved toxicology issues related to the drug product and novel excipients (please see PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION, dated 13-Dec-2006, for further information).

Based on this memorandum, Sections S.2.1 for the drug substances (methyl salicylate and *l*-menthol) and P.3.1 for the drug product of the Review #1 shall be revised as follows:

S.2.1 Manufacturers

The following vendor manufactures the methyl salicylate, NF for the applicant.

[redacted] b(4)

Evaluation:

All manufacturing operations and testing, including stability studies, for methyl salicylate are conducted at this facility. A Pre-Approval Inspection of drug substance manufacturing/testing site was performed 16-Nov-2006. Final recommendation for this manufacturing/testing site is "ACCEPTABLE" based on inspection (Attachment 1).

S.2.1 Manufacturers

The following vendor manufactures the *l*-menthol, NF for the applicant.

[redacted] b(4)

Evaluation:
All manufacturing operations and testing, including stability studies, for *l*-menthol are conducted at this facility. A Pre-Approval Inspection of drug substance manufacturing/testing site was performed 24-Nov-2006. Final recommendation for this manufacturing/testing site is "ACCEPTABLE" based on inspection (Attachment 1).

P.3.1 Manufacturers

Hisamitsu Pharmaceutical Co., Inc.
Tashirodaikan-machi, 408
Tosu, Saga
Japan 841-0017
(FDA Registration Number: 1000266995)

This site is responsible for the manufacturing, packaging, labeling, and drug product testing (release and stability)

Evaluation:
All manufacturing operations and testing, including stability studies, for the drug product are conducted at this facility. A Pre-Approval Inspection of drug product manufacturing/testing site was performed 30-Nov-2006. Final recommendation for this manufacturing/testing site is "ACCEPTABLE" based on inspection (Attachment 1).

Conclusion and Recommendation:
From the chemistry, manufacturing and controls standpoint, the NDA is still **approvable** pending resolution of the labeling issue to include a statement to "Discard patches 14 days after opening pouch" or similarly approved verbiage.

Attachment 1.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22029/000
Org Code : 563
Priority : 3&S

Stamp Date : 27-FEB-2006
PDUFA Date : 27-DEC-2006
Action Goal :
District Goal: 28-OCT-2006

Sponsor: HISAMITSU PHARM
HO CITY, , XX

Brand Name : SALONPAS POWER PLUS(METHYL SALICYLATE/MN
Recab. Name:
Generic Name: 10 % METHYL SALICYLATE & 3 % MENTHOL
Dosage Form: ITRANSDERMAL SYSTEM)
Strength : 10%

FDA Contacts:	L. MULLINS ATHEY	Project Manager (HFD-830)		301-796-2096
	T. OCHELTREE	Review Chemist (CDER-830)		301-796-1698
	S. DING	Team Leader		301-796-1343

Overall Recommendation: ACCEPTABLE on 18-DEC-2006by S. ADAMS (CDER-338) 301-827-9151

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

DMF No: [redacted] ANDA:

b(4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN DAI Status: [redacted]
IMMC Milestone: OC RECOMMENDATION
Milestone Date: 18-DEC-06
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
HISAMITSU PHARMACEUTICAL CO INC
TASHIROQUAINAI-MACHI 408
TOSU, SAGA, , JA 841-0017

DMF No: ANDA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : SNC CMS Status: MONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-DEC-06
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

b(4)

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

/s/

Terrance Ocheltree
12/20/2006 11:08:42 AM
CHEMIST

Moo-Jhong Rhee
12/20/2006 11:29:10 AM
CHEMIST
Chief, Branch III

NDA 22-029

FS-67 Topical Patch

Hisamitsu Pharmaceutical Co., Inc.

Terrance Ocheltree, Ph.D.

DIVISION OF NONPRESCRIPTION CLINICAL EVALUATION

Review of Chemistry, Manufacturing, and Controls

Table of Contents

b(4)

Chemistry Review Data Sheet

1. NDA 22-029

2. REVIEW #: 1

3. REVIEW DATE: 14-Nov-2006

4. REVIEWER: Terrance Ocheltree, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 62-735	12-Jun-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	27-Feb-2006
Amendment	12-Sep-2006
Amendment	12-Oct-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Hisamitsu Pharmaceutical Co., Inc.
Address:	Tashiro Daikan-machi 408, Soga Tosu, Japan 841-0017
Representative:	Cheryl Blume, Ph.D. President, Pharmaceutical Development Group 13902 North Dale Mabrey Highway, Suite 122 Tampa, FL 33618
Telephone:	(813) 963-3062

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Salonpas [redacted], b(4)

b) Non-Proprietary Name (USAN): 10% Methyl Salicylate & 3% *l*-Menthol Topical Patch

c) Code Name/#: N/A

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3, 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: OTC Analgesic

Temporarily relieves mild to moderate aches and pains of muscles and joints associated with: arthritis, simple backache, strain, bruises, and sprains.

11. DOSAGE FORM: Topical Patch

12. STRENGTH/POTENCY: 10% Methyl Salicylate & 3% *l*-Menthol per system

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: ____Rx __**X**__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Drug Substance 1:

Chemical Name: 2-Hydroxybenzoic acid methyl ester

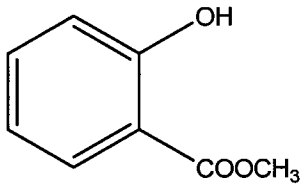
USAN Name: Methyl Salicylate

Chemical Formula: $C_8H_8O_3$

Molecular Weight: 152.15

CAS Registry #: 119-36-8

Structure:



Drug Substance 2:

Chemical Name: 5-Methyl-2-(1-methylethyl)-cyclohexanol

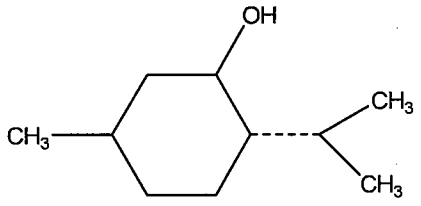
USAN Name: *l*-Menthol

Chemical Formula: $C_{10}H_{20}O$

Molecular Weight: 156.27

CAS Registry #: 2216-51-5

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

b(4)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	14-Nov-2006	Terrance Ocheltree
	II			1	Adequate	14-Nov-2006	Terrance Ocheltree
	III			1	Adequate	14-Nov-2006	Terrance Ocheltree
	III			1	Adequate	14-Nov-2006	Terrance Ocheltree
	III			1	Adequate	14-Nov-2006	Sharmista Chatterjee
	IV			1	Adequate	14-Nov-2006	Sharmista Chatterjee
	IV			1	Adequate	14-Nov-2006	Sharmista Chatterjee
	IV			1	Adequate	14-Nov-2006	Sharmista Chatterjee

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62,735	Hisamitsu's IND for FS-67 Topical Patch

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	16-Nov-2006	
Pharm/Tox	*	16-Nov-2006	
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMETS			
EA	Categorical exclusion claimed by applicant is acceptable	16-Nov-2006	Terrance Ocheltree
Microbiology	N/A		

* Pharm/Tox is still finalizing their review of the three novel excipients [redacted]. Since (1) the novel excipients do not impact the quality or performance of the drug product, (2) the quality of each excipient and the drug product are assured through release testing, and (3) all impurities, [redacted] in the finished drug product are limited to not more than [redacted] the excipients are acceptable from the CMC perspective.

b(4)

The Chemistry Review for NDA 22-029

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the application is **approvable** pending: satisfactory recommendation of GMP status by the Office of Compliance for the two drug substances and the drug product manufacturing sites and resolution of Labeling to include a statement to "Discard patches 14 days after opening pouch" or similarly approved verbiage.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has agreed to evaluate the process overages during the validation campaign for commercial scale production. They will make appropriate adjustments in the percent overage of drug substances as necessary during this campaign. An additional five lots will be monitored for further adjustments. A report of this work will be submitted to the FDA within six months of the NDA approval date.

The applicant is developing a dissolution method in place of the originally proposed *in vitro* release method. The final method and supporting data will be provided to the FDA within six months of the NDA approval date.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Product

The drug product, FS-67 Topical Patch, is a non-sterile patch developed for topical application in the relief of minor aches and pains. The patch is designed to topically deliver the drug substances for local affect as opposed to typical transdermal patches that provide systemic delivery. Each patch consists of a adhesive mass containing the two drug substances and associated excipients backing cloth . It is supplied as a 7.1 cm x 10 cm rectangular patch, containing — methyl salicylate and — *l*-menthol and is packaged either 5 (market presentation) patches per pouch . polyethylene, aluminum foil, polyethylene) heat sealed pouches.

b(4)

The patch is described by the applicant as containing two drug substances, methyl salicylate and *l*-menthol, and nine excipients. The excipients are the backing, [redacted] styrene-isoprene-styrene block copolymer (SIS), polyisobutylene 1,200,00 NF and polyisobutylene NF (PIB), mineral oil, USP, synthetic aluminum silicate, and alicyclic saturated hydrocarbon resin (ASH) [redacted]. SIS, ASH, and the backing cloth are novel excipients. Toxicology studies have been conducted by either the applicant or the DMF Holder to support their safe uses in the proposed drug product. References are made to DMFs for all non-USP/NF compendial excipients including the backing cloth and the [redacted] film. DMF references are not provided for the two PIBs, the mineral oil, [redacted] since these are readily commercially available in USP/NF grades. b(4)

[redacted] b(4)

The manufacturing process requires a significant overage of the two active ingredients due to [redacted]. The actual amount of drug substance lost during manufacturing was related to batch size. Therefore, the to-be-marketed formulation is the same formulation, as that used in the clinical studies and registration stability batches except for the amount of drug overages used to assure 100% potency. The batch size of the clinical and registration stability lots is [redacted] which is [redacted] of the proposed commercial batch size [redacted] b(4)

The applicant proposes an expiry period of 36 months for the market presentation stored at 25°C with excursions permitted to 15-30°C. Stability data provided in the original NDA submission to support the expiry period include 42 months at 25°C/60% RH and 6 months at 40°C/75% RH for 3 pilot scale [redacted] lots packaged as 7 patches per pouch and 3 months at 25°C/60% RH and 40°C/75% RH for three additional pilot-scale batches packaged in the commercial presentation, 5 patches per pouch. No significant changes in assay or related substances have been observed for either packaging configuration, and the stability data is similar for both configurations (5 patches per pouch versus 7 patches per pouch). Therefore, the proposed 36 month expiration date is acceptable. The applicant also provided b(4)

opened pouches [redacted] Therefore, the applicant has been requested to label the product to state that it should be discarded 14 days after opening.

2. Drug Substances

The applicant references DMFs [redacted] for the two drug substances, methyl salicylate NF and *l*-menthol USP, respectively. The DMFs were prepared by the respective b(4)

DMF Holders specifically for the development of this product and therefore have not been reviewed prior to this review. Initially both DMFs were found to be inadequate to support this NDA and information request letters were sent to the respective holders. Satisfactory responses have been received for each of the DMFs. The DMFs are now adequate to support this NDA.

The NDA applicant, Hisamitsu, provided adequate characterization of both methyl salicylate and *l*-menthol to confirm the drug substance structures. Hisamitsu performs full acceptance testing for both drug substances including all compendial test for methyl salicylate and menthol, plus additional testing (where applicable) for assay, purity and related substances to assure the quality of the incoming drug substances. All drug substances must meet USP/NF monograph specifications and additional acceptance criteria before use in the manufacturing of the drug product. The applicant retests the drug substances b(4)

B. Description of How the Drug Product is Intended to be Used

FS-67 is applied to the skin by removing the plastic film and placing the adhesive mass in contact with the site being treated. The cloth backing is left on the adhesive mass as a protective outer layer. Once applied, the patches can be left in place for up to 8 hours and are removed by peeling off the skin. It is recommended that: only one patch be used at time per affected area; no more than two patches be used per affected area per day; b(4)

The proposed packaging for the commercial product consists of five patches per pouch. This choice was selected by the applicant to be consistent with the directions for use and observed use during clinical studies. The applicant states that the number of patches per container is suitable for use within a short period, and is reasonable to allow full consumptions of the patches in a single pouch in the 14-day time) designated for use after initial opening.

b(4)

C. Basis for Approvability or Not-Approval Recommendation

The original application and subsequent amendments contain adequate information regarding the quality of the drug substance and the drug product. During the review several minor issues, including the following, were resolved.

The drug substance specifications for both *l*-menthol and methyl salicylate were revised to include Appearance based on USP/NF descriptions.

The applicant committed to evaluating the percent of drug substance overages used in the manufacturing of the drug product, adjust them as necessary during the commercial validation campaign, and submitting a report of this within six months of approval.

The applicant committed to continue developing a dissolution method and submitting a final report, including method and results, within six months of approval.

The drug product specifications were revised to include a pouch integrity test according to ASTM F1140. The stability protocol was also revised to include this test at 12, 24 and 36 months.

However, at the time of this review, the following issues have not been resolved.

GMP status recommendation has not been finalized by the Office of Compliance. Pre-Approval Inspections are pending for the two drug substance and the drug product sites and should be completed prior to the PDUFA date.

The applicant was requested to add labeling to discard any un-used patches 14 days after opening a pouch. [redacted] b(4)

Thus, the NDA is recommended as "approvable" from CMC perspective.

III. Administrative

A. Reviewer's Signature

DFS

B. Endorsement Block

Chemist Name/Date: Terrance Ocheltree/14-Nov-2006
Chemistry Team Leader Name/Date
Project Manager Name/Date

C. CC Block

Terrance Ocheltree
Moo-Jhong Rhee
Linda Athey
Keith Olin
Daniel Mellon

82 Page(s) Withheld

6 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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

/s/

Terrance Ocheltree
11/16/2006 04:32:12 PM
CHEMIST

Moo-Jhong Rhee
11/16/2006 05:09:14 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Nonprescription Clinical Evaluation
NDA:	22-029
Applicant:	Hisamitsu Pharmaceutical Co., Inc.
Stamp Date:	Feb. 27, 2006
PDUFA Date:	Dec. 27, 2006
Trademark:	SALONPAS® ———
Established Name:	Methyl Salicylate 10% and L-Menthol 3% b(4)
Dosage Form:	Topical Patch
Route of Administration:	Topical
Indication:	Temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

A. Summary

Hisamitsu Pharmaceutical is submitting a 505(b) (1) New Drug Application (NDA) for OTC marketing of a topical patch which contains 10% of methyl salicylate and 3% of l-menthol. The proposed indication is temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains.

The applicant references DMFs ——— for the two drug substances, methyl salicylate NF and l-menthol USP, respectively. The two DMFs have never been reviewed. b(4)

The proposed drug product is a topical patch which consists of a ——— adhesive mass ——— backing cloth and a ——— film. The adhesive mass contains the two active ingredients and the following six excipients: styrene-isoprene-styrene block copolymer (SIS), polyisobutylene 1,200,00 NF, polyisobutylene NF, mineral oil USP, synthetic aluminum silicate, and alicyclic saturated hydrocarbon resin (ASH). SIS and ASH are novel excipients, and toxicology studies have been conducted by the applicant to support their safe uses in the proposed drug product. The backing cloth is the third novel excipient stated in the NDA. Except mineral oil, references are made to DMFs for all excipients including the backing cloth and the ——— film.

The proposed drug product is packaged in ——— pouch. Each pouch holds 5 (market presentation) ——— patches, and is sealed ———. b(4)

The to-be-marketed formulation is the same formulation used in the clinical studies and registration stability batches. The batch size of the clinical and registration stability lots

The proposed commercial manufacturing scale . The process consists of and requires a significant overage for the two active ingredients due to Among are considered to be most critical. Many critical process parameters have still yet to be established for their operation ranges in the commercial scale. b(4)

The applicant proposes an expiry period of 36 months for the market presentation stored at 25°C with excursions permitted to 15-30°C. Stability data provided in the initial submission to support the expiry period include 3 months at 25°C/60% RH and 40°C/75% RH from three pilot-scale batches packaged in the market presentation. Additional supporting stability data provided in the NDA include 42 months at 25°C/60% RH and 6 months at 40°C/75% RH from 3 pilot scale lots packaged at a different configuration (7 patches per pouch). The applicant also provides in-use stability study results b(4)

B. Critical issues for review

Novel Excipients

- The proposed drug product involves five non-USP/NF excipients: backing cloth, styrene-isoprene-styrene block copolymer (SIS), alicyclic saturated hydrocarbon resin (ASH), synthetic aluminum silicate, and the film. The applicant considers only the first three as novel excipients. The synthetic aluminum silicate and the film are claimed by the applicant as non-novel excipients for the reason that they are listed in the FDA's inactive ingredient data base. A search in the inactive ingredient data base, however, does not produce conclusive results to confirm the applicant's claim. A closer review of the referenced DMFs is necessary in order to determine the regulatory status of these two excipients for this NDA. If synthetic aluminum silicate and/or the film turn out to be also novel excipients, pharm/tox will need to be informed immediately. b(4)

Permeation of Container/Closure System

- The proposed drug product is packaged in pouch. The permeation of the pouch is an issue which should be addressed because it potentially can impact drug product stability. The applicant does not provide such information in the NDA but it may exist in the referenced DMF. b(4)

Extractables

- There is no information regarding extractables in the NDA. The information may exist in the referenced DMFs. This issue needs to be addressed for various components of the formulation including backing cloth and the film. The pouch should comply with USP<661> Containers. b(4)

Linking of Commercial Scale to Pilot Scale

- The proposed commercial scale is ten time of the demonstrated pilot scale at which clinical and registration batches were made. The scale up has not taken place, and many aspects of the process (such as manufacturing overage and the operation ranges of many critical process parameters) are still to be determined. Since it is a significant scale up of a unique process, how do we assure that the large commercial batches will perform b(4)

comparably to the small clinical batches? The Agency should address this issue with the applicant early in the review, and agree on a testing plan, which include properties to be tested, sampling plan, methods and acceptance criteria, for the process validation.

The firm mentions in the Pharmaceutical Development section that an in-vitro dissolution test is being developed. Perhaps, this test can be used to link the two scales. However, the dissolution test needs to be evaluated first for its discrimination ability. The applicant does not provide analytical procedure for this test in the NDA. Nor any dissolution data are provided for the clinical batches. It is still a method under development.

b(4)

It is noted that the batch size of the demonstrated scale (100 kg or 10% whichever is larger).

Characterization of Adhesive Mass

- The adhesive mass contains the two active ingredients and is a backing cloth and a film. . No characterization information is provided in the NDA regarding the adhesive mass

b(4)

. It is uncertain what the physical status of l-menthol is in the mass (eutectic? amorphous? crystalline?). The lack of characterization information increases the difficulty in the attempt to link the large commercial scale to the small pilot scale.

Weigh Loss and Water Content

- Weight loss and water content are not monitored in registration stability studies. It is uncertain if there is any significant change in product weight upon storage. In the absence of the information regarding weight change, analytical assay methods need to be evaluated to ensure that the accuracy of the method is not impacted by weight change. The labeling needs to be evaluated for the accuracy of the representation of the label claim for active ingredients.

Storage and expiry dating for the product after opening of the pouch

- The proposed drug product is not individually wrapped in an pouch. After opening the pouch, the shelf-life of the exposed patch is reduced. The applicant conducted an in-use stability study Whether this kind of instruction is acceptable will need to be assessed. A request of samples for evaluation for this aspect is recommended.

b(4)

Microbiological testing

- The proposed drug product . A microbial limit test (USP<61>) is included in the drug product specification. The firm, however, proposes to eliminate the microbial limit test after 5 production batches.

Foreign Inspection:

- Both the drug substance and drug product manufacturing sites are located in Japan. GMP inspection requests will be submitted shortly after the filing meeting.

C. Comments for 74-Day Letter

None.

D. Recommendation:

This NDA is fileable from a CMC perspective.

Shulin Ding
Pharmaceutical Assessment Lead

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists

1. Drug Substance Referenced to DMFs ——— b(4)

		Does the section contain synthetic scheme with in-process parameters?	Not applicable.
		Does the section contain structural elucidation data?	Not applicable.
		Does the section contain specifications?	Not applicable.
		Does the section contain information on impurities?	Not applicable.
		Does the section contain validation data for analytical methods?	Not applicable.
		Does the section contain container and closure information?	Not applicable.
		Does the section contain stability data?	Not applicable.

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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

/s/

Shulin Ding
4/25/2006 01:32:28 PM
CHEMIST

Moo-Jhong Rhee
4/27/2006 10:19:04 AM
CHEMIST
Chief, Branch III