CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-029

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-029
Submission Dates	8/17/2007; 9/14/2007
Brand Name	Salonpas® [redacted] b(4)
Generic Name	10% Methyl Salicylate & 3% ∠Menthol
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology 2
OND Division(s)	Office of Non-Prescription Products/Division of Non-Prescription Clinical Evaluation (ONP/DNCE) and Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Applicant	Hisamitsu Pharmaceutical Co., Inc.
Relevant IND	IND 62,735
Type of Submission; Code	Resubmission: Complete Response to Deficiencies Identified in The Action Letter; Safety Update
Reference Listed Drug	None
Formulation	Topical Patch
Indication	Over-the-Counter (OTC) use -- temporarily relieves mild to moderate aches & pains of muscles & joints associated with: arthritis, simple backache, strains, bruises and sprains.
Proposed Dosage Regimen	[redacted] b(4)

[redacted]

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1 EXECUTIVE SUMMARY

This NDA is a 505 (b)(2) application for an Over-The-Counter (OTC) topical patch product, Salonpas® [redacted] containing methyl salicylate ([redacted] 10%) and *l*-menthol ([redacted] 3%) (also named as FS-67 patch or FS-67-A patch in the NDA). The proposed indication is for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, sprains and bruises. The Sponsor received an approvable letter from the FDA in December 2006. With regard to Clinical Pharmacology, the following deficiency is cited as Item #4 in the action letter: b(4)

> 4. In view of the analytical assay methodology issues and the unreliability of the data submitted in the NDA, submit newly acquired pharmacokinetic data using adequately validated analytical assay methods. The new data should include the pharmacokinetics of methyl salicylate, salicylic acid, and l-menthol in male and female subjects dosed according to the proposed labeling. These data may be acquired from a stand alone pharmacokinetic study or from a subset of patients participating in a clinical study.

To address the deficiencies cited in the approvable (AE) letter, a post-action meeting between the Sponsor and the FDA was held on February 8, 2007. With regard to Clinical Pharmacology, the Sponsor reached agreement with the FDA regarding the design of the new PK study.

The Sponsor submitted their complete response to AE letter on July 17 (Amendment 17) and August 17, 2007 (Amendment 18). The submission includes results from the new PK study (Study 67-FS-15R). This review is mainly focused on the review of the newly acquired PK data that addressed the Deficiency Item #4 in the approvable letter.

1.1 Recommendations

From a Clinical Pharmacology perspective, the Sponsor has addressed the Deficiency Item #4 in the approvable letter and therefore, NDA 22-029 is acceptable.

1.2 Phase 4 Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Pharmacokinetics of methyl salicylate (MS), its metabolite, salicylic acid, and *l*-menthol (LM) following a single application of 4 patches were evaluated in 24 healthy male and female subjects (12 males and 12 females) (Study 67-FS-15R). In terms of clinical use of the product, the Sponsor proposes application of a single patch for 8 hours in the affected area followed by a second patch for another 8 hours if pain persists. In general, the patients are expected to apply less than 2 patches per day. Therefore, four patches are considered to represent the maximal usage condition.

The PK results from Study 67-FS-15R are shown in Table 1.

Table 1. Baseline-corrected pharmacokinetic parameters for methyl salicylate (MS), salicylic acid, and *l*-menthol (four patches, single dose, patches were removed after 8 hours) (Mean ± SD, ranges are in parentheses).

		C_{max} (ng/mL)	AUC_t (ng•hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)
Methyl Salicylate	Male (N=12)	17.1 ± 15.6 (3.63-60.1)	50.5 ± 38.6 (9.21-139)	1.3 ± 0.7	N/C*
	Female (N=12)	9.3 ± 5.9 (2.54-20.4)	24.2 ± 18.7 (3.72-56.9)	1.4 ± 0.5	N/C*
	All (N=24)	13.2 ± 12.2	37.4 ± 32.6	1.36 ± 0.6	N/C*
Salicylic Acid	Male (N=12)	1658 ± 933 (562-4100)	11065 ± 5654 (3651-24731)	3.2 ± 0.58	2.4 ± 0.30 (N=12)
	Female (N=12)	1644 ± 699 (638-3290)	11260 ± 4305 (4584-20361)	3.42 ± 0.67	2.2 ± 0.24 (N=11)
	All (N=24)	1651 ± 806	11162 ± 4916	3.3 ± 0.6	2.3 ± 0.3 (N=23)
l-Menthol	Male (N=12)	17 ± 13 (2.6-51)	91 ± 69 (11-273)	3 ± 0.6	4.5 ± 2 (N=2)
	Female (N=12)	13 ± 5.7 (4.2-26.5)	74 ± 32 (16-137)	2.7 ± 0.65	3.5 ± 0.74 (N=5)
	All (N=24)	15 ± 9.9	82 ± 54	2.8 ± 0.64	3.8 ± 1.1 (N=7)

* N/C: Not calculated. Elimination half-life was not calculated for methyl salicylate (MS) because MS levels in most subjects were below 2 ng/mL at 8 hours.

After application of four FS-67-A patches to healthy subjects, LM, MS, and salicylic acid were detectable in plasma with the highest exposure observed for salicylic acid. Large variability in exposure was observed (CV 40-80%). Baseline levels of LM, MS and salicylic acid for most subjects were below limit of quantitation (LOQ) and thus exposure (C_{max} and AUC) was generally similar before and after adjusting for baseline for all analytes.

The T_{max} was approximately 1.4 hours for MS, 3.3 hours for salicylic acid and 3 hours for ∠ menthol. Half-lives were generally short, less than 6 hours. Methyl salicylate plasma levels were less than 2 ng/mL (LOQ) in most subjects at 8 hours.

Males showed greater mean exposure to MS (2-fold) and LM (40% higher) compared to females although there was considerable overlap in exposure between genders (Table 1). The higher mean exposure in males was in part driven by data from one male subject (Subject 009) who had significantly higher exposure compared to the rest of the group. There were no apparent gender differences based on mean salicylic acid levels.

The maximum salicylic acid C_{max} level obtained from this study (4 patches, single dose) was 4,100 ng/mL, ~3-6% of the therapeutic concentration for salicylate (150-300 µg/mL) and 3% of lowest salicylate level associated with adverse medical events (122 µg/mL).

2 DETAILED LABELING RECOMMENDATIONS

The label for an OTC product does not contain PK information. Please refer to the appropriate reviews from ONP/DNCE for details of labeling review comment.

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_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

3.2 Individual Study Review

3.2.1 Study FS-67-15R: A Single Dose, One Period, Evaluation Designed to Determine the Percutaneous Absorption of Methyl Salicylate and Menthol Following the Application of the Topical Patch Product, FS-67-A, in Healthy Volunteers (REPORT NO. 7691-109)

Study Period: February 23, 2007 to March 30, 2007
Principle Investigator: StephenD. Flach, MD, PhD
Study Center: Covance Clinical Research Unit Inc., 3402 Kinsman Boulevard, Madison, WI 53704
Analytical Site: Covance Clinical Research Unit Inc., 3301 Kinsman Boulevard, Madison, WI 53704
Analytical Dates: March 9, 2007 to May 30, 2007

Objectives: To determine the systemic exposure to the 10% methyl salicylate (MS) and 3% *l*-menthol (LM) components of the FS-67-A patch when applied to healthy subjects.

Study Design: This was an open-label, single-dose, single-center, 1-period, Phase 1 study in 24 healthy male and female subjects (12 males and 12 females). The study consisted of a screening period, followed within 21 days by a dosing period including 4 days/3 nights of study confinement (beginning the morning of Study Day -2 to Study Day 2). Subjects were confined to the study center for approximately 2 days prior to the day of test sample application to ensure no moderate to high levels of salicylate- or menthol-containing foods or drugs were ingested. Follow-up was performed by telephone from 7 to 10 days after Study Day 2 (Final Day of Confinement).

Subjects were instructed neither to shower nor bath 8 hours prior to dosing until 12 hours postdose. Following application of the patches on Study Day 1, blood samples were collected at specified intervals for 24 hours. The patches were removed after approximately 8 hours of application.

Twenty-four subjects (12 males and 12 females) were enrolled and completed the study. Subjects' ages ranged from 19 to 45 years with a mean age of 32. Subjects had a mean weight of 73.3 kg (range of 53.0 to 97.5 kg) and a mean height of 171.1 cm (range of 156.1 to 188.4 cm). The self-reported ethnicities of the 24 subjects were 2 (8.3%) Hispanic or Latino and 22 (91.7%) not Hispanic or Latino. The self-reported races of the 24 subjects were 20 (83.3%) White and 4 (16.7%) Black or African American. See Attachment Table for details.

Treatment Administered: Four patches of FS-67-A (7 cm x 10 cm each; 280 cm^2 total) containing 10% methyl salicylate (MS) [redacted] and 3% *l*-menthol (LM) [redacted] (Batch No. FSA061201-04) were applied on the subject's back to each side of the backbone in a fasted state. The patches were removed after approximately 8 hours of application. b(4)

Sample Collection: Blood samples were collected in Monoject tubes containing potassium oxalate and sodium fluoride. Samples were collected at approximately the following timepoints relative to dosing: -24, -18, -12 hours, and 0 hour (approximately 10 minutes prior to patch application) for assessment of baseline levels of MS, its metabolite, salicylic acid, and LM (10 mL each timepoint).

Following the patch application, blood samples were collected for 24 hours at approximately the following timepoints relative to dosing: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after application (10 mL each timepoint). The blood draw at 8 hours was taken just prior to patch removal.

Sample Analysis: The concentrations of salicylic acid in human plasma were determined using high performance LC/MS/MS detection, and the concentrations of MS and LM in human plasma were determined using GC with spectrometric detection at Covance Laboratories, Inc. (Madison, WI) with validated analytical methods. The LLQ was defined as 2.00 ng/mL for MS and LM with a sample volume of 0.5 mL, and 30.0 ng/mL for salicylic acid with a sample volume of 0.2 mL (Table 3.2.1.1). The assay is selective for the analytes with acceptable precision and accuracy.

The LM and MS and their respective internal standards were extracted from human plasma by [redacted] An aliquot of the organic layer was analyzed using GC/MS. b(4)

The salicylic acid and the internal standard were extracted from human plasma by [redacted] The elute was analyzed using LC/MS/MS. Due to the difficulty of finding salicylic acid-free blank plasma, the QC samples, calibrators, blank matrix, and control zero (blank matrix with internal standard only) samples was prepared using charcoal stripped plasma.

Table 3.2.1.1. Summary of Analytical Methods.

Analyte	Matrix	Analytical Method	Internal Standard	Limit of Quantitation (Linear Range)	QC (ng/mL)	Matrix Stability (-10 to -30°C)
***l*-Menthol**	Human Plasma	GC/MS [redacted] b(4)	Menthol-d_4	2 ng/mL (2-150 ng/mL)	5, 50, 125	77 Days
Methyl Salicylate	Human Plasma	GC/MS [redacted]	Methyl salicylate-d_4	2 ng/mL (2-150 ng/mL)	5, 50, 125	77 Days
Salicylic Acid	Human Plasma	LC/MS/MS [redacted] b(4)	Salicylic acid-d_6	30 ng/mL (30-2000 ng/mL)	60, 200, 1600, 10000 (10% dilution)	197 Days

Pharmacokinetic Results: Baseline levels of LM, MS and salicylic acid for most subjects were below LOQ. Baseline adjustment was calculated as the overall mean of the -24 hour, -18 hour and -12 hour prior to patch application concentrations. The baseline-adjusted data were very similar to the unadjusted data. Mean concentration-time profiles for MS, salicylic acid, and LM were shown in figures below.

Figure 14.2.1-1c: Mean Concentration-Time Profiles for Methyl Salicylate (MS) in the Normal and Log-linear Scales: Overall

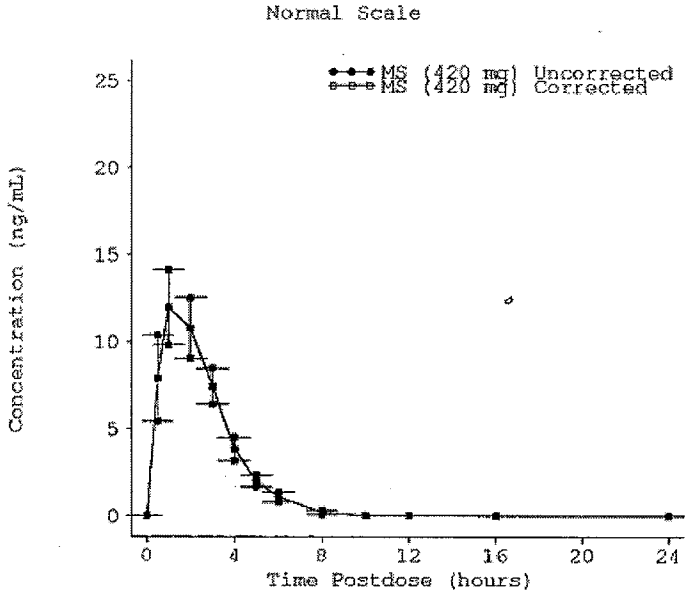


Figure 14.2.1-2c: Mean Concentration-Time Profiles for Free Salicylic Acid (FS) in the Normal and Log-linear Scales: Overall

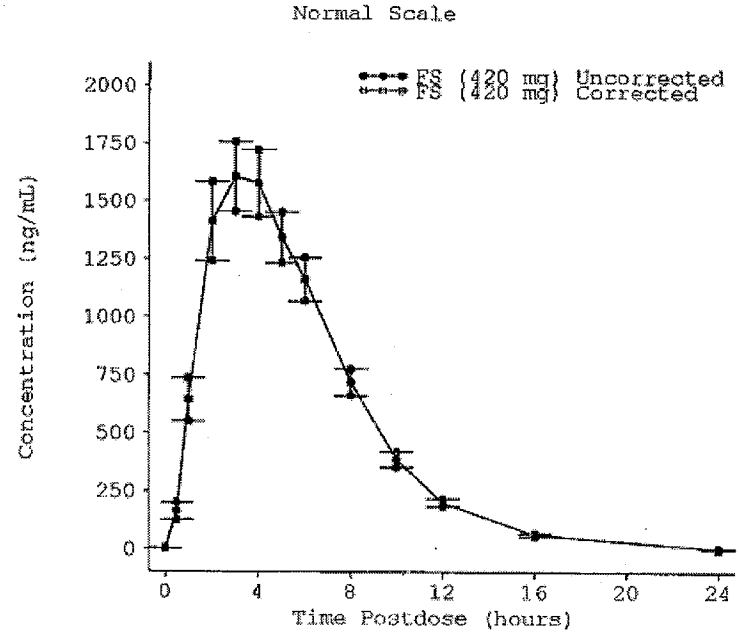
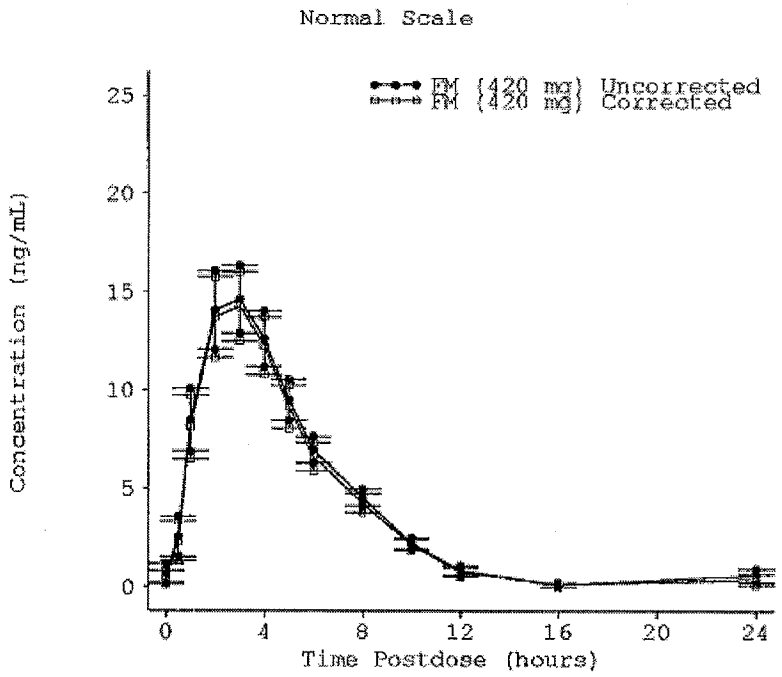


Figure 14.2.1-3c: Mean Concentration-Time Profiles for Free Menthol (FM) in the Normal and Log-linear Scales: Overall



Methyl Salicylate (MS)

PK parameters were shown in Tables 11-1 and 11-4 (baseline-adjusted). Mean AUC and C_{max} values were approximately 2-fold higher in males than females. A few male subjects, in particular Subject 009, showed significantly higher exposure than the rest of groups, making mean exposure values in males subjects higher (Figure MS).

Table 11-1 Summary of Methyl Salicylate Pharmacokinetic Parameters

Gender		C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	kel (1/hr)	$t_{1/2}$ (hr)	AUC/AUC_{inf}
M	Mean	17.1	1.00	50.5	NA	NA	NA	NA
	SD	(15.6)	(0.500, 3.00)	(38.6)	(NA)	(NA)	(NA)	(NA)
	N	12	12	12	0	0	0	0
F	Mean	9.28	1.01	24.2	NA	NA	NA	NA
	SD	(5.87)	(1.00, 2.02)	(18.7)	(NA)	(NA)	(NA)	(NA)
	N	12	12	12	0	0	0	0

Note: The parameters kel, $t_{1/2}$, AUC_{inf}, and the AUC/AUC_{inf} ratio could not be calculated for subjects with BLQ concentrations after 8 hours postdose due to the lack of a distinct elimination phase.

NA: Not applicable.

Source: Table 14.2.2-1b.

[a] Median (min, max) shown for T_{max}.

Table 11-4 Summary of Methyl Salicylate Baseline Adjusted Pharmacokinetic Parameters

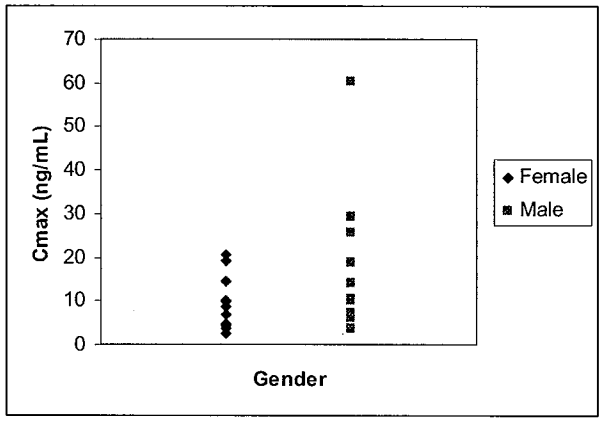
Gender		C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	kel (1/hr)	$t_{1/2}$ (hr)	AUC/ AUC_{inf}
M	Mean	17.1	1.00	50.5	NA	NA	NA	NA
	SD	(15.6)	(0.500, 3.00)	(38.6)	(NA)	(NA)	(NA)	(NA)
	N	12	12	12	0	0	0	0
F	Mean	9.28	1.01	24.2	NA	NA	NA	NA
	SD	(5.87)	(1.00, 2.02)	(18.7)	(NA)	(NA)	(NA)	(NA)
	N	12	12	12	0	0	0	0

Note: The parameters kel, $t_{1/2}$, AUC_{inf}, and the AUC/AUC_{inf} ratio could not be calculated for subjects with BLQ concentrations after 8 hours postdose due to the lack of a distinct elimination phase.

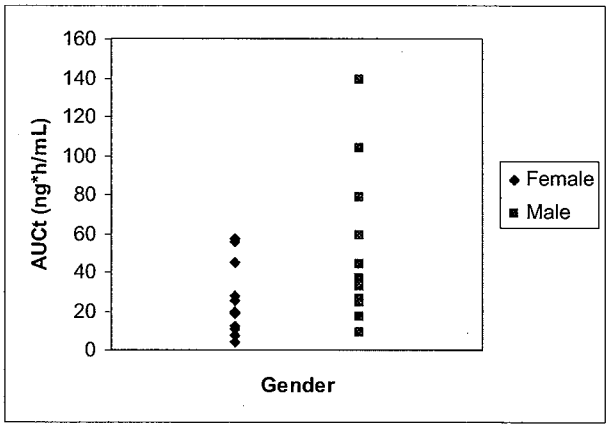
NA: Not applicable.

Source: Table 14.2.2-1a.

[a] Median (min, max) shown for T_{max}.



a. Cmax



b. AUCt

Figure MS. Scatter Plot of Methyl Salicylate Cmax and AUCt in Females (F) and Males (M).

Salicylic Acid

PK parameters were shown in Tables 11-2 and 11-5 (baseline-adjusted). Mean AUC and C_{max} values of salicylic acid were similar between males and females.

Table 11-2 Summary of Salicylic Acid Pharmacokinetic Parameters

Gender		C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	kel (1/hr)	$t_{1/2}$ (hr)	AUC/ AUC_{inf}
M	Mean	1658	3.00	11065	11318	0.297	2.37	0.974
	SD	(933)	(2.00, 4.00)	(5654)	(5706)	(0.0405)	(0.301)	(0.0100)
	N	12	12	12	12	12	12	12
F	Mean	1645	3.50	11297	11495	0.319	2.19	0.983
	SD	(698)	(2.00, 4.02)	(4302)	(4566)	(0.0313)	(0.238)	(0.00637)
	N	12	12	12	11	11	11	11

Note: The parameters kel, $t_{1/2}$, AUC_{inf}, and the AUC/AUC_{inf} ratio could not be calculated for subjects with BLQ concentrations after 8 hours postdose due to the lack of a distinct elimination phase.

Source: Table 14.2.2-2b.

[a] Median (min, max) shown for T_{max}.

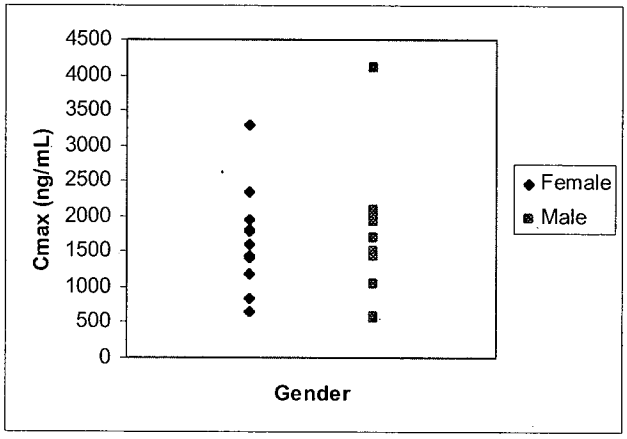
Table 11-5 Summary of Salicylic Acid Baseline Adjusted Pharmacokinetic Parameters

Gender		C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	kel (1/hr)	$t_{1/2}$ (hr)	AUC/ AUC_{inf}
M	Mean	1658	3.00	11065	11318	0.297	2.37	0.974
	SD	(933)	(2.00, 4.00)	(5654)	(5706)	(0.0405)	(0.301)	(0.0100)
	N	12	12	12	12	12	12	12
F	Mean	1644	3.50	11260	11495	0.319	2.19	0.983
	SD	(699)	(2.00, 4.02)	(4305)	(4566)	(0.0313)	(0.238)	(0.00637)
	N	12	12	12	11	11	11	11

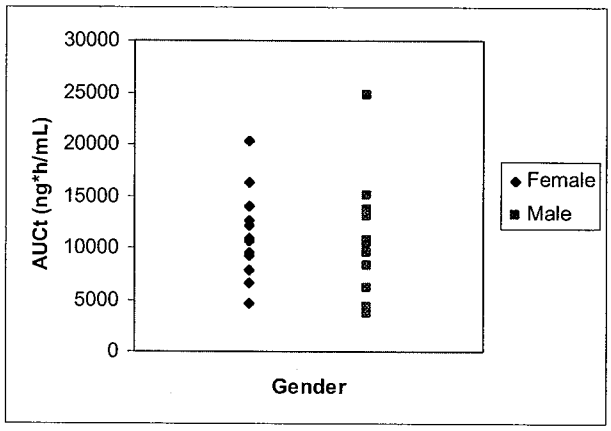
Note: The parameters kel, $t_{1/2}$, AUC_{inf}, and the AUC/AUC_{inf} ratio could not be calculated for subjects with BLQ concentrations after 8 hours postdose due to the lack of a distinct elimination phase.

Source: Table 14.2.2-2a.

[a] Median (min, max) shown for T_{max}.



a. Cmax



b. AUCt

Figure SA. Scatter Plot of Salicylic Acid Cmax and AUCt in Females and Males.

l-Menthol (LM)

PK parameters were shown in Tables 11-3 and 11-6 (baseline-adjusted). Mean exposure to LM was approximately 40% higher in males than females. One male subject, Subject 009, showed significantly higher exposure than the rest of volunteers in the study, making mean exposure values in males subjects higher (Figure LM).

Table 11-3 Summary of Free Menthol Pharmacokinetic Parameters

Gender		C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	kel (1/hr)	$t_{1/2}$ (hr)	AUC/ AUC_{inf}
M	Mean	17.9	3.00	102	204	0.170	4.52	0.918
	SD	(12.2)	(2.00, 4.00)	(66.0)	(127)	(0.0752)	(2.00)	(0.0168)
	N	12	12	12	2	2	2	2
F	Mean	12.8	3.00	73.9	105	0.204	3.53	0.878
	SD	(5.66)	(2.00, 4.02)	(31.8)	(27.9)	(0.0446)	(0.739)	(0.0491)
	N	12	12	12	5	5	5	5

Notes: The parameters kel, $t_{1/2}$, AUC_{inf}, and the AUC/AUC_{inf} ratio could not be calculated for subjects with BLQ concentrations after 8 hours postdose due to the lack of a distinct elimination phase. Subjects 1, 6, and 17 showed positive predose values greater than 5% of C_{max}. These subjects were included in the PK analysis and descriptive statistics.

Source: Table 14.2.2-3b.

[a] Median (min, max) shown for T_{max}.

Table 11-6 Summary of Free Menthol Baseline Adjusted Pharmacokinetic Parameters

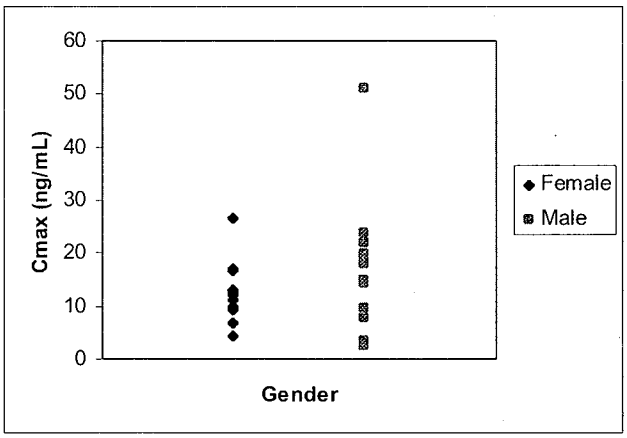
Gender		C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	kel (1/hr)	$t_{1/2}$ (hr)	AUC/ AUC_{inf}
M	Mean	17.2	3.00	90.6	204	0.170	4.52	0.918
	SD	(12.7)	(2.00, 4.00)	(69.4)	(127)	(0.0752)	(2.00)	(0.0168)
	N	12	12	12	2	2	2	2
F	Mean	12.8	3.00	73.9	105	0.204	3.53	0.878
	SD	(5.66)	(2.00, 4.02)	(31.8)	(27.9)	(0.0446)	(0.739)	(0.0491)
	N	12	12	12	5	5	5	5

Notes: The parameters kel, $t_{1/2}$, AUC_{inf}, and the AUC/AUC_{inf} ratio could not be calculated for subjects with BLQ concentrations after 8 hours postdose due to the lack of a distinct elimination phase. Subjects 1, 6, and 17 showed positive predose values greater than 5% of C_{max}. These subjects were included in the PK analysis and descriptive statistics.

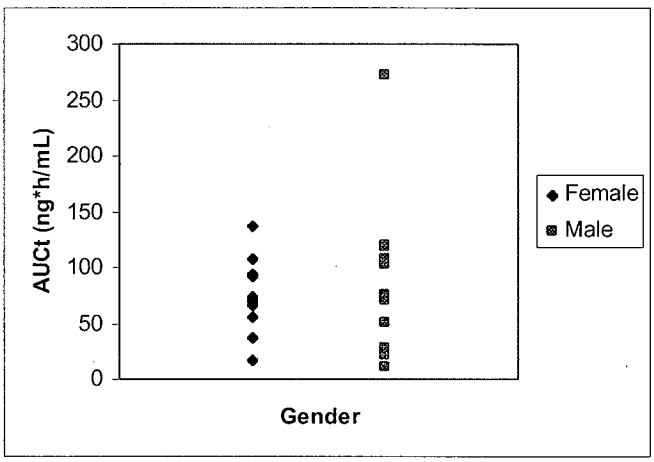
NA: Not applicable.

Source: Table 14.2.2-3a.

[a] Median (min, max) shown for T_{max}.



a. Cmax



b. AUCt

Figure LM. Scatter Plot of *L*-Menthol Cmax and AUCt in Females and Males.

Safety Results: Overall, 10 AEs were reported by 6 subjects. All of the 10 AEs were mild in severity. Six treatment-related AEs were reported by 5 subjects. Systemic exposure of MS, salicylic acid and LM in these 5 subjects are listed in Table 3.2.1.2. No deaths or SAEs occurred during this study. No AE led to study discontinuation. All AEs resolved with no action taken.

Adverse events that were considered by the Investigator to be related to study drug included the following:

- General Disorders and Administration Site Conditions:
  - application site erythema (Subject Nos. 001, 008, 009, and 010; all considered definitely related to study drug);
  - fatigue (Subject No. 023; possibly related to study drug).
- Skin and Subcutaneous Tissue Disorders:
  - ecchymosis (Subject No. 009; probably related to study drug).

Table 3.2.1.2. Systemic Exposure in 5 Subjects who reported treatment-related AE.

Subject	Gender	Methyl Salicylate		Salicylic Acid		*L*-Menthol	
		Cmax (ng/mL)	AUCt (ng•h/mL)	Cmax (ng/mL)	AUCt (ng•h/mL)	Cmax (ng/mL)	AUCt (ng•h/mL)
001	Male	10.2	35.9	2080	15014	17.9	119
008	Male	18.6	59	1700	10522	23.7	120
009*	Male	60.1	139	4100	24731	51	273
010	Male	10.3	32.5	1930	13013	19.3	104
023	Female	2.54	3.72	1820	12663	12.8	70.3
Mean (All Subjects)		13.2	37.4	1651	11162	15	82.2

*Subject 009 demonstrated the highest exposure to MS, salicylic acid and LM among 24 subjects enrolled in the study.

Conclusions:

- After application of four FS-67-A patches to healthy subjects, LM, MS, and salicylic acid were detectable in plasma with the highest exposure observed for salicylic acid. Large variability in exposure was observed (CV 40-80%). Baseline levels of LM, MS and salicylic acid for most subjects were below LOQ and thus exposure (C_{max} and AUC) was generally similar before and after adjusting for baseline for all analytes.

- The T_{max} was approximately 1.4 hour for MS, 3.3 hours for salicylic acid and 3 hours for LM. Half-lives were generally short, less than 6 hours. Methyl salicylate plasma levels were below 2 ng/mL in most subjects at 8 hours.

- Males showed higher mean exposure to MS (2-fold) and LM (40% higher) compared to females although there was considerable overlap in exposure between genders. The higher mean exposure in males was in part driven by data from one male subject (Subject 009) who had significantly higher exposure compared to the rest of the group. There were no apparent gender differences for mean salicylic acid levels.

Attachment

Table 3.2.1.3. Subject Demographics.

Subject Number	Gender	Hispanic or Latino?	Race	Date of Birth	Age (years)	Height (cm)	Body Weight (kg)
001	Male	No	White		44	162.6	78.6
002	Male	No	Black or African American		43	182.0	78.1
003	Male	No	White		24	182.4	87.7
004	Male	No	White		32	168.0	79.4
005	Male	No	White		23	172.8	65.1
006	Male	No	Black or African American		34	178.1	60.8
007	Male	No	White		19	180.4	79.1
008	Male	No	White		44	178.4	76.7
009	Male	No	White		20	176.0	76.3
010	Male	No	White		30	187.1	97.5
011	Male	No	White		23	188.4	76.7
012	Male	No	White		22	184.6	81.7
013	Female	No	White		44	160.3	74.2
014	Female	No	White		38	165.9	77.4
015	Female	No	White		30	159.7	61.7
016	Female	No	White		21	158.2	63.6
017	Female	No	White		25	158.3	53.2
018	Female	Yes	White		35	157.3	70.3
019	Female	No	White		23	175.4	80.7
020	Female	No	Black or African American		38	162.5	65.0
021	Female	No	White		27	175.0	81.7
022	Female	No	White		38	168.0	84.6
023	Female	No	White		38	169.2	55.9
024	Female	Yes	Black or African American		45	156.1	53.0

b(6)

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/s/

Lei K Zhang
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Suresh Doddapaneni
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4/15/7

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Office of Clinical Pharmacology (Division of Clinical Pharmacology 2) Tracking/Action Sheet for Formal/Informal Consults**			
From: Lei Zhang, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 3/16/2007	IND No.: Serial No.:	NDA No. 22-029 000-Amendment 14	DATE OF DOCUMENT	1/24/2007
NAME OF DRUG **b(4)** **[Salonpas [redacted] (10% Methyl Salicylate & 3% l-Menthol)]**	PRIORITY CONSIDERATION **Standard**		Date of informal/Formal Consult:	2/1/2007
NAME OF THE SPONSOR: **[Hisamitsu Pharmaceutical Co., Inc]**				

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☒ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☒ MEETING PACKAGE (POST AE meeting)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [Teshara Bouie]	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☒ Comments communicated in	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others	meeting/Telecon. see meeting minutes dated: [signed-off on 3/8/2007 in DFS]	☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☒ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

The meeting package is for the Type-A meeting to discuss the approvable letter issued on December 27, 2006. The meeting date is Feb 8, 2007.

The proposed indication of the drug product is for the OTC use for temporary relief of mild to moderate aches & pains of muscles & joints. To address the clinical deficiency, the Sponsor needs to conduct new clinical studies to establish a dosing interval to support the multiple patch use of the drug product in an OTC market. With regard to Clinical Pharmacology, a PK study protocol (FS-67-15R) was attached to address the deficiency #3 in the approvable letter:

> *3. In view of the analytical assay methodology issues and the unreliability of the data submitted in the NDA, submit newly acquired pharmacokinetic data using adequately validated analytical assay methods. The new data should include the pharmacokinetics of methyl salicylate, salicylic acid,*

and l-menthol in male and female subjects dosed according to the proposed labeling. These data may be acquired from a stand alone pharmacokinetic study or from a subset of patients participating in a clinical study.

Protocol Outline

Title: A Single Dose, One Period, Evaluation Designed to Determine the Percutaneous Absorption of Methyl Salicylate and Menthol Following the Application of the Topical Patch Product, FS-67-A, in Healthy Volunteers

Objective: To determine the systemic exposure to the 10% methyl salicylate and 3% *l*-menthol components of the FS-67-A patch when applied to healthy male and female volunteers.

Study Design: single dose, 4 patch/subject, patch will be removed after 8 hour. 12 male and 12 female subjects will be enrolled.

PK Sampling: -24, -18, -12 hours and approximately 10 minutes prior to patch application; 0.5 and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after patch application.

Sample Analysis: (Site: COVANCE Lab, Madison, WI)

Plasma samples will be analyzed for plasma methyl salicylate, free salicylic acid and free menthol using chromatographic procedures developed at COVANCE if the subjects complete the study. Samples from dropouts will not be assayed.

LC/MS/MS method:	*Analytical range:*
Free salicylic acid	*10-2000 ng/mL*
GC method:	*Analytical range:*
Methyl salicylate	*2-150 ng/mL*
Free menthol	*2-150 ng/mL*

Whenever possible, all samples from each subject will be analyzed on the same standard curve. Standard and quality control samples will be distributed through each batch of study samples assayed. Samples with drug concentrations greater than the upper limit of the validated range of the assay will be diluted with the appropriate drug-free biological fluid or water for menthol and reassayed; those which are below the lower limit of the range will be reported as being below LOQ. Repeat assays, if necessary, will be performed on the second tube of frozen sample rather than on the remainder from the first tube, wherever possible. The analysts will not have access to the randomization scheme.

Conclusion

The adequacy of the PK study protocol was reviewed. Results from this single dose PK study will provide information on systemic exposure of methyl salicylate, salicylic acid and menthol for systemic safety and will help putting into proper perspective the previous PK data submitted in the original NDA and obtained with questionable analytical assay methodology. If warranted, PK of multiple doses could be estimated from the single dose results.

The following is Sponsor's question (Question 6) related to Clinical Pharmacology and agency's response:

Clinical Pharmacology

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

The ——— methods underwent a method technical transfer and revalidation at Covance Laboratories Inc. In general, the methods developed and validated by Covance are identical (or highly similar) to the original ——— methods. However, Covance modified the ——— method in one significant aspect in that the employed LLOQ for salicylic acid was increased. In addition, Covance has 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.

At the meeting, the Sponsor 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.

The final meeting minutes is signed-off in DFS on March 8, 2007.

SIGNATURE OF REVIEWER: Lei Zhang, Ph.D. **SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.**	Date Date
CC.: HFD # [ ]; TL: [ ]	**Project Manager: Keith Olin, R.Ph.** **Date**

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/s/

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11/15/06

CLINICAL PHARMACOLOGY REVIEW

NDA	22-029
Submission Dates	2/27/2006, 8/18/2006
Brand Name	Salonpas® [redacted] b(4)
Generic Name	10% Methyl Salicylate & 3% *l*-Menthol
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology 2
OND Division(s)	Office of Non-Prescription Products/Division of Non-Prescription Clinical Evaluation (ONP/DNCE) and Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Applicant	Hisamitsu Pharmaceutical Co., Inc.
Relevant IND	IND 62,735
Type of Submission; Code	505 (b)(2); 3, 4S
Reference Listed Drug	None
Formulation	Topical Patch
Indication	Over-the-Counter (OTC) use -- temporarily relieves mild to moderate aches & pains of muscles & joints associated with: arthritis, simple backache, strains, bruises and sprains.
Proposed Dosage Regimen	[redacted] b(4)

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

This NDA is a 505 (b)(2) application for an Over-The-Counter (OTC) topical patch product, Salonpas® [redacted], containing methyl salicylate (— 10%) and *l*-menthol (— 3%) (also named as FS-67 patch or FS-67-A patch in the NDA). The proposed indication is for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, sprains and bruises. It will be the first topical analgesic patch product under NDA if approved. b(4)

Methyl salicylate and *l*-menthol (both as single ingredients and in combination) have been comprehensively reviewed by the Expert Panel for Over-The-Counter (OTC) Topical Analgesic Drug Products, and were found to be generally recognized as safe and effective (GRAS/E) (Category 1) for the intended indications in 1979. A Tentative Final Monograph (TFM) for OTC External Analgesic Drug Products was published by the U.S. Food and Drug Administration in 1983 (48 FR 5852). The TFM provides for topically applied ointments (or lotions or creams) containing methyl salicylate in the range of 10%-60% and menthol in the range of 1.25%-16% (both as single ingredients and when combined) as counterirritants, but the TFM does not include the dosage form of topical patch.

Several topical patch products are on the market prior to TFM (e.g., Salonpas Patch, Tiger Balm patch and Bengay patch). The active ingredients in these patches include menthol, methyl salicylate, camphor, or capsicum extract or in combination. The Sponsor of this NDA has marketed the Salonpas patch for over-the-counter use as an external analgesic drug product for 70 years in 45 countries. The current marketed Salonpas patch includes methyl salicylate (132mg, 6.3%), menthol (120mg, 5.7%), and *dl*-camphor (26mg, 1.2%) as counter-irritants for the relief of minor aches and pains of the muscles and joints.

The subject of this NDA (Salonpas® [redacted] is a new formulation of Salonpas patch that contains only methyl salicylate ([redacted] 10%) and *l*-menthol ([redacted] 3%). In addition, it is formulated with [redacted] backing. The size of patch, 70cm^2, is wider than Salonpas, 27.3cm^2. b(4)

To support clinical efficacy and safety, one pivotal Phase 3 trial and 5 skin safety (3 Irritation and 2 Sensitization) trials were conducted. They were reviewed by Dr. Christina Fang (efficacy) and Dr. Joseph Porres (safety), respectively. The statistical analyses were reviewed by Dr. Yongman Kim. The pivotal Phase 3 trial, Study FS-67-E02, was a single-dose, 12-hour, double-blind, placebo-controlled, multi-center study to investigate the safety and analgesic effect of FS-67 topical patch in subjects with muscle strain with a treatment period of 8 hours and observation period of 12 hours. The study showed a statistically significant difference between FS-67 topical patch and placebo patch in the summed pain intensity difference (SPID) with movement from baseline to hour 8. However, from efficacy data, the patch may be applied less frequently (>12 hours interval) to maintain efficacy. The medium time to rescue/re-medication was not identified with the single-dose efficacy data. In terms of safety, local irritation increases in proportion to the length of application, the frequency of dosing, and the number of patches used at the same time. Therefore, determining the optimal dosing interval to balance risk and benefit is critical for the approval of this OTC topical product. Please refer to their reviews for details.

To support human PK and biopharmaceutics requirement, FS-67 patch was studied in a total of 6 *in vivo* PK studies (5 studies in male subjects and 1 study in female subjects). The studies determined exposure of methyl salicylate, its major active metabolite, salicylic acid, and menthol under maximal usage conditions per the proposed labeling (single and multiple doses), interactions between methyl salicylate and menthol, exposure of methyl salicyalte/salicylic acid, and menthol compared to respective ointment formulations defined by TFM, and PK data in male and female subjects. The Clinical Pharmacology data contribute to understanding the systemic safety of the drug product.

All samples were analyzed at the [redacted] The site was found to have multiple deficiencies that indicated "widespread problems" following several FDA inspections. On 8/31/06, FDA issued a warning letter [redacted] related to these problems (www.fda.gov/cder/warn/2006/[redacted]). As a part of the resolution of these problems, [redacted] agreed to undertake a review of bioequivalence studies conducted between January 2000 and December 2004 (*a.k.a.* "5-year review plan") to determine the validity of the study results. During the review cycle, the Sponsor notified the Agency that two of the PK studies in this NDA, Studies FS-67-03-L and FS-67-03-M, were reviewed under the "5-year review plan" and they received the draft closure reports from [redacted]. In the draft closure report for Study FS-67-03-L, [redacted] concluded that the validation method and study data for *l*-menthol were considered valid. In their draft closure report for study FS-67-03-M, [redacted] questioned the validity of the salicylic acid (metabolite) method. In addition, [redacted] found the method validation results for methyl salicylate to be acceptable but questioned the validity of the production runs for the FS-67-03-M study sample analyses. b(4)

Based on the deficiencies identified in the draft closure reports, the Agency can not accept either methyl salicylate or salicylic acid results for Study FS-67-03-M.

The other 4 PK studies were not reviewed, [redacted] because they were considered outside the scope of the "5-year review plan". However, the same analytical issues potentially apply to these PK studies as well. Because analytical method is not validated for salicylic acid, the Agency cannot accept salicylic acid data from the other 4 PK studies. For methyl salicylate and menthol, although analytical methods were validated, without investigation, data validity for methyl salicylate and menthol in the other 4 studies cannot be reliably confirmed due to the widespread and systematic problems identified with this analytical site. b(4)

Nature of this product and general comparison of systemic levels with published data for similar products[1] and known therapeutic/toxicity concentrations of methyl salicylate and salicylic acid indicates that systemic toxicity for this product may be low and comparable with other marketed products of this nature. However, in light of the unreliability of the data, sponsor should submit newly acquired data using adequately validated analytical assay methodology.

An OCP briefing (Required Office Level) was held on November 9, 2006 to obtain input on the action to be taken for this NDA from a Clinical Pharmacology perspective. Attendees include: Suresh Doddapaneni, Chandra Sahajwalla, Mehul Mehta, John Lazor, Atiq Rahman, Tapash Gosh, Joel Schiffenbauer, Andrea Leonard-Segal, Joseph Porres, Keith Olin, Michelle Williamson, Sang Chung, Jaya Vaidyanathan, Sally Choe, and Partha Roy.

1.1 Recommendations

From a Clinical Pharmacology perspective, NDA 22-029 is not acceptable because the PK data obtained were not reliable in the NDA submission due to the well documented analytical issues at the [redacted] analytical site. Newly acquired PK data using adequately validated analytical methodology are needed. b(4)

The following deficiency should be conveyed to the sponsor:
In view of the documented analytical assay methodology issues and the unreliability of the submitted data in the NDA submission, submit newly acquired pharmacokinetic data using adequately validated analytical assay methods. The new data should include pharmacokinetics of methyl salicylate, salicylic acid, and *l*-menthol in male and female subjects under the likely maximal usages conditions according to the proposed labeling.

1.2 Phase 4 Commitments

Not applicable.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics (CPB) Findings

The Sponsor has included six pharmacokinetic trials (five in males and one in females) in support of the FS-67 patch application. These studies monitored unconjugated concentrations of

[1] D Martin, *et.al.*, Dermal Absorption of Camphor, Menthol, and Methyl Salicylate in Humans, *The Journal of Clinical Pharmacology*, 2004; 44:1151-1157.

salicylic acid (the major metabolite of methyl salicylate present in plasma), methyl salicylate, and menthol (Table 1).

The summary of PK results reported by the sponsor is listed in Table 2 and Table 3. Because methyl salicylate, salicylic acid and menthol are commonly present in fruits, vegetables and drinks, consequently, levels were detected in pre-dose samples. Therefore, PK data were calculated with correction for baseline levels as well. The baseline corrected data were not very different from the uncorrected data. See Appendix 4.2 for individual study reviews.

Table 1. Tabulation of Pharmacokinetic Studies

Study Ref. No.	Study Objective	Study Design	# Subjects (M/F) Type Age: mean (range)	Treatments and Product ID
FS-67-03-M	To compare the absorption of the 10% methyl salicylate component of the FS-67-A patch with two reference ointments, one containing 10% methyl salicylate and the other containing 60% methyl salicylate when applied to healthy male volunteers.	Open-label, randomized, 3-way crossover study	33 (33/0) Healthy Male Volunteers. 32 y (19 – 45)	FS-67-A Patch (Containing 10% Methyl Salicylate and 3% l-Menthol) = Batch No: FSA0002 10% Methyl Salicylate Ointment : Batch No: FSA11 60% Methyl Salicylate Ointment : Batch No: FSB11
FS-67-03-L	To compare the absorption of the 3% menthol component of the FS-67-A patch with two reference ointments, one containing 1.25% menthol and the other containing 16% menthol when applied to healthy male volunteers	Open-label, randomized, 3-way crossover single-dose study	40 (37 Completed) (40/0) Healthy Male Volunteers. 27 y (18 – 44)	FS-67-A Patch (containing 10% methyl salicylate and 3% l-menthol) : Batch No: FSA0002 1.25% l-menthol ointment : Batch No: FSC11 16% l-menthol ointment : Batch No: FSD11
FS-67-14-P1	1) To assess the effect of topical l-menthol (LM) on the pharmacokinetics of topical methyl salicylate (MS) and its primary metabolite, salicylic acid 2) to assess the effect of topical methyl salicylate (MS) on the pharmacokinetics of topical l-menthol (LM)	Open-label, randomized, 3-way crossover single-dose study	18 (18/0) Healthy Male Volunteers. 24 y (18 – 39)	FS-67-A Patch containing 10% methyl salicylate [redacted] patch) and 3% l-menthol [redacted] patch) : Lot No: FSA0003-1 FS-67-M patch containing 10% methyl salicylate [redacted] patch) : Lot No: FSM0001-1 FS-67-L patch containing 3% l-menthol [redacted] patch) : Lot No: FSL0001-1
FS-67-121	To determine the safety and tolerability of FS-67-A patches containing 10% methyl salicylate and 3% l-menthol, when given at the maximum dose possibly applied by product users, under single-dose conditions, to healthy non-smoking male volunteers.	Open-label, single period, single-dose study	22 (22/0) Healthy Male Volunteers. 22 y (19 – 42)	FS-67-A patches containing 10% methyl salicylate [redacted] patch) and 3% l-menthol [redacted] patch) : Batch #: FSA0003

b(4)

Study Ref. No.	Study Objective	Study Design	# Subjects (M/F) Type Age: mean (range)	Treatments and Product ID
FS-67-122	To determine the safety and tolerability of FS-67-A patch containing 10% methyl salicylate and 3% l-menthol when applied for five days at doses significantly exceeding the maximum labeling recommendation	Open-label, single treatment, multiple dose study	19 (17 completed) (19/0) Healthy Male Volunteers. 31 y (20 – 41)	FS-67-A patches containing 10% methyl salicylate [redacted] patch) and 3% l-menthol [redacted] patch) : Batch #: FSA0004
FS-67-15	To determine the systemic exposure to the 10% methyl salicylate and 3% l-menthol components of the FS-67-A patch when applied to healthy female volunteers	Open-label, single period, single-dose study	18 (0/18) Healthy Female Volunteers. 29 y (21 – 44)	FS-67-A patches containing 10% methyl salicylate [redacted] patch) and 3% l-menthol [redacted] patch) : Batch #: FSA0003

b(4)

Addition: For Study FS-67-03-M, 30 subjects completed the study.

Table 2. Overall Summary of Pharmacokinetic Studies - Arithmetic Mean (SD) Pharmacokinetic Parameters for Salicylic Acid and Methyl Salicylate

		Plasma Salicylic Acid Uncorrected			Plasma Salicylic Acid Baseline-Corrected			Plasma Methyl Salicylate Uncorrected			Plasma Methyl Salicylate Baseline-Corrected		
Study No. Protocol No.	Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
FS-67-03-M	4 x Patch FS-67-A (N=30)	1181 (369)	3.24 (0.63)	8738 (2601)	1158 (366)	3.24 (0.63)	8187 (2454)	38.5 (20.2)	3.45 (2.41)	403 (195)	35.1 (20.3)	3.45 (2.41)	321 (184)
	10% Methyl Salicylate Ointment (N=30)	713 (189)	3.00 (0.91)	5003 (1080)	691 (185)	3.00 (0.91)	4469 (977)	37.7 (16.0)	4.33 (3.06)	400 (149)	34.0 (15.3)	4.33 (3.06)	311 (127)
	60% Methyl Salicylate Ointment (N=30)	1346 (492)	4.77 (0.77)	10932 (3512)	1325 (495)	4.77 (0.77)	10433 (3567)	37.7 (15.9)	3.55 (1.56)	405 (145)	34.2 (15.1)	3.55 (1.56)	323 (119)
FS-67-14-P1	4 x Patch FS-67-A (N=18)	1284 (257)	3.61 (0.78)	8894 (2139)	1277 (255)	3.61 (0.78)	8737 (2077)	8.31 (4.92)	1.39 (0.78)	23.6 (14.8)	8.21 (4.82)	1.39 (0.78)	22.3 (13.7)
	4 x Patch FS-67-M (10% Methyl Salicylate) (N=18)	1313 (267)	3.78 (0.81)	9482 (2454)	1306 (265)	3.78 (0.81)	9324 (2406)	5.89 (3.84)	1.39 (0.78)	15.2 (9.97)	5.89 (3.84)	1.39 (0.78)	16.2 (10.5)
FS-67-121	10 x FS-67-A Patches (N=18)	5214 (1589)	3.67 (0.77)	38525 (12204)	5196 (1586)	3.67 (0.77)	38079 (12106)	33.4 (21.8)	1.42 (0.73)	113 (62.8)	33.3 (21.9)	1.42 (0.73)	114 (63.6)
FS-67-122	Patch FS-67-A 2 Patches q8h (N=18) Day 1	623 (193)	3.35 (0.61)	3348 (1023)	613 (192)	3.35 (0.61)	3274 (1009)	4.40 (3.09)	1.44 (1.07)	12.2 (6.99)	NA	NA	NA
	Patch FS-67-A 2 Patches q8h (N=18) Day 5	1435 (603)	NA	7628 (2988)	1426 (602)	NA	7551 (2978)	15.2 (10.3)	NA	27.4 (13.4)	NA	NA	NA
FS-67-15	4 x FS-67-A Patches Females (N=18)	1186 (430)	3.80 (0.94)	9339 (4389)	1130 (411)	3.80 (0.94)	7986 (3858)	24.8 (16.5)	1.82 (1.49)	139 (64.2)	23.9 (16.5)	1.82 (1.49)	115 (67.1)

Correction for the table: N=17 for Study FS-67-122; AUC_{0-24} should be AUC_{0-8} for Study FS-67-122.

Table 3. Overall Summary of Pharmacokinetic Studies - Arithmetic Mean (SD) Pharmacokinetic Parameters for Menthol

		Plasma Menthol Uncorrected			Plasma Menthol Baseline-Corrected			Urine Menthol Uncorrected			Urine Menthol Baseline-Corrected		
Study No. Protocol No.	Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	Ae_{0-24} (µg)	R_{max} (µg/hr)	T_{max} (hr)	Ae_{0-24} (µg)	R_{max} (µg/hr)	T_{max} (hr)
FS-67-03-L	4 x Patch FS-67-A (N=34)	15.5 (5.07)	3.30 (3.04)	129 (34.5)	14.5 (4.85)	3.30 (3.04)	104 (30.6)	NA	NA	NA	NA	NA	NA
	1.25% l-Menthol Ointment (N=34)	5.14 (2.04)	5.94 (6.26)	57.9 (22.6)	4.06 (1.74)	5.94 (6.26)	33.1 (17.5)	NA	NA	NA	NA	NA	NA
	16% l-Menthol Ointment (N=34)	24.2 (10.1d)	3.74 (0.90)	220 (81.0)	23.1 (10.2)	3.74 (0.90)	194 (82.6)	NA	NA	NA	NA	NA	NA
FS-67-14-P1	4 x Patch FS-67-A (N=18)	10.4 (2.83)	3.39 (0.98)	91.8 (22.8)	9.26 (3.10)	3.39 (0.98)	64.8 (31.1)	9374 (3542)	911 (333)	3.00 (0.00)	8502 (2888)	874 (313)	3.00 (0.00)
	4 x Patch FS-67-L (3% l-Menthol) (N=18)	9.26 (2.08)	4.00 (2.22)	84.4 (27.1)	7.85 (2.28)	4.00 (2.22)	50.9 (26.8)	8201 (2437)	781 (237)	3.00 (0.00)	6948 (1950)	729 (236)	3.00 (0.00)
FS-67-121	10 x FS-67-A Patches (N=18)	40.9 (12.6)	3.28 (0.75)	319 (87.1)	39.1 (12.9)	3.28 (0.75)	275 (89.5)	NA	NA	NA	NA	NA	NA
FS-67-122	Patch FS-67-A 2 Patches q8h (N=18) Day 1	6.51 (2.93)	3.39 (1.73)	33.6 (14.5)	5.06 (2.71)	3.39 (1.73)	22.5 (12.6)	NA	NA	NA	NA	NA	NA
	Patch FS-67-A 2 Patches q8h (N=18) Day 5	21.2 (8.67)	NA	97.4 (36.8)	19.8 (8.35)	NA	85.5 (34.9)	NA	NA	NA	NA	NA	NA
FS-67-15	4 x FS-67-A Patches Females (N=18)	9.76 (4.43)	2.92 (1.00)	89.0 (35.9)	8.50 (4.16)	2.92 (1.00)	60.1 (28.7)	NA	NA	NA	NA	NA	NA

Correction for the table: N=17 for Study FS-67-122; AUC_{0-24} should be AUC_{0-8} for Study FS-67-122.

Data for *l*-menthol in Study FS-67-03-L were considered valid. The results suggested that exposure of menthol from four FS-67 patch application was within the range of menthol exposure from 1.25% and 16% menthol ointment (the menthol concentration ranges defined by TFM) when applied to the same size of the body surface area.

Salicylic acid data in Study FS-67-03-M were not considered valid because both analytical method and production run were not considered valid. The main deficiency was that multiple validation batches had interference (unexpected high levels) observed in blanks, reagent blanks, zero standards and/or pre-dose samples that affected the accuracy and precision of QCs (Please see Section 2.6.1 and 4.2.2 for details).

Methyl salicylate data in Study FS-67-03-M were not considered valid because although analytical method was considered valid, the production run was not. The main deficiency was that 38% samples were above the highest calibration standard (ULOQ) and were required to be repeated with a dilution factor. Almost half of the values obtained with dilution factors did not confirm with the original extrapolated values in the production runs (46% data with a difference of >30%) (Please see Section 4.2.2 for details).

The other 4 PK studies were not reviewed [redacted] because they were considered outside the scope of the "5-year review plan". However, the same analytical issues potentially apply to these PK studies as well. Because analytical method is not validated for salicylic acid, the Agency cannot accept salicylic acid data from the other 4 PK studies. Although analytical methods were validated for methyl salicylate and menthol, without investigation, data validity for methyl salicylate and menthol in the other 4 studies cannot be reliably confirmed due to the widespread and systematic problems identified with this analytical site. b(4)

Cross study data comparison for menthol and salicylic acid indicate data differences were within 2-fold (Tables 2 and 3). For methyl salicylate, data were more variable among studies (Table 2).

Although data were questionable due to analytical issues, methyl salicylate/salicylic acid and menthol are not new molecular entities and PK data are available from various dosage forms and routes. Systemic levels for menthol and methyl salicylate were compared to published data[1] for similar products (Table 4 and Table 5). Menthol data were similar to the literature data and methyl salicylate had lower exposure than data reported in the literature at the same dose if assuming PK is dose-proportional. Salicylic acid was not monitored in the study reported in the literature.

Table 4. Exposure of Menthol (4 patches, single dose for 8 hours) (Mean and SD).

	Cmax (ng/mL)	Tmax (hr)	AUC0-24 (ng*hr/mL)
FS-67-03-L	14.5 (4.85)	3.30 (3.04)	104 (30.6)
Literature[1]	19.0 (5.4)	2.2 (1.2)	N.A.

Salonpas: [redacted] menthol per patch
Literature patch: 37.44 mg menthol per patch (Mean Cmax was 16 ng/mL at a dose of 31 mg if assuming PK is dose-proportional)

Table 5. Exposure of Methyl Salicylate (4 patches, single dose for 8 hours) (Mean and SD).

	Cmax (ng/mL)	Tmax (hr)	AUC0-24 (ng*hr/mL)
FS-67-14-P1	8.2 (4.8)	1.4 (0.78)	22 (14)
Literature	16.8 (6.8)	1.3 (0.6)	N.A.

Salonpas: [redacted] methyl salicylate per patch
Literature patch: 74.88 mg methyl salicylate per patch (Mean Cmax was 23.6 ng/mL at a dose of 105 mg if assuming PK is dose-proportional.)

In terms of dose, maximal proposed daily dose of methyl salicylate patch [redacted]) were low compared to the maximal daily dose of aspirin (3.6 g). Aspirin also yields salicylic acid as its metabolite and normally is 80-100% absorbed. It is likely that systemic levels of salicylic acid from patch application are below the therapeutic level and levels that would cause adverse events. Peak salicylate level obtained from the 10-patch single dose study (Study FS-67-121), although not reliable, was reported to be ~5,200 ng/mL by the sponsor, ~20-30-fold lower than the therapeutic concentration for salicylate (150-300 µg/mL) and lowest salicylate level associated with adverse medical events (122 µg/mL). However, in light of the unreliability of the data, sponsor will be required to submit newly acquired data using adequately validated analytical assay methodology.

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2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Table 2.1.1.1. Physical-Chemical Properties of Methyl Salicylate.

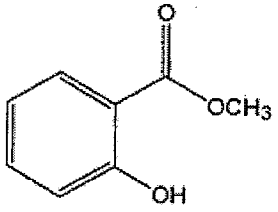
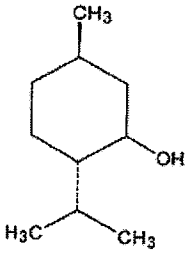
Drug Name	Methyl Salicylate
Chemical Name	2.Hydroxybenzoic acid methyl ester
Structure and Molecular Formula	 $C_8H_8O_3$
Molecular Weight	152.15
Appearance	Colorless to pale yellow liquid with a strong characteristic odor
Melting Range	219°C to 224°C.
Solubility	Slightly soluble in water; soluble in chloroform and ether.

Table 2.1.1.1. Physical-Chemical Properties of *l*-Menthol

Drug Name	*l*-Menthol
Chemical Name	5-Methyl-2-(I-methylethyl)-cyclohexanol
Structure and Molecular Formula	 $C_{10}H_{20}O$
Molecular Weight	156.27
Appearance	Colorless crystalline with a characteristic odor, and has an initial burning taste followed by a refreshing taste
Melting Range	41°C to 44°C.
Solubility	Slightly soluble in water; very soluble in alcohol, chloroform, ether and hexane; freely soluble in mineral oil

The drug product contains the counterirritant agents methyl salicylate (10%) and *l*-menthol (3%) as active ingredients. The FS-67 patch (7 x 10 cm) consists of [redacted] backing cloth and a [redacted] film. The [redacted] b(4)

contains the two active ingredients. The patch is applied to the skin by removing the —— film and placing the adhesive mass in contact with the site, leaving the cloth backing as a protective outer layer. The drug content of each patch is —— methyl salicylate and —— l-menthol (See Section 2.5.1). b(4)

2.1.2 What is the proposed mechanism of drug action and therapeutic indication?

The FS-67 topical patch contains two active ingredients, methyl salicylate and *l*-menthol. Methyl salicylate converts to salicylic acid in the body. Both methyl salicylate and salicylic acid have anti-inflammatory and analgesic properties. Menthol is a counterirritant that causes a sensation of coolness.

In this application, the Sponsor is seeking the OTC indication for 10% methyl salicylate/3% *l*-menthol topical patch to temporarily relieve mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains.

2.1.3 What are the proposed dosage recommendations and route of administration of FS-67 topical patch for the proposed indication?

Topical patch.

The following language is proposed by the sponsor regarding dosage and administration:

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— ——————————————

2.2 General Clinical Pharmacology

2.2.1 What are the clinical pharmacology and clinical studies used to support dosing or claims?

To support human PK and biopharmaceutics requirement, FS-67 patch was studied in a total of 6 *in vivo* PK studies (5 studies in male subjects and 1 study in female subjects). The studies include exposure of methyl salicylate/salicylic acid and menthol under maximal usage conditions per the proposed labeling (single and multiple doses), interactions between methyl salicylate and menthol, exposure of methyl salicyalte/salicylic acid, and menthol compared to ointment formulations defined by TFM, and PK data in male and female subjects.

To support clinical efficacy and safety, one pivotal Phase 3 trial and 5 skin safety trials were conducted. They were reviewed by Dr. Christina Fang (efficacy) and Dr. Joseph Porre (safety), respectively.

The pivotal efficacy trial, Study FS-67-E02, was a 12-hour, single-dose, double-blind, placebo-controlled, multi-center study to investigate the safety and analgesic effect of FS-67 topical patch

in subjects with muscle strain. In the study, 208 patients were randomized to FS-67 topical patch single dose (n = 105) or placebo topical patch single dose (n = 103) in a 1:1 ratio. The primary efficacy outcome variable was SPID8 (summed pain intensity difference to from baseline to Hour 8) with movement. Secondary efficacy variables were SPID8 at rest, TOTPAR8 (total pain relief with movement and at rest at hour 8), PID (pain intensity difference) with movement over several assessment time points, onset of analgesia (perceptible and meaningful pain relief) based on double stopwatches, and subject global satisfaction.

Overall, the study was successful in showing superiority of FS-67 topical patch over placebo in terms of pain reduction in the acute setting. However, from efficacy data, the patch may be applied less frequently (>12 hours interval) to maintain efficacy. The medium time to rescue/re-medication was not identified with the single-dose efficacy data.

In terms of safety, local irritation increases in proportion to the length of application, the frequency of dosing, and the number of patches used at the same time.

Therefore, determining the optimal dosing interval to balance risk and benefit is critical for the approval of this OTC topical product. Please refer to their reviews for details.

2.2.2 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Unconjugated concentrations of salicylic acid (the major metabolite of methyl salicylate present in plasma), methyl salicylate, and menthol were monitored in human plasma.

All samples were analyzed at the [redacted] analytical site [redacted]. The site was found to have multiple deficiencies that indicated "widespread problems" following several FDA inspections. The site underwent a "5-year review plan" to retrospectively review analytical data of all the bioequivalence studies for the past 5 years (Jan 2001-Dec 2004) for validity of the results. During the review cycle, the Sponsor notified the Agency that two of the PK studies in this NDA, Study FS-67-03-L and FS-67-03-M, were selected to be reviewed under the "5-year review plan" and they received the draft closure reports [redacted]. In the draft closure reports, [redacted] concluded that the validation method and study data for l-menthol in study FS-67-03-L were considered valid. In their draft closure report of study FS-67-03-M, [redacted] questioned the validity of the salicylic acid (metabolite) method. In addition, [redacted] found the method validation results for methyl salicylate to be acceptable but questioned the validity of the production runs for the FS-67-03-M study sample analyses. Please refer to Section 2.6 Analysis for analytical details.

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2.2.4 What is exposure of l-menthol from various studies?

Table 38. Cross-study comparison of menthol C_{max}, T_{max} and AUC after administration of FS-67 patches and menthol ointments.

			Plasma Menthol Uncorrected			Plasma Menthol Baseline-Corrected		
Study No. Protocol No.	Treatment		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
FS-67-03-L	4 x Patch FS-67-A (N=34)		15.5 (5.07)	3.30 (3.04)	129 (34.5)	14.5 (4.85)	3.30 (3.04)	104 (30.6)
	1.25% l-Menthol Ointment (N=34)		5.14 (2.04)	5.94 (6.26)	57.9 (22.6)	4.06 (1.74)	5.94 (6.26)	33.1 (17.5)
	16% l-Menthol Ointment (N=34)		24.2 (10.1d)	3.74 (0.90)	220 (81.0)	23.1 (10.2)	3.74 (0.90)	194 (82.6)
FS-67-14-P1	4 x Patch FS-67-A (N=18)		10.4 (2.83)	3.39 (0.98)	91.8 (22.8)	9.26 (3.10)	3.39 (0.98)	64.8 (31.1)
	4 x Patch FS-67-L (3% l-Menthol) (N=18)		9.26 (2.08)	4.00 (2.22)	84.4 (27.1)	7.85 (2.28)	4.00 (2.22)	50.9 (26.8)
FS-67-121	10 x FS-67-A Patches (N=18)		40.9 (12.6)	3.28 (0.75)	319 (87.1)	39.1 (12.9)	3.28 (0.75)	275 (89.5)
FS-67-122	Patch FS-67-A 2 Patches q8h (N=18)	Day 1	6.51 (2.93)	3.39 (1.73)	33.6 (14.5)	5.06 (2.71)	3.39 (1.73)	22.5 (12.6)
		Day 5	21.2 (8.67)	NA	97.4 (36.8)	19.8 (8.35)	NA	85.5 (34.9)
FS-67-15	4 x FS-67-A Patches Females (N=18)		9.76 (4.43)	2.92 (1.00)	89.0 (35.9)	8.50 (4.16)	2.92 (1.00)	60.1 (28.7)

Correction for the table: N=17 for Study FS-67-122; AUC_{0-24} should be AUC_{0-8} for Study FS-67-122.

Data for *l*-menthol in Study FS-67-03-L were considered valid. The results suggested that exposure of menthol from four FS-67 patch application was within the range of menthol exposure from 1.25% and 16% menthol ointment (the menthol concentration ranges defined by TFM) when applied to the same size of the body surface area.

Menthol data from the rest four PK studies were not considered reliable without investigation due to widespread and systemic problems identified with the analytical site. Cross-study comparison was made for general understanding of the variability of the data. When four (4) FS-67 patches were applied (Studies FS-67-03-L, FS-67-14-Pl and FS-67-15), the Cmax and AUC values ranged from 9.3 to 14.5 ng/mL and 60.1 to 104 ng*hr/mL, respectively (see Table 38). When 10 patches (2.5 times of 4 patches) were simultaneously applied (Study FS-67-121), the concentrations of menthol increased 3 to 4-fold as compared to 4-patch data. In addition when 2 patches were applied three times daily for five consecutive days (Study FS-67-122), the Day 1

Cmax values were approximately half of those attained after single dose administration of 4 patches. Exposure of menthol in females (Study FS-67-15) were somewhat lower when compared to males (Study FS-67-03-L) (AUC 60 vs. 104 ng*hr/mL). It is not clear whether the difference is due to assay issues or gender differences.

2.2.5 What is exposure of methyl salicylate from various studies?

Table 39. Cross-study comparison of methyl salicylate C_{max} and AUC after administration of FS-67 patches and methyl salicylate ointments.

			Plasma Methyl Salicylate Uncorrected			Plasma Methyl Salicylate Baseline-Corrected		
Study No. Protocol No.	Treatment		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
FS-67-03-M	4 x Patch FS-67-A (N=30)		38.5 (20.2)	3.45 (2.41)	403 (195)	35.1 (20.3)	3.45 (2.41)	321 (184)
	10% Methyl Salicylate Ointment (N=30)		37.7 (16.0)	4.33 (3.06)	400 (149)	34.0 (15.3)	4.33 (3.06)	311 (127)
	60% Methyl Salicylate Ointment (N=30)		37.7 (15.9)	3.55 (1.56)	405 (145)	34.2 (15.1)	3.55 (1.56)	323 (119)
FS-67-14-P1	4 x Patch FS-67-A (N=18)		8.31 (4.92)	1.39 (0.78)	23.6 (14.8)	8.21 (4.82)	1.39 (0.78)	22.3 (13.7)
	4 x Patch FS-67-M (10% Methyl Salicylate) (N=18)		5.89 (3.84)	1.39 (0.78)	15.2 (9.97)	5.89 (3.84)	1.39 (0.78)	16.2 (10.5)
FS-67-121	10 x FS-67-A Patches (N=18)		33.4 (21.8)	1.42 (0.73)	113 (62.8)	33.3 (21.9)	1.42 (0.73)	114 (63.6)
FS-67-122	Patch FS-67-A 2 Patches q8h (N=18)	Day 1	4.40 (3.09)	1.44 (1.07)	12.2 (6.99)	NA	NA	NA
		Day 5	15.2 (10.3)	NA	27.4 (13.4)	NA	NA	NA
FS-67-15	4 x FS-67-A Patches Females (N=18)		24.8 (16.5)	1.82 (1.49)	139 (64.2)	23.9 (16.5)	1.82 (1.49)	115 (67.1)

Correction for the table: N=17 for Study FS-67-122; AUC_{0-24} should be AUC_{0-8} for Study FS-67-122.

Data from Study FS-67-03-M were not considered valid (please refer to Section 4.2.2, individual study review, for details). Methyl salicylate data from the rest four PK studies were also not considered reliable without investigation due to widespread and systemic problems identified with the analytical site.

Cross-study comparison was made for general understanding of the variability of the data. When four (4) FS-67 patches were applied (FS-67-14-P1 and FS-67-15), the methyl salicylate Cmax values were low and variable; the mean (SD) values for the two studies were 8.21 (4.82) ng/mL and 23.9 (16.5) ng/mL, respectively (see Table 39). The mean (SD) AUC values were also variable accordingly. When methyl salicylate concentrations are compared between men and women receiving 4 FS-67 patches, the methyl salicylate AUC and Cmax values in women were higher than those observed in males (Study FS-67-14-P1) (AUC 115 vs. 22 ng*hr/mL). It is not clear whether the differences in exposure observed were due to assay issues or gender difference.

2.2.6 What is exposure of salicylic acid from various studies?

Table 37. Cross-study comparison of salicylic acid C_{max}, T_{max} and AUC after administration of FS-67 patches and methyl salicylate ointments.

			Plasma Salicylic Acid Uncorrected			Plasma Salicylic Acid Baseline-Corrected		
Study No. Protocol No.	Treatment		C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
FS-67-03-M	4 x Patch FS-67-A (N=30)		1181 (369)	3.24 (0.63)	8738 (2601)	1158 (366)	3.24 (0.63)	8187 (2454)
	10% Methyl Salicylate Ointment (N=30)		713 (189)	3.00 (0.91)	5003 (1080)	691 (185)	3.00 (0.91)	4469 (977)
	60% Methyl Salicylate Ointment (N=30)		1346 (492)	4.77 (0.77)	10932 (3512)	1325 (495)	4.77 (0.77)	10433 (3567)
FS-67-14-P1	4 x Patch FS-67-A (N=18)		1284 (257)	3.61 (0.78)	8894 (2139)	1277 (255)	3.61 (0.78)	8737 (2077)
	4 x Patch FS-67-M (10% Methyl Salicylate) (N=18)		1313 (267)	3.78 (0.81)	9482 (2454)	1306 (265)	3.78 (0.81)	9324 (2406)
FS-67-121	10 x FS-67-A Patches (N=18)		5214 (1589)	3.67 (0.77)	38525 (12204)	5196 (1586)	3.67 (0.77)	38079 (12106)
FS-67-122	Patch FS-67-A 2 Patches q8h (N=18)	Day 1	623 (193)	3.35 (0.61)	3348 (1023)	613 (192)	3.35 (0.61)	3274 (1009)
		Day 5	1435 (603)	NA	7628 (2988)	1426 (602)	NA	7551 (2978)
FS-67-15	4 x FS-67-A Patches Females (N=18)		1186 (430)	3.80 (0.94)	9339 (4389)	1130 (411)	3.80 (0.94)	7986 (3858)

Correction for the table: N=17 for Study FS-67-122; AUC_{0-24} should be AUC_{0-8} for Study FS-67-122.

The analytical assay for salicylic acid was not considered valid. The low concentration samples were likely to be impacted the most (please refer to Section 2.6 and Section 4.2.1 for details). Cross-study comparison was made for general understanding of the variability of the data. When four (4) FS-67 patches were applied (Studies FS-67-03-M, FS-67-14-P1 and FS-67-15), the Cmax and AUC values were comparable (see Table 37). When 10 patches were simultaneously applied (Study FS-67-121), the concentrations of salicylic acid increased (Cmax = 5196 ng/mL), ~4-5 fold of the 4 patch data. When 2 patches were applied three times daily for five consecutive days, the Day 1 Cmax values were approximately half of those attained after single dose administration of 4 patches. When salicylate concentrations are compared between men and women receiving 4 FS-67 patches, similar pharmacokinetic data were observed.

2.3 Intrinsic Factors

Not Applicable.

Gender: 5 PK studies were conducted in male subjects and one study in female subjects. Because data were not considered valid, gender comparison would not be made.

2.4 Extrinsic Factors

Not Applicable.

2.5 General Biopharmaceutics

2.5.1 What is formulation (quantitative composition) of FS-67 topical patch?

The drug product, FS-67 Topical Patch, is formulated as a patch product and is intended to be topically applied. The FS-67 patch (7 x 10 cm) consists of an adhesive mass that delivers the active ingredients, which are contained between a [redacted] backing cloth and a removable [redacted] film. The adhesive mass contains two active ingredients, methyl salicylate, NF (MS) and *l*-menthol, USP (LM). The patch is applied to the skin by removing the [redacted] film and placing the adhesive mass in contact with the site, leaving the cloth backing as a protective outer layer. The drug content of each patch is 10% MS [redacted] and 3% LM [redacted] (Table 2.5.1.1). b(4)

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Table 2.5.1.1. Quantitative Composition of FS-67 Topical Patch

Component	Reference to Quality Standard	Function	% w/w	mg per patch
Methyl salicylate	NF	Active ingredient	10.00*	
l-Menthol	USP	Active ingredient	3.00*	
Styrene-isoprene-styrene block copolymer	JPE			
Polyisobutylene 1,200,000	NF			
Polyisobutylene	NF			
Mineral oil	USP			
Synthetic aluminum silicate	JP			
Alicyclic saturated hydrocarbon resin	HSE			
Total	---	---		
Backing cloth	HSE			
Film	HSE			

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* Due to the volatility of the active pharmaceutical ingredients, a manufacturing overage of both *l*-menthol and methyl salicylate corrects for losses during the manufacturing process. This results in a final product containing of methyl salicylate (10%) and of *l*-menthol (3%) per patch.

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USP United States Pharmacopeia
NF National Formulary
JPE Japanese Pharmaceutical Excipient
HSE In-house specification
JP Japanese Pharmacopoeia

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2.5.2 Which batches were used in the pivotal clinical and bioavailability studies?

Table 2.5.2.1. FS-67 Topical Patch Batches Used in Clinical Studies and NDA Primary Stabilty Studies.

FS-67 Lot Number	Methyl Salicylate			*l*-Menthol			FS-67 Batch Size	FS-67 Process and Overage	FS-67 DOM	Clinical Study Number	Study Type
	Lot	Batch Size	DOM	Lot	Batch Size	DOM					
FSA0001	Y001	[redacted]	18 May 00	54-143	[redacted]	25 Sep 00	[redacted]	[redacted]	20 Nov 00	FS-67-02 FS-67-10 FS-67-11	Skin Safety study
FSA0002	Y001		18 May 00	54-143		25 Sep 00			21 Nov 00	FS-67-03-M FS-67-03-L FS-67-01	PK study & Skin Safety study
FS15301A[1)]	Y063		08 Feb 01	54-368		22 Feb 01			30 May 01	FS-67-121 FS-67-15 FS-67-14-P1	PK study & Stability study
FS15312A[2)]	Y063		08 Feb 01	54-368		22 Feb 01			31 May 01	FS-67-122 FS-67-011	PK study & Skin Safety study & Stability study
FS16013A	Y063		08 Feb 01	54-368		22 Feb 01			1 Jun 01	N.A.	Stability study
FS16044A[3)]	Y063		08 Feb 01	54-368		22 Feb 01			4 Jun 01	FS-67-E01	Efficacy study
FS1030501	Y224		11 Apr 03	56-306		20 Dec 02			21 May 03	FS-67-E02	Efficacy study

DOM = Date of Manufacture

1) The lot # FS15301A is same as the lot# of the clinical sample label, FSA0003
2) The lot # FS15312A is same as the lot# of the clinical sample label, FSA0004
3) The lot # FS16044A is same as the lot# of the clinical sample label, FSA0006

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2.6 Analytical

2.6.1 Were the analytical methods used to determine menthol, methyl salicylate, and salicylic acid in biological fluids adequately validated?

Yes, assays for menthol and methyl salicylate were validated. However, assay for salicylic acid was not validated.

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Table 2.6.1.1. Summary of Analytical Methods.

Analyte	Matrix	Analytical Method	Internal Standard	Limit of Quantitation (Linear Range)
***l*-Menthol**	Human Plasma	GC/MS		1 ng/mL (1-44 ng/mL)
***l*-Menthol**	Human Urine	GC/MS		0.951 µg/mL (0.951-47.57 µg/mL)
Methyl Salicylate	Human Plasma	GC/MS		1.02 ng/mL (1.02-15.25 ng/mL)
Salicylic Acid	Human Plasma (EDTA or oxalate)	LC/MS/MS	D6-salicylic acid	5 ng/mL (5-2000 ng/mL)

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Note: Sponsor used free menthol, methyl salicylate, and salicylic acid to represent unconjugated component in the report (free does not mean protein unbound).

Menthol:
The following table summarizes the validation method for menthol provided by the Sponsor.

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Table 2.6.1.2. Validation Summary for Determination of Menthol in Human Plasma.

Working Instruction [redacted] Standard Operating Procedure [redacted] A High Resolution Gas Chromatographic Method for the Determination of Free Menthol in Human Plasma by Mass Spectrometric Detection Specific to Hisamitsu Pharmaceuticals Co. Unless specified otherwise, data for human plasma (EDTA) is presented. b(4)

Validation Summary	
Analyte	Free Menthol
Matrix / Anticoagulant	Human Plasma / EDTA or Potassium Oxalate
Preservative	[redacted] (2.5 mg/mL) b(4)
Assay Volume Required	500 mcL
Detection Method	Electron impact (GC-MSD)
Standard Curve Range in Water	1.10 ng/mL to 43.92 ng/mL
Regression Type	1/Concentration Linear
Quantitation Method	Peak Area Ratio
Sensitivity (Between-Batch)	**Precision:** 18.9% (QC D) **Accuracy:** 91.0% (QC D)
(Within-Batch)	**Precision:** 17.0% (QC D) **Accuracy:** 94.9% (QC D)
(Within-Batch) in Human Plasma (Potassium Oxalate)	**Precision:** 6.1% (QC D) **Accuracy:** 103.1% (QC D)
Between-Batch Precision and Accuracy	**Precision:** 12.2% (QC A), 5.5% (QC B), 5.1% (QC C) **Accuracy:** 95.3% (QC A), 98.5% (QC B), 102.2% (QC C)
Within-Batch Precision and Accuracy	**Precision:** 6.4% (QC A), 2.0% (QC B), 1.7% (QC C) **Accuracy:** 98.1% (QC A), 94.6% (QC B), 97.9% (QC C)

Within-Batch Precision and Accuracy in Human Plasma (Potassium Oxalate)	**Precision:** 3.7% (QC A), 3.0% (QC B), 0.8% (QC C) **Accuracy:** 94.5% (QC A), 98.3% (QC B), 100.7% (QC C)
Dilution Integrity	118.85 ng/mL (DF : 5)
Freeze and Thaw Stability	5 cycles at -22°C
Freeze and Thaw Stability in Human Plasma (Potassium Oxalate)	4 cycles at -22°C
Freeze and Thaw Stability in Water	1 cycle at -22°C
Bench Top Stability	29.05 hours at room temperature
Bench Top Stability in Human Plasma (Potassium Oxalate)	77.2 hours at room temperature
Bench Top Stability in Water	2.9 hours at room temperature
Long Term Stability	124 days at -22°C
Long Term Stability in Human Plasma (Potassium Oxalate)	7 days at -22°C
Long Term Stability in Water	8 days at -22°C
Stock Solution Stability (Free Menthol)	202 day [redacted] at -22°C
Stock Solution Stability [redacted]	153 days [redacted] at -22°C
Processed Sample Integrity	103 hours (4.2 days) at room temperature
Processed Sample Integrity of Human Plasma (Potassium Oxalate) extracts	158 hours (6.5 days) at room temperature
Autosampler Stability	18.9 hours
Batch size (ME Batch)	105 injections

b(4)

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Table 2.6.1.3. Validation Summary for Determination of Menthol in Human Urine.

Validation method SOP [redacted] High Resolution Gas Chromatographic Method for the Determination of Total Menthol in Human Urine using Mass Spectrometric Detection Specific to Hisamitsu Pharmaceuticals Co., Inc. b(4)

Analyte	Total menthol
Matrix / Anticoagulant	Human Urine
Assay Volume Required	250 mcL
Detection Method	Mass Spectrometry (GC-MSD)
Standard Curve Range	0.951–47.570 mcg/mL
Regression Type	Quadratic (1/concentration)
Quantitation Method	Peak Area Ratio
Within Batch Precision and Accuracy Sensitivity (LLOQ QC)	Precision: 4.6 % Accuracy: 96.6%
Between Batch Precision and Accuracy Sensitivity (LLOQ QC)	Precision: 8.6% Accuracy: 93.6 %
Between Batch Precision and Accuracy (LOW, MEDIUM AND HIGH QC)	Precision: 2.1 to 8.4% Accuracy: 92.7 to 95.4 %
Within Batch Precision and Accuracy (LOW, MEDIUM AND HIGH QC)	Precision: 2.1 to 2.7% Accuracy: 86.8 to 94.8%
Dilution Integrity	1:5 and 1:10 at 203.180 mcg/mL
Freeze and Thaw Stability	4 cycles at –22°C
Bench Top Stability	17.0 hours at room temperature
Long Term Stability	49 days at –22°C
Stock Solution Stability	95 days [redacted] at –22°C 40 days [redacted] at –22°C Menthol stock in [redacted] at –22°C is in progress b(4)
Processed Sample Integrity	99.9 hours at room temperature
Autosampler Stability	11.7 hours at ambient temperature
Batch size (ME Batch)	[redacted]

Methyl Salicylate:

The analytical method for the determination of methyl salicylate in human plasma was developed

b(4)

Human plasma (500 mcL) containing methyl salicylate to which internal standard) was added, . A solution was added prior The tubes were then transferred to clean amber vials. The samples were injected into a GC/MSD system using MS detection. Methyl salicylate is quantitated by peak area ratio to its internal standard by mass spectrometry using a single ion monitoring mode.

human plasma lots, free of significant interference, were pooled and used to prepare calibration standard and human plasma lots, free of significant interference, were pooled and used to prepare QC samples.

The following table summarizes the validation method for salicylic acid provided by the Sponsor. b(4)

Table 2.6.1.4.

Table 8. Validation summary for the determination of methyl salicylate in human plasma by mass spectrometric detection

Validation Summary	
Analyte	Methyl Salicylate
Matrix / Anticoagulant	Human Plasma / Potassium Oxalate
Preservative	[redacted] (2.5 mg/mL)
Assay Volume Required	500 mcL
Detection Method	GC/Mass Spectrometric Detection
Standard Curve Range	1.02 to 15.25 ng/mL
Regression Type	Linear (1/concentration)
Quantitation Method	Peak Area
Sensitivity (Between-Batch) (Within-Batch)	Precision: 13.9% (QC D) Accuracy: 93.7% (QC D) Precision: 10.9% (QC D) Accuracy: 96.4% (QC D)
Between-Batch Precision and Accuracy	Precision: 8.2% (QC A), 5.1% (QC B), 4.1% (QC C) Accuracy: 97.1% (QC A), 105.3% (QC B), 107.3% (QC C)
Within-Batch Precision and Accuracy	Precision: 6.6% (QC A), 6.0% (QC B), 4.2% (QC C) Accuracy: 97.4 % (QC A), 99.8 % (QC B), 99.7 % (QC C)
Dilution Integrity	261.55 ng/mL
Freeze and Thaw Stability	5 cycles at -22°C
Recovery	Methyl Salicylate: 102.4% (QC A), 96.5% (QC B), 99.1% (QC C) [redacted] (IS): 105.0%
Bench Top Stability	21.5 hours at Rm. T.
Long Term Stability	154 days at –20°C
Stock Solution Stability	82 days in [redacted] at -22°C 42 days in [redacted] at -22°C
Internal Standard Stock Stability	153 days in [redacted] at -22°C
Processed Sample Integrity	129.2 hours at Rm. T.
Autosampler Stability	16.1 hours at Rm. T.
Batch size (ME Batch)	

b(4)

b(4)

b(4)

Source: Validation Report entitled: "Validation Of A High Resolution Gas Chromatographic Method For The Determination Of Methyl Salicylate In Human Plasma (Potassium Oxalate) By Mass Spectrometric Detection Specific To Hisamitsu Pharmaceuticals Co." [redacted] Project No. 002417/QBB, Addendum Report #1 Dated: July 22, 2002 (see analytical sections of study reports).

b(4)

b(4)

Salicylic Acid:

The method SOP was used for the measurement of salicylic acid assay in human plasma. Because salicylic acid is commonly present in fruits, vegetables and drinks, consequently, it is difficult to obtain salicylic acid free matrices. Therefore the calibration curve standards are prepared in 0.6% acetic acid in water solution and QC samples in human plasma. b(4)

Samples containing free salicylic acid, D_6-salicylic acid (internal standard) and 0.6% acetic acid in water solution are extracted on extraction plate. Eluates are then subjected to a high performance liquid chromatographic (HPLC) analysis on a column. Free salicylic acid and its internal standard are detected and quantitated by mass spectrometry operating under selected reaction monitoring (SRM) MS/MS conditions. Quantitation is by ratio of peak area of the analyte to its internal standard. The concentration of the analyte in samples is predicted from a weighed (1/concentration) linear regression of a calibration curve of free salicylic acid in 0.6% acetic acid in water solution. The lower limit of quantitation (LLOQ) is 5.00 ng/mL using 200 mcL of human plasma sample. Reference SOP b(4)

As indicated in the Executive Summary of this review, the draft "5-year review plan" closure report indicated that this validation method is not valid. The main reason was due to "unexpected values" of Free Salicylic Acid, i.e., percent deviation greater than 50% of nominal concentration, reported for QC samples at the LLOQ and low levels in validation PMC. These unexpected values significantly impact the intra-and inter-batch precision and accuracy results".

Summary of Investigation Report (IR-102):

The review of method validation 002417 PMC-PUF reported observations relating to *(a)* interference at the drug retention time (analyte response > 20% of lower limit of quantitation - LLOQ) in blanks, reagent blanks, zero standards and/or pre-dose samples and *(b)* percent deviation greater than 50% of nominal concentration in calibration standards and/or QC samples. These observations are reported for multiple validation batches.

The validation report excluded these "unexpected values" which was not appropriate.

The following facts indicate data validity issues for method SOP b(4)

1. Multiple occurences of interference levels in blank-related samples
2. Several QC samples with a deviation greater than 50% of nominal concentration
3. A frequency of 2.8% of the calibration standards and QC samples at the LLOQ and low levels present unexpected values
4. A cause for the unexpected values was not identified and therefore the unexpected values should be included in the intra-and inter-batch precision and accuracy evaluation
5. Inclusion of unexpected QC values results in the failure of the intra- and inter-batch precision and accuracy according to current criteria as well as those in effect at the time. Inclusion of these values significantly impacts the precision by increasing the CV to 79.9% and 29.3% for LLOQ and low QC samples and the accuracy to 143.7% of nominal concentration.
6. The cross-validation of human K/oxalate plasma relies on the validation data of the human EDTA plasma which does not meet intra-and inter-batch precision and accuracy.

Based on the above-mentioned facts, the validation data (human EDTA plasma) and cross-validation data (human K/oxalate plasma) are thereby considered to be not valid. Therefore, analytical method outlined in SOP LMS-6975-00 does not meet the validation requirements as per current criteria as well as those in effect at the time validation was performed.

3 DETAILED LABELING RECOMMENDATIONS

The label for an OTC product does not contain PK information. Please refer to the appropriate reviews from ONP/DNCE for details of labeling review comments.

2 Page(s) Withheld

_____ Trade Secret / Confidential

2 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

4.2 Individual Study Review

Reviewer's Note: The analytical site underwent a "5-year review plan" to retrospectively review analytical data of all the bioequivalence studies for the past 5 years (Jan 2001-Dec 2004) for validity of the results. During the review cycle, the Sponsor notified the Agency that two of the PK studies in this NDA, Study FS-67-03-L and FS-67-03-M, were selected to be reviewed under the "5-year review plan" and they just received the draft closure reports from [redacted]. In their draft closure reports, [redacted] concluded that the validation method and study data for l-menthol in study FS-67-03L were considered valid. In their draft closure report of study FS-67-03M, [redacted] questioned the validity of the salicylic acid (metabolite) method. In addition, [redacted] found the method validation results for methyl salicylate to be acceptable but questioned the validity of the production runs for the FS-67-03M study sample analyses. b(4)

Based on the deficiencies identified in the draft closure report, the Agency can not accept either methyl salicylate or salicylic acid results for Study FS-67-03-M.

Although the other 4 PK studies were not selected to be reviewed under the "5-year review plan", the same issues are applied to them as well.

In this review, for studies that have questionable PK results, data were listed for reference purpose, and no conclusion was drawn.

The actions taken by this Reviewer are:

- *For menthol, data are accepted for Study 67-03-L but not other studies*
  - *Although method was valid, validity of the production runs for other studies were questionable due to the analytical site problems*
- *For methyl salicylate, data were not accepted for all the studies*
  - *Although method was valid, production run for Study 67-03-M was not valid*
  - *Validity of the production runs for other studies were questionable due to the analytical site problems*
- *For salicylic acid, data were not accepted for all the studies*
  - *Method was not valid*

4.2.1 Study FS-67-03-L: A Three Treatment Randomized, Single Dose, Crossover. Evaluation Designed To Compare the Percutaneous Absorption of Menthol Following the Application of the Topical Patch Product, FS-67-A, and Two Reference Ointments in Healthy Male Volunteers (Report No. 011450)

Date of Report:	August 14, 2002
Date of Study:	21 October 2001 – 03 December 2001
Test Formulations:	**Treatment A:** FS-67-A Patch (containing 10% methyl salicylate and 3% l-menthol) Manufactured by: Hisamitsu Pharmaceutical Co., Inc. Batch No: FSA0002 Expiration date: October 2002 **Treatment B:** FS-1.25LM-OINT (1.25% l-menthol ointment) Manufactured by: Hisamitsu Pharmaceutical Co., Inc.Batch No: FSC11 Expiration date: June 2003 **Treatment C:** FS-16LM-OINT (16% l-menthol ointment) Manufactured by: Hisamitsu Pharmaceutical Co., Inc. Batch No: FSD11 Expiration date: June 2003
Sponsor:	Hisamitsu Pharmaceutical Co., Inc.
Protocol/Study No.:	Sponsor Protocol No. FS-67-03-L MDS Pharma Services Project No. 011450
Development Phase of Study:	Phase I pharmacokinetic study in healthy subjects
Number of Subjects:	A total of 40 male healthy non-smoking adult volunteers were enrolled in the study, and 37 subjects completed the study.
Principal Investigator: **Clinical Site:**	Mark J. Allison, M.D. MDS Pharma Services 4639 South 36th Street Phoenix, Arizona 85040
Author(s):	b(4)

Objectives: The objective of this study was to compare the absorption of the 3% menthol component of the FS-67-A patch with two reference ointments, one containing 1.25% menthol and the other containing 16% menthol when applied to healthy male volunteers.

Study Design: This was designed as an open-label, randomized, 3-way crossover, single-dose evaluation to compare the absorption of l-menthol (LM) in healthy non-smoking male volunteers following application of 4 (four) FS-67-A patches, 1.25% LM ointment and 16% LM ointment.

Methods: Pharmacokinetic parameters were calculated from the plasma concentrations of free menthol obtained following application of the investigational patch and ointment formulations. Endogenous menthol concentrations were also quantified on the days preceding each drug administration to allow calculation of baseline-adjusted pharmacokinetic data.

In addition, residual data analyses were performed by the Sponsor.

Subject Demographics (N=40): 3 Subjects discontinued. The mean age of the subjects was 27 years (range 18 - 44 years), the mean height of the subjects was 69.1 inches (range 60.5 - 73.0 inches), and the mean weight of the subjects was 162.7 pounds (range 132 - 199 pounds). With regard to race, 17 subjects were Caucasians, 19 were Hispanic, 2 were black, 1 was Asian and 1 was American Indian.

There were 3 subjects who were discontinued/withdrawn from the study:

Sub. No.	Init.	Release Date	Release Reason
5	[redacted]	30 Oct 2001 07:52	Due to an adverse event, subject was dropped on Day 1 of Period 2 (after Treatment A) by the Principal Investigator.
19	[redacted]	29 Oct 2001 08:06	Due to an adverse event, subject was dropped on Day -1 of Period 2 (after Treatment A) by the Principal Investigator.
39	[redacted]	18 Nov 2001 07:59	Prior to dosing, subject withdrew from the study on Day 2 in Period 2 (after Treatment B) due to personal reasons.

b(6)

Treatment Administered: Four patches of FS-67 -A, or an amount of ointment, 2800 mg / 280cm^2 were applied to each study volunteer on one occasion (Study Day 1 in each period) according to a randomization scheme generated at MDS Pharma Services. Ville Saint-Laurent, Canada.

- Treatment A – 4 patches (FS-67-A, 10% methyl salicylate and 3% l-menthol) applied, 2 patches to each side of the backbone, one above the other, covering an area of 20 cm in length and 7 cm in width.

- Treatment B – 2.8 gm of FS-1.25LM-OINT (1.25% l-menthol ointment) applied evenly to the designated dosing area, 20 cm in length and 7 cm in width. The ointment was applied using the same surface area and placement as the patches.

- Treatment C – 2.8 gm of FS-16LM-OINT (16% l-menthol ointment) applied evenly to the designated dosing area, 20 cm in length and 7 cm in width. The ointment was applied using the same surface area and placement as the patches.

The dose of menthol in each patch is [redacted] so total dose of menthol in 4 patches is [redacted] 2.8 mg of 1.25% menthol ointment contains 35 mg menthol and 2.8 mg of 16% menthol ointment contains 448 mg menthol.

Sample Collection: Blood samples (7 mL) were collected during each study period at hours -24, -18, -12, and 0 (predose) and at Hours 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 (postdose). Samples were collected and processed under fluorescent lighting at room temperature. Plasma samples were separated by centrifugation, flash frozen in methanol and dry ice and then kept frozen at -20°C, packed in dry ice, and sent to the MDS Pharma Services in Montreal, Quebec. b(4)

Sample Analysis: Bioanalysis was performed on samples from 34 subjects that successfully completed all three phases of the study.

The drug assays, data analysis and statistics were performed at:

MDS Pharma Services
2350 Cohen Street,
Saint-Laurent (Montreal),
Quebec, Canada
H4R 2N6

Analyte	Validation Report No.	Analytical Method	Analytical Range
Menthol in plasma	002417-OUF	GC/MS	1.01-40.40 ng/mL

Reviewer's Note: The analytical method validation and production run were reviewed under "5-year review plan" and considered valid.

Pharmacokinetic Data Analysis: Statistical and pharmacokinetic analyses were performed on data from 34 subjects: Nos. 1-4, 6, 9-11, 13, 14, 16-18, 20, 21, 24, 25, 27, 30 and 32 (Group 1), 37, 38.40 -49, 52 and 54 (Group 2). Subjects 50, 51 and 53 were considered alternates and did not complete the study.

Non-zero pre-dose concentrations values were observed for free menthol in plasma, The 0-hr and post-dose plasma concentrations for free menthol in plasma were baseline adjusted using the mean of the pre-dose concentration values (values at -24, -18, -12 and 0 hours). In the case where a pre-dose value was Below the Limit of Quantitation (BLQ), this value was set to zero in the calculation of the mean baseline value for that subject. *(Reviewer's Note: Same was done for all the PK studies where endogenous levels were detected.)*

Pharmacokinetic Results:

Table 14. Study FS-67-03-L Overall Pharmacokinetic Summary: Arithmetic Means (SD)

		Plasma Menthol Uncorrected			Plasma Menthol Baseline-Corrected		
Treatment	**Statistic**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**AUC_{0-t} (ng•hr/mL)**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**AUC_{0-24} (ng•hr/mL)**
A Patch FS-67-A (N=34)	Arithmetic Mean (SD)	15.5 (5.07)	3.30 (3.04)	129 (34.5)	14.5 (4.85)	3.30 (3.04)	104 (30.6)
	LS Means	-	-	-	13.76	-	100.83
B 1.25% l-Menthol Ointment (N=34)	Arithmetic Mean (SD)	5.14 (2.04)	5.94 (6.26)	57.9 (22.6)	4.06 (1.74)	5.94 (6.26)	33.1 (17.5)
	LS Means	-	-	-	3.81	-	31.12
C 16% l-Menthol Ointment (N=34)	Arithmetic Mean (SD)	24.2 (10.1)	3.74 (0.90)	220 (81.0)	23.1 (10.2)	3.74 (0.90)	194 (82.6)
	LS Means	-	-	-	21.37	-	180.11
A vs. B Patch vs 1.25% Ointment	Ratio of LS Means (%)						
	p-value	-	-	-	0.0001	-	0.0001
	95% Lower Confidence Bound	-	-	-	1.169	-	1.035
	Difference				1.284		1.176
A vs. C Patch vs 16% Ointment	Ratio of LS Means (%)						
	p-value	-	-	-	0.0001	-	0.0001
	95% Upper Confidence Bound	-	-	-	-0.327	-	-0.442
	Difference				-0.440		-0.5801

Residual Analysis:
The residual potencies (amounts of menthol as a % of the original doses) of each patch ointment doses were determined and are summarized in Table below. It is noted that they may not represent the amount of drug absorbed by the body. Drug may be lost due to other factors other than transdermal absorption. FS-67 is formulated with [redacted] backing. Because *l*-menthol is volatile, it could be lost to the air during patch application. Thus, unlike other transdermal systems, residual potencies may not be used to determine absorbed doses. b(4)

Study FS-67-03-L: Residual menthol amounts (% of original potency) left after 8 hr application period

Treatment	Residual Potency (%)
A Patch FS-67-A (N=39)	
B 1.25% l-Menthol Ointment (N=38)	
C 16% l-Menthol Ointment (N=37)	

b(4)

Safety: No serious Adverse Events were reported during the Study. 93% of the Adverse Events were mild in severity and 7% were moderate in severity. Four (4) Adverse Events were considered by the Investigator to be possibly or probably drug related.

Table B
(FS-67-A Patch)
Reported Adverse Medical Events While on Treatment

# Subjects	Description	Serious	Severity	Resolution	Considered Study Related
3	Cough	NS	Mild-Moderate	Resolved	None
1	Watery Eyes	NS	Mild	Resolved	None
1	Dyspnoea NOS	NS	Mild	Resolved	None
1	Haemoptysis	NS	Mild	Resolved	None
2	Headache NOS	NS	Mild	Resolved	Possible
2	Nasal Congestion	NS	Mild	Resolved	None
1	Rhinorrhoea	NS	Mild	Resolved	None
1	Throat irritation	NS	Mild	Resolved	None

Summary: The patch formulation produces systemic concentrations of menthol that are greater than the 1.25% but less than the 16% *l*-menthol ointments when applied to the same size of the body surface area.

b(4)

4.2.2 Study FS-67-03-M: A Three Treatment Randomized, Single Dose, Crossover. Evaluation Designed To Compare the Percutaneous Absorption of Menthol Following the Application of the Topical Patch Product, FS-67-A, and Two Reference Ointments in Healthy Male Volunteers (Report No. 011450)

Date of Report:	August 16, 2002
Date of Study:	18 October 2001 – 12 November 2001
Test Formulations:	**Treatment A:** FS-67-A Patch (containing 10% methyl salicylate and 3% l-menthol) Manufactured by: Hisamitsu Pharmaceutical Co., Inc. Batch No: FSA0002 Expiration date: October-2002 **Treatment B:** FS-10MS-OINT (10% methyl salicylate ointment) Manufactured by: Hisamitsu Pharmaceutical Co., Inc. Batch No: FSA11 Expiration date: June-2003 **Treatment C:** FS-60MS-OINT (60% methyl salicylate ointment) Manufactured by: Hisamitsu Pharmaceutical Co., Inc. Batch No: FSB11 Expiration date: June-2003
Sponsor:	Hisamitsu Pharmaceutical Co., Inc.
Protocol/Study No.:	Sponsor Protocol No. FS-67-03-M MDS Pharma Services Project No. 011449
Development Phase of Study:	Phase I pharmacokinetic study in healthy subjects
Number of Subjects:	A total of 33 subjects enrolled in the study and 30 subjects completed the study.
Principal Investigator: **Clinical Site:**	Mark J. Allison, M.D. MDS Pharma Services 4639 South 36th Street Phoenix Arizona 85040
Author(s):	[redacted] b(4)
Objectives:	The objective of this study was to compare the absorption of the 10% methyl salicylate component of the FS-67-A patch with two reference ointments, one containing 10% methyl salicylate and the other containing 60% methyl salicylate when applied to healthy male volunteers.

b(4)

Study Design: This was designed as an open-label, randomized, 3-way crossover, single-dose evaluation to compare the absorption of methyl salicylate (MS) in healthy non-smoking male volunteers following application of 4 (four) FS-67-A patches, 10% MS ointment and 60% MS ointment.

Methods: Pharmacokinetic parameters were calculated from the plasma concentrations of free salicylic acid and methyl salicylate obtained following application of the one investigational patch product and two investigational ointments. Endogenous levels of these analytes were also quantified on the days preceding drug administration to allow calculation of baseline-adjusted pharmacokinetic data.

In addition, residual data analyses were performed by the Sponsor.

Subject Demographics (N=33): 3 Subjects discontinued (one due to high blood pressure, and 2 other due to personal reasons). The mean age of the subjects was 32 years (range of 19 through 45), the mean height of the subjects was 70.2 inches (range of 67 through 75), and the mean weight of the subjects was 171.7 Lbs (range 125 through 214). With regard to race, 15 subjects were Caucasians, 11 were Hispanic, 6 were black, and 1 was American Indian.

Treatment Administered: Four patches of FS-67-A, or an amount of ointment, 2800 mg / 280cm^2 were applied to each study volunteer on one occasion (Study Day 1 in each period) according to a randomization scheme generated at MDS Pharma Services, Ville Saint-Laurent, Canada.

- Treatment A – four patches of FS-67-A (10% MS —— /patch; 3% LM —— patch) b(4)
- Treatment B – 2.8gm of FS-10MS-OINT ointment
- Treatment C – 2.8gm of FS-60MS-OINT ointment

(The dose of methyl salicylate in each patch is —— so total dose of methylicylate in 4 patches is —— 2.8 mg of 10% methyl salicylate ointment contains 280 mg methyl salicylate and 2.8 mg of 60% methyl salicylate ointment contains 4667 mg methyl salicylate.)

Sample Collection: Blood samples (10 mL) were collected during each study period at hours -24, -18, -12, and 0 (predose) and at Hours 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 (postdose). Samples were collected and processed under fluorescent lighting at room temperature. Plasma samples were separated by centrifugation, flash frozen in methanol and dry ice and then kept frozen at -20°C, packed in dry ice, and sent to the MDS Pharma Services in Montreal, Quebec.

Sample Analysis: Sample analysis was performed at MDS Pharma Services, Saint-Laurent (Montreal), Quebec, Canada.

Analyte	Validation Report No.	Analytical Method	Analytical Range
Methyl Salicylate in plasma	002417-QBB	GC/MS	1.02-15.25 ng/mL
Salicylic Acid in plasma*	002417-PMC/PUF	LC/MS	5.00-2000.00 ng/mL

** The validation method was not considered valid.*

Analytical data for this study were reviewed under "5-year review plan". The method validation and production run were not considered valid for salicylic acid.

Main deficiency for salicylic acid validation runs: b(4)

The following facts indicate data validity issues for method SOP

1. Multiple occurences of interference levels in blank-related samples
2. Several QC samples with a deviation greater than 50% of nominal concentration
3. A frequency of 2.8% of the calibration standards and QC samples at the LLOQ and low levels present unexpected values
4. A cause for the unexpected values was not identified and therefore the unexpected values should be included in the intra-and inter-batch precision and accuracy evaluation
5. Inclusion of unexpected QC values results in the failure of the intra- and inter-batch precision and accuracy according to current criteria as well as those in effect at the time. Inclusion of these values significantly impacts the precision by increasing the CV to 79.9% and 29.3% for LLOQ and low QC samples and the accuracy to 143.7% of nominal concentration.
6. The cross-validation of human K/oxalate plasma relies on the validation data of the human EDTA plasma which does not meet intra-and inter-batch precision and accuracy.

Based on the above-mentioned facts, the validation data (human EDTA plasma) and cross-validation data (human K/oxalate plasma) are thereby considered to be not valid. Therefore, analytical method outlined in SOP does not meet the validation requirements as per current criteria as well as those in effect at the time validation was performed. b(4)

Main deficiency for salicylic acid production runs:

Based on the fact that (a) unexpected values are observed in study 011449-QMK similar to those observed in validation, (b) an assignable cause is not identified for these unexpected values, (c) the inter-batch precision of study 011449-QMK at the low QC level reflects that obtained in validation and (d) this study relies on a method SOP in which the validation data is considered not valid, bioanalytical data of study 011449-QMK is thereby considered not valid.

The analytical method was considered valid for methyl salicylate, however, the production runs were invalid.

Main deficiency for methyl salicylate production runs:

Assay for methyl salicylate was validated for a concentration range of 1.02-15.25 ng/mL. The concentration range was not appropriate for the study because at least 38% (559 of 1440) of the subject concentration values were above the highest calibration standard, i.e., upper limit of quantitation (ULOQ). These samples were repeated with a dilution factor. The difference between the extrapolated original value and repeat value ranges from 0.3 to 126%. The repeat value for almost half of the 559 subject samples that required repeat analysis with a dilution factor (i.e., 46.2%) the repeat value does not confirm with the original value (>30% see Table below). This discrepancy was not observed with the QC samples analyzed with a dilution factor.

In addition, 12 of the 30 subject pre-dose values of treatment period 1 (-0.17 hour prior to dosing) present unexpectedly high levels of methyl salicylate. Other unexpected results include no difference in PK of methyl salicylate with different treatments and removal of patch or ointment did not result in lower levels of methyl salicylate in subject samples.

Therefore, the analytical results are not considered valid.

Table 2: The percent difference between the original (extrapolated) value and repeat value

% Difference	# Repeats = 559	
	# Samples	%
0 - 10%	96	17.2
0 - 20%	201	36.0
0 - 30%	301	53.8
30 - 50%	148	26.5
> 50%	110	19.7

Pharmacokinetic Results:

(Data were not considered valid for either salicylic acid or methyl salicylate.)

Table 11. Study FS-67-03-M Pharmacokinetic Summary: Plasma Salicylic Acid

		Plasma Salicylic Acid Uncorrected			Plasma Salicylic Acid Baseline-Corrected					
Treatment	**Statistic**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**AUC_{0-t} (ng•hr/mL)**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**AUC_{0-24} (ng•hr/mL)**	**$AUC_{0-\infty}$ (ng•hr/mL)**	**Kel (hr^{-1})**	**Half-Life (hr)**
Treatment A Patch FS-67-A (N=30)	Arithmetic Mean (SD)	1181 (369)	3.24 (0.63)	8738 (2601)	1158 (366)	3.24 (0.63)	8187 (2454)	8317 (2465)	0.2049 (0.0958)	3.85 (1.30)
	LS Means	-	-	-	1119	-	7941.94	8070	-	-
Treatment B 10% Methyl Salicylate Ointment (N=30)	Arithmetic Mean (SD)	713 (189)	3.00 (0.91)	5003 (1080)	691 (185)	3.00 (0.91)	4469 (977)	4625 (998) (n=28)	0.2039 (0.1498) (n=28)	4.39 (1.77) (n=28)
	LS Means	-	-	-	679.8	-	4441	4476	-	-
Treatment C 60% Methyl Salicylate Ointment (N=30)	Arithmetic Mean (SD)	1346 (492)	4.77 (0.77)	10932 (3512)	1325 (495)	4.77 (0.77)	10433 (3567)	10537 (3549)	0.2366 (0.0829)	3.18 (0.81)
	LS Means	-	-	-	1263	-	10027.56	10148	-	-
A vs. B Patch vs. 10% Methyl Salicylate Ointment	Ratio of LS Means (%)	162.5	-	170.2	164.7	-	178.8	180.3	-	-
	p-value	0.0001	-	0.0001	0.0001	-	0.0001	0.0001	-	-
	95% Lower Confidence Bound	-	-	-	0.41452	-	0.49592	0.50278	-	-
	Difference				0.49872		0.58128	0.58950		
A vs. C Patch vs. 60% Methyl Salicylate Ointment	Ratio of LS Means (%)	88.7	-	79.9	88.6	-	79.2	79.5	-	-
	p-value	0.0184	-	0.0001	0.0198	-	0.0001	0.0001	-	-
	95% Lower Confidence Bound	-	-	-	-0.036541	-	-0.14783	-0.14468	-	-
	Difference				-0.12074		-0.23318	-0.22909		

Table 12. Study FS-67-03-M Pharmacokinetic Summary: Plasma Methyl Salicylate

		Plasma Methyl Salicylate Uncorrected			Plasma Methyl Salicylate Baseline-Corrected		
Treatment	Statistic	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
Treatment A Patch FS-67-A (N=30)	Arithmetic Mean (SD)	38.5 (20.2)	3.45 (2.41)	403 (195)	35.1 (20.3)	3.45 (2.41)	321 (184)
	LS Means				31.9		297.8
Treatment B 10% Methyl Salicylate Ointment (N=30)	Arithmetic Mean (SD)	37.7 (16.0)	4.33 (3.06)	400 (149)	34.0 (15.3)	4.33 (3.06)	311 (127)
	LS Means				30.2		285.0
Treatment C 60% Methyl Salicylate Ointment (N=30)	Arithmetic Mean (SD)	37.7 (15.9)	3.55 (1.56)	405 (145)	34.2 (15.1)	3.55 (1.56)	323 (119)
	LS Means				31.6		306.1
A vs. B Patch vs. 10% Methyl Salicylate Ointment	Ratio of LS Means (%)	104.6	-	101.9	105.7	-	104.5
	p-value	0.5069	-	0.5818	0.4585	-	0.3212
	95% Lower Confidence Bound				-0.069337		-0.02962
	Difference				0.055893		0.044137
A vs. C Patch vs. 60% Methyl Salicylate Ointment	Ratio of LS Means (%)	101.5	-	98.6	101.0	-	97.3
	p-value	0.8208	-	0.6875	0.8960	-	0.5388
	95% Lower Confidence Bound				0.13506		0.04648
	Difference				0.009827		-0.02727

Residual Analysis:

The residual potencies (amounts of methyl salicylate as a % of the original doses) of each patch and ointment doses were determined and are summarized in Table below.

Study FS-67-03-M: Residual methyl salicylate amounts (% of original potency) left after 8 hr application period

Treatment	Residual Potency (%)
A Patch FS-67-A (N=33)	
B 10% Methyl Salicylate Ointment (N=33)	
C 60% Methyl Salicylate Ointment (N=30)	

b(4)

4.2.3 Study FS-67-121: A single maximum dose study of FS-67-A methyl salicylate and menthol patch in healthy male volunteers (Report No. 011527)

REPORT NO. 011527

A SINGLE MAXIMUM DOSE STUDY OF FS-67-A METHYL SALICYLATE AND MENTHOL PATCH IN HEALTHY MALE VOLUNTEERS

Test Formulations:	**Treatment A:** FS-67-A Patch (containing 10% methyl salicylate and 3% l-menthol) Manufactured by: Hisamitsu Pharmaceutical Co., Inc. Batch No: FSA0003 Expiration date: April 2003
Sponsor:	Hisamitsu Pharmaceutical Co., Inc.
Protocol/Study No.:	Sponsor Protocol No. FS-67-121 MDS Pharma Services Project No. 011527
Development Phase of Study:	Phase I pharmacokinetic study in healthy, non-smoking subjects
Number of Subjects:	A total of 22 male subjects were enrolled in and completed the study.
Principal Investigator: **Clinical Site:**	James C. Kisicki, MD MDS Pharma Services 621 Rose Street Lincoln, Nebraska 68502 USA
Author(s):	[redacted] b(4)
Sponsor Signatory:	Mr. Kenichi Furuta, General Manager International Development Department Hisamitsu Pharmaceutical Co., Inc. 500 Chiswick High Road London W4 5RG United Kingdom Tel: +44 20 8956 2600, Fax: +44 20 8956 2599
GCP Compliance:	This study was conducted in compliance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (1996), including the archiving of essential documents.
Date of Report:	July 3, 2002
Date of Study:	19 October 2001 – 28 October 2001

Objectives:	The objective of this study was to determine the safety and tolerability of FS-67-A patches containing 10% methyl salicylate and 3% l-menthol, when given at the maximum dose possibly applied by product users, under single-dose conditions, to healthy non-smoking male volunteers. Ten patches is more than twice the maximum daily dose recommended for this product in the proposed labelling [redacted] b(4)
Study Design:	This was an open-label, one period study performed in 18 healthy non-smoking adult male volunteers and 4 alternates. Subjects were housed from the evening before Day -1 until after their 24-hour blood draw following patch application on Day 2.
Methods:	The safety and tolerability assessments included adverse event reports, vital signs measurements, physical examination results, electrocardiogram results and serum chemistry, haematology and urinalysis data. The AUC 0-t, Cmax and tmax pharmacokinetic parameters were calculated for plasma free menthol, free salicylic acid and methyl salicylate (unadjusted and adjusted for baseline data). The AUCinf, AUC/AUCinf, kel and half-life pharmacokinetic parameters were calculated for plasma free salicylic acid (adjusted for baseline).

Subject Demographics (N=22): The mean age of the subjects was 22 years (range of 19 through 42), the mean height of the subjects was 70.8 inches (range of 65 through 76 inches), and the mean weight of the subjects was 168.2 pounds (range 130 through 200 pounds). In terms of race, 20 subjects were Caucasian, one was Asian, and one was Hispanic.

Treatment Administered: Ten patches of FS-67-A were applied as a single-dose to each study volunteer on one occasion (Study Day 1) for a period of 8 hours. Five patches were applied on the subject's back, on each side of the backbone. The patches were paired one above the other on each side of the backbone. Each volunteer was in the sitting position as the patches were applied.

Sample Collection: Blood samples were collected in vacutainers containing potassium oxalate and 2.5 mg/mL [redacted] (preservative) at each collection time point. Blood samples were collected at -24, -18, -12 hours, predose, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours post-dose. A total of 16 blood samples (224 mL) were drawn during the study for drug analysis. Samples were collected and processed as per protocol. Plasma samples were separated by centrifugation, flash frozen, stored at -22°C ± 10°C, and kept frozen, packed in dry ice, and sent to MDS Pharma Services in St. Laurent (Montreal), Quebec. b(4)

Sample Analysis: The laboratory analyzed plasma from the first 18 subjects that completed the study (as indicated in the protocol).

The drug assays, data analysis and statistics were performed at:

MDS Pharma Services
2350 Cohen Street,
Saint-Laurent (Montreal),
Quebec, Canada
H4R 2N6

Analyte	Validation Report No.	Analytical Method	Analytical Range
Menthol in plasma	002417-OUF	GC/MS	1.03-41.28 ng/mL
Methyl Salicylate in plasma	002417-QBB	GC/MS	1.02-15.25 ng/mL
Salicylic Acid in plasma*	002417-PMC/PUF	LC/MS	5.00-2000.00 ng/mL

** The validation method was not considered valid.*

Pharmacokinetic Results (N=18): ***(Data were not reliable due to the well documented assay issues at the analytical site.)***

Table 24. Study FS-67-121 Overall Pharmacokinetic Summary

Plasma Salicylic Acid Uncorrected			Plasma Salicylic Acid Baseline-Corrected				
C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	Half-Life (hr)
5214 (1589)	3.67 (0.77)	38525 (12204)	5196 (1586)	3.67 (0.77)	38079 (12106)	38230 (12151)	2.72 (0.26)

Plasma Methyl Salicylate Uncorrected			Plasma Methyl Salicylate Baseline-Corrected		
C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
33.4 (21.8)	1.42 (0.73)	113 (62.8)	33.3 (21.9)	1.42 (0.73)	114 (63.6)

Plasma Menthol Uncorrected			Plasma Menthol Baseline-Corrected		
C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
40.9 (12.6)	3.28 (0.75)	319 (87.1)	39.1 (12.9)	3.28 (0.75)	275 (89.5)

Safety: This study represents the maximal dose applied after a single 8-hour application (10 patches). There were two mild, treatment-emergent AEs reported by two subjects. No serious adverse events were reported during the study. Subject 7 experienced erythema at the patch site almost 24 hours following patch placement. The erythema lasted for approximately 11 days; very slight erythema was noted at the discharge physical exam although the subject reported it was resolved later. The Investigator considered the event definitely study drug related. Subject 10 experienced paraesthesia 13 minutes following patch placement. The episode lasted for seven hours, resolving before discharge. The Investigator considered the event probably related to study drug.

4.2.4 Study FS-67-122: A multiple maximum dose study of FS-67-A methyl salicylate and menthol patch in healthy male volunteers (Report No. 011529)

REPORT NO. 011529

A MULTIPLE MAXIMUM DOSE STUDY OF FS-67-A METHYL SALICYLATE AND MENTHOL PATCH IN HEALTHY MALE VOLUNTEERS

Test Formulations:	Treatment A: FS-67-A patch (containing 10% methyl salicylate and 3% l-menthol) Manufactured by Hisamitsu Pharmaceutical Co., Inc. Batch No.: FSA0004, Expiration date: Apr 2003
Sponsor:	Hisamitsu Pharmaceutical Co., Inc.
Protocol/Study No.:	Sponsor Protocol No. FS-67-122 MDS Pharma Services Project No. 011529
Development Phase of Study:	Phase I pharmacokinetic study in healthy, non-smoking subjects
Number of Subjects:	A total of 19 male subjects were enrolled in the study, and 17 subjects completed the study.
Principal Investigator: **Clinical Site:**	James C. Kisicki, MD MDS Pharma Services 621 Rose Street Lincoln, Nebraska 68502 USA
Date of Report:	July 3, 2002
Date of Study:	03 November 2001 – 19 November 2001.

Objectives: The objective of this study was to determine the safety and tolerability of FS-67-A patches containing 10% methyl salicylate and 3% l-menthol when given at daily dose (6 patches) exceeding the maximum labelling instructions b(4)

Study Design: This was an open-label, one period study performed in 19 healthy non-smoking adult male volunteers. Subjects were housed from the evening before Day -1 through Day 6 (to at least 24 hours after the final patch application).

Methods: The safety and tolerability assessments included adverse event reports, vital signs measurements, physical examination results, electrocardiogram results and serum chemistry, haematology and urinalysis data. The AUC 0-7.92, AUC 95.83-104, Cmax and tmax pharmacokinetic parameters were calculated for plasma free menthol (unadjusted and adjusted for baseline data), free salicylic acid (unadjusted and adjusted for baseline data) and methyl salicylate.

Subject Demographics (N=19): 2 subjects withdrew due to adverse reactions (ringing in ears and rash and itching in skin). The mean age of the subjects was 31 years (range 20 - 41 years), the mean height of the subjects was 70.2 inches (range 64 - 75 inches), and the mean weight of the subjects was 171.1 pounds (range 135 - 201 pounds). With regard to race, 16 subjects were Caucasians, 2 were Hispanic, and 1 was black.

Treatment Administered: Two patches of FS-67-A were applied to the subjects' back on thirteen (13) separate occasions (Study Day 1 through Study Day 5). Subjects received 2 patches of FS-67-A approximately every 8 hours (+/- 1 hour) starting on the morning of Day 1. Prior to the application of the new patches the ones previously applied approximately 8 hours earlier were removed. On Day 5 the final application of the patches was the 8:00 application.

Sample Collection: Blood samples were collected in vacutainers contain potassium oxalate and 2.5 mg/mL disodium fluoride (preservative). On Day -1, blood samples were collected at -24, -18, and -12 hours prior to patch application. On Study Day 1, blood samples were collected at the following times relative to dosing: 0 hour (approximately 10 minutes prior to patch application), 0.5, 1, 2 ,3 ,4, 5, 6, 8, 10, 12, 16 and 24 hours after application. On Days 2 - 5 (10 minutes prior to the morning patch application (time estimated)), blood was collected. On Day 5, relative to the final patch application, blood samples were collected at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after final patch application. A total of 31 blood samples (434 mL) were drawn during the study for drug analysis. Samples were collected and processed. Plasma samples were separated by centrifugation, frozen at -20°C, and kept frozen, packed in dry ice, and sent to MDS Pharma Services in St. Laurent (Montreal), Quebec.

Sample Analysis: Sample analyses menthol, methyl salicylate and salicylic acid in plasma were performed by the same lab with the same methods as other studies.

Pharmacokinetic Results (N=17): ***(Data were not reliable due to the well documented assay issues at the analytical site.)***

All baseline data for methyl salicylate was BLQ. Therefore, only uncorrected data were shown for methyl salicylate.

Table 28. Study FS-67-122 Overall Pharmacokinetic Summary

	Plasma Salicylic Acid Uncorrected			Plasma Salicylic Acid Baseline-Corrected			Plasma Methyl Salicylate Uncorrected		
Study Day	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-8}* (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-8}* (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-8}* (ng•hr/mL)
Day 1	623 (193)	3.35 (0.61)	3348 (1023)	613 (192)	3.35 (0.61)	3274 (1009)	4.40 (3.09)	1.44 (1.07)	12.2 (6.99)
Day 5	1435 (603)	NA	7628 (2988)	1426 (602)	NA	7551 (2978)	15.2 (10.3)	NA	27.4 (13.4)

	Plasma Menthol Uncorrected			Plasma Menthol Baseline-Corrected		
Study Day	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-8}* (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-8}* (ng•hr/mL)
Day 1	6.51 (2.93)	3.39 (1.73)	33.6 (14.5)	5.06 (2.71)	3.39 (1.73)	22.5 (12.6)
Day 5	21.2 (8.67)	NA	97.4 (36.8)	19.8 (8.35)	NA	85.5 (34.9)

*AUC_{0-8} = AUC_{96-104} for Day 5

Accumulation Ratio (Day 5/Day 1)	Cmax	AUC
Menthol	3.9	3.8
Methyl Salicylate	3.5	2.3
Salicylic Acid	2.3	2.3

Safety: This study represents the maximal dose applied after multiple dose application — b(4)
No serious adverse events were reported during the study. All subjects dosed (19) experienced some forms of erythema on application site during the study, 26% experienced gastrointestinal disorders, 11% experienced ear and labyrinth disorders, nervous system disorders and skin and subcutaneous tissue disorders. Among all the subjects, 88% of adverse events experienced were administration site related.

Two patients were discontinued from the study, one patient (Subject 2) after reporting tinnitus, a known salicylate-related event. Another patient (Subject 14) was dropped for a faint rash and itching on his torso, legs and arms. Both of these patients' symptoms resolved.

4.2.5 Study FS-67-14-P1: A three treatment randomized single-dose crossover evaluation design to examine the interaction between methyl salicylate and menthol following application of single entity and combination patch products to healthy male volunteers (Report No. 011490)

REPORT NO. 011490

A THREE TREATMENT RANDOMIZED SINGLE-DOSE CROSSOVER EVALUATION DESIGN TO EXAMINE THE INTERACTION BETWEEN METHYL SALICYLATE AND MENTHOL FOLLOWING APPLICATION OF SINGLE ENTITY AND COMBINATION PATCH PRODUCTS TO HEALTHY MALE VOLUNTEERS

Test Formulations:	**Treatment A:** FS-67-A patch (containing 10% methyl salicylate and 3% l-menthol) Manufactured by: Hisamitsu Pharmaceutical Co Inc Lot No: FSA0003-1, Expiration date: April 2003
	Treatment B: FS-67-M patch (containing 10% methyl salicylate) Manufactured by: Hisamitsu Pharmaceutical Co Inc Lot No: FSM0001-1, Expiration date: April 2003
	Treatment C: FS-67-L patch (containing 3% l-menthol) Manufactured by: Hisamitsu Pharmaceutical Co Inc Lot No: FSL0001-1, Expiration date: April 2003
Sponsor:	Hisamitsu Pharmaceutical Co., Inc.
Protocol/Study No.:	Sponsor Protocol No. FS-67-14-P1 MDS Pharma Services Project No. 011490
Development Phase of Study:	Phase I pharmacokinetic study in healthy, non-smoking subjects
Number of Subjects:	A total of 18 healthy non-smoking adult males were enrolled in and completed the study.
Principal Investigator: **Clinical Site:**	Johnston Stewart, M.D. MDS Pharma Services Clinical Research Center 22-24 Lisburn Road Belfast BT9 6AD Northern Ireland
Date of Report:	August 16, 2002
Date of Study:	24 September 2001 – 18 October 2001

Objectives:	The objectives of this study were 1) to assess the effect of topical l-menthol (LM) on the pharmacokinetics of topical methyl salicylate (MS) and its primary metabolite, salicylic acid under fasting conditions, 2) to assess the effect of topical methyl salicylate (MS) on the pharmacokinetics of topical l-menthol (LM) under fasting conditions.
Study Design:	This was an open-label, randomized, 3-way crossover, single-dose evaluation study performed in 18 healthy non-smoking adult male volunteers. Subjects were housed from the evening before Day 1 until after their 24-hour blood draw following patch application on Day 3.
Methods:	Pharmacokinetic parameters were calculated from the plasma concentrations of free menthol, free salicylic acid and methyl salicylate obtained following application of the three investigational patch products. Endogenous levels of these analytes were also quantified on the days preceding drug administration to allow calculation of baseline-adjusted pharmacokinetic data.

Subject Demographics (N=18): The mean age of the subjects was 24 years (range of 18 through 39), the mean height of the subjects was 176 cms (range of 164 through 185), and the mean weight of the subjects was 74.5 kgs (range 62.8 through 95.6). With regard to race, all subjects were Caucasians.

Treatment Administered: Four patches of FS-67-A, FS-67-M and FS-67-L were applied as single-dose to each study volunteer on three separate occasions (Study Day 2 of each period) according to a randomization scheme generated at MDS Pharma Services. The patches were applied on the subject's back, on each side of the backbone. The patch application on each side covered an area of 20 cm in length and 7 cm in width. The patches were paired one above the other on each side of the backbone. Each volunteer was in the sitting position as the patches were applied. Each period was separate by a washout of at least 7 days.

Sample Collection: Blood samples were collected at each specified time point in vacutainers containing potassium oxalate and 2.5 mg/mL sodium fluoride. Blood samples for all treatments were collected at -24, -12, predose, and at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 10.0, 12.0, 16.0 and 24 hours postdose. A total of 60 blood samples (420 mLs) were drawn during the study for drug analysis. Plasma samples were separated by centrifugation and transferred into aliquots. All samples were then frozen at -20°C and kept frozen. The samples were subsequently packed in dry ice, and sent to MDS Pharma Services, Montreal, Canada, for analysis.

Urine samples were collected -24 to -18 hours, -18 to -12 hours and -12 to 0 hour predose for urine baseline assessments. Urine samples were also collected 0-6 hours, 6-12 hours and 12-24 hours post dose. At the end of each interval, the pH and total volume were measured and recorded and four aliquots were taken and frozen at -20°C. At the end of the study the urine aliquots were packed in dry ice and shipped to MDS Pharma Services, Montreal, Canada, for analysis.

Sample Analysis: Sample analyses for menthol, methyl salicylate and salicylic acid in plasma were performed by the same lab with the same methods as other studies. Menthol in urine was assayed with a GC/MS method (Validation Report No.002418-OYE). The analytical range is 1.00-50.03 µg/mL.

Pharmacokinetic Results: ***(Data were not reliable due to the well documented assay issues at the analytical site.)***
For methyl salicylate and menthol, the lower limit of quantitation (LOQ) of the analytical method accounted for more than 5% of the observed average Cmax. These results suggest that the pharmacokinetics of methyl salicylate and menthol calculated in this study was not robust. Therefore 90% confidence intervals were not calculated for either Cmax or AUC.

Table 16. Study FS-67-14-P1 Overall Pharmacokinetic Summary

	Plasma Salicylic Acid Uncorrected			Plasma Salicylic Acid Baseline-Corrected				
Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	Half-Life (hr)
Treatment A Patch FS-67-A (N=18)	1284 (257)	3.61 (0.78)	8894 (2139)	1277 (255)	3.61 (0.78)	8737 (2077)	8794 (2093)	3.16 (0.74)
Treatment B Patch FS-67-M (10% Methyl Salicylate) (N=18)	1313 (267)	3.78 (0.81)	9482 (2454)	1306 (265)	3.78 (0.81)	9324 (2406)	9369 (2424)	2.92 (0.53)

	Plasma Methyl Salicylate Uncorrected			Plasma Methyl Salicylate Baseline-Corrected		
Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
Treatment A Patch FS-67-A (N=18)	8.31 (4.92)	1.39 (0.78)	23.6 (14.8)	8.21 (4.82)	1.39 (0.78)	22.3 (13.7)
Treatment B Patch FS-67-M (10% Methyl Salicylate) (N=18)	5.89 (3.84)	1.39 (0.78)	15.2 (9.97)	5.89 (3.84)	1.39 (0.78)	16.2 (10.5)

	Plasma Menthol Uncorrected			Plasma Menthol Baseline-Corrected		
Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
Treatment A Patch FS-67-A (N=18)	10.4 (2.83)	3.39 (0.98)	91.8 (22.8)	9.26 (3.10)	3.39 (0.98)	64.8 (31.1)
Treatment C Patch FS-67-L (3% l-Menthol) (N=18)	9.26 (2.08)	4.00 (2.22)	84.4 (27.1)	7.85 (2.28)	4.00 (2.22)	50.9 (26.8)

Table 18. Study FS-67-14-P1: Salicylic acid C_{max} and AUC least-square means, ratios and 90% confidence intervals

	Treatment A FS-67-A Patch 10% MS/ 3% LM	Treatment B FS-67-M Patch 10% MS	Ratio (90% Confidence Intervals)
In $AUC_{0-\infty}$ (ng·h/mL)	8558	9074	94.3% (90.0 – 98.8%)
In C_{max} (ng/mL)	1253	1279	98.0% (93.0 – 103.2%)

Urine data:

Table 40. Urinary total menthol excretion after administration of four FS-67 patches and four 3% patches.

		Urine Menthol Uncorrected			Urine Menthol Baseline-Corrected		
Study No. Protocol No.	Treatment	Ae_{0-24} (µg)	R_{max} (µg/hr)	T_{max} (hr)	Ae_{0-24} (µg)	R_{max} (µg/hr)	T_{max} (hr)
FS-67-14-P1	Patch FS-67-A (N=18)	9374 (3542)	911 (333)	3.00 (0.00)	8502 (2888)	874 (313)	3.00 (0.00)
	Patch FS-67-L (3% l-Menthol) (N=18)	8201 (2437)	781 (237)	3.00 (0.00)	6948 (1950)	729 (236)	3.00 (0.00)

4.2.6 Study FS-67-15: A single dose, one period, evaluation designed to determine the percutaneous absorption of methyl salicylate and menthol following the application of the topical patch product, FS-67-A, in healthy female volunteers (REPORT NO. AA04248)

A SINGLE DOSE, ONE PERIOD, EVALUATION DESIGNED TO DETERMINE THE PERCUTANEOUS ABSORPTION OF METHYL SALICYLATE AND MENTHOL FOLLOWING THE APPLICATION OF THE TOPICAL PATCH PRODUCT, FS-67-A, IN HEALTHY FEMALE VOLUNTEERS

Test Formulation:	FS-67-A Patch (— methyl salicylate/ — l-menthol) patch. b(4) Manufactured by: Hisamitsu Pharmaceutical Co., Inc. Lot No: FSA0003 Expiration date: July 2004
Sponsor:	Hisamitsu Pharmaceutical Co., Inc.
Protocol/Study No.:	Sponsor Protocol No. FS-67-15 MDS Pharma Services Project No. AA04248
Development Phase of Study:	Phase I pharmacokinetic study in healthy females
Number of Subjects:	A total of 18 female subjects enrolled in and completed the study.
Principal Investigator: **Clinical Site:**	Magdy Shenouda, M.D. MDS Pharma Services 1930 Heck Ave. Bldg 2 Neptune, NJ 07753
Author(s):	b(4)
Sponsor Signatory:	Mr. Kenichi Furuta, General Manager Hisamitsu Pharmaceutical Co., Inc. PCP21F, 1-11-1 Marunouchi, Chiyoda-ku Tokyo, Japan, 100-6221 Tel: +81-3-5293-1712 Fax: + 81-3-5293-1730
GCP Compliance:	This study was conducted in compliance with the U.S. Code of Federal Regulations, Good Clinical Practice, 21 CFR Parts 50 and 312 and the ICH Harmonized Tripartite Guideline for Good Clinical Practice (1996), including the archiving of essential documents.
Date of Report:	July 29, 2004
Date of Study:	08 May 2003 – 20 May 2003

Objectives: The objective of this study was to determine the systemic exposure to the 10% methyl salicylate and 3% l-menthol components of the FS-67-A patch when applied to healthy female volunteers.

Study Design: This was an open-label, single-dose, one-period, evaluation to measure the systemic exposure of methyl salicylate (MS) and menthol (LM) in healthy non-smoking female volunteers following application of four FS-67-A patches (two to each side of the backbone) for eight hours. This study was conducted at one study center by a single principal investigator. The study consisted of a screening period, followed within 14 days by a dosing period consisting of three days of study confinement.

Methods: A general physical examination, medical and drug history, clinical laboratory tests, a 12-lead electrocardiogram (ECG), vital signs, and adverse event assessments were evaluated during this study.

Pharmacokinetic parameters were calculated from the plasma concentrations of methyl salicylate, free salicylic acid and free menthol obtained following application of four FS-67-A patches for eight hours. Endogenous levels of these analytes were also quantified on the day preceding drug administration to allow for the calculation of baseline-adjusted pharmacokinetic data.

In addition, the Sponsor performed residual data analyses, verified the results, and provided them to MDS Pharma Services.

Subject Demographics (N=18): The mean age of the female subjects was 29 years (range of 21 through 44), the mean height of the subjects was 164 cm (range of 156 through 171), and the mean weight of the subjects was 64.3 kg (range 51.5 through 84.3). In terms of race, eight (44%) were Black, seven (39%) were Caucasian, two (11 %) were Asian and one (6%) was Hispanic.

Treatment Administered: Four patches of FS-67-A (two to each side of the backbone) were applied to each study volunteer on one occasion (Study Day 1). The patch application site on each side of the backbone covered an area of 20 cm in height and 7 cm in width. The patches were paired one above the other on each side of the backbone. The patches remained in place for approximately eight hours and were removed following the eight hour post-dose blood collection. The removed patches were then placed in tubes identified for each subject and sent to Hisamitsu for analysis. There was no showering or bathing from eight hours prior to dosing until 12 hours post-dose.

Sample Collection: Blood samples (16 mL) were collected prior to patch application at -24, -18, -12 and 0 hours (10 minutes pre-dose) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours post-dose. Samples were collected and processed at room temperature under fluorescent light. Plasma samples were separated by centrifugation, quick-frozen and stored at -20°C, kept frozen, packed in dry ice, and sent to be assayed at MDS Pharma Services in Saint-Laurent (Montreal), Quebec, Canada.

Sample Analysis: Sample analyses menthol, methyl salicylate and salicylic acid in plasma were performed by the same lab with the same methods as for other studies.

Pharmacokinetic Results (N=18): ***(Data were not reliable due to the well documented assay issues at the analytical site.)***

Table 32. Study FS-67-15: Overall pharmacokinetic summary after application of four (4) FS-67-A patches to 18 healthy female subjects

Plasma Salicylic Acid Uncorrected			Plasma Salicylic Acid Baseline-Corrected				
C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	Half-Life (hr)
1186 (430)	3.80 (0.94)	9339 (4389)	1130 (411)	3.80 (0.94)	7986 (3858)	8616 (4829) n=11	4.30 (2.45) n=11

Plasma Methyl Salicylate Uncorrected			Plasma Methyl Salicylate Baseline-Corrected				
C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	Half-Life (hr)
24.8 (16.5)	1.82 (1.49)	139 (64.2)	23.9 (16.5)	1.82 (1.49)	115 (67.1)	105 (35.7) n=12	7.14 (4.99) n=12

Plasma Menthol Uncorrected			Plasma Menthol Baseline-Corrected				
C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	Half-Life (hr)
9.76 (4.43)	2.92 (1.00)	89.0 (35.9)	8.50 (4.16)	2.92 (1.00)	60.1 (28.7)	30.5 (2.91) n=4	12.6 (18.3) n=4

Residual Analysis:

The residual potencies (amounts of methyl salicylate and menthol as a % of the original doses) of each patch were determined and are summarized in Table below. It is noted that they may not represent the amount of drug absorbed by the body. Drug may be lost due to other factors other than transdermal absorption. FS-67 is formulated with [redacted] backing. b(4)
Because both methyl salicylate and l-menthol are volatile, these components are lost to the air during patch application. Thus, unlike other transdermal systems, residual potencies may not be used to determine absorbed doses.

Table 36. Study FS-67-15: Residual methyl salicylate and menthol amounts (% of original potency) left after 8 hr application period

	Residual Potency (%)	
Treatment	Methyl Salicylate	Menthol
A Patch FS-67-A (N=18)	[redacted]	[redacted]

b(4)

4.3 OCP Filing and Review Form

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	22-029	Brand Name	N/A
OCPB Division (I, II, III)	DCP2	Generic Name	10% methyl Salicylate & 3% L-Menthol
Medical Division	ONP/DNCE (HFD-560)	Drug Class	Methyl Salicylate: anti-inflammatory, analgesic and counterirritant Menthol: Counterirritant
OCPB Reviewer	Lei Zhang, Ph.D.	Indication(s)	OTC use -- temporarily relieves mild to moderate aches & pains of muscles & joints associated with: arthritis, simple backache, strains, bruises and sprains.
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Topical Patch
		Dosing Regimen	[redacted] b(4)
Date of Submission	2/27/2006	Route of Administration	Topical
Estimated Due Date of OCPB Review	11/15/2006	Sponsor	Hisamitsu Pharmaceutical Co., Inc.
PDUFA Due Date	12/27/2006	Priority Classification	
Division Due Date	11/27/2006	Relevant IND	IND 62,735

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

Healthy Volunteers-				
single dose:	X	1	1	FS-67-121 (maximal usage condition, all male subjects)
multiple dose:	X	1	1	FS-67-122 (maximal usage condition, all male subjects)
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	FS-67-14-P1 (effect of each active ingredient of the combination product on the other active ingredient)
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	FS-67-15 (female subjects)
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	2	2	FS-67-03-M (compare to 10-60% methyl salicylate ointment, all males) FS-67-03-L (compare to 1.25-16% menthol ointment, all males)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			Ask for waiver for pediatric study requirements
Literature References	X			
In Vitro Flux Study	X			Summary of results
Total Number of Studies		6	6	

Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?				
QBR questions (key issues to be considered)	• What is the exposure of methyl salicylate, its metabolite salicylic acid, and menthol under the maximal usage condition indicated by the labeling? • Is there interaction between methyl salicylate and menthol in this combination product?			
Other comments or information not included above	In vitro release test is under development at the time of NDA submission.			
Primary reviewer Signature and Date	Lei Zhang, 4/20/2006			
Secondary reviewer Signature and Date	Suresh Doddapaneni, 4/20/2006			

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

/s/

Lei K Zhang
11/16/2006 04:57:58 PM
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Suresh Doddapaneni
11/17/2006 06:11:04 AM
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Chandra Sahajwalla
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