CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-029

SUMMARY REVIEW

NDA 22-029

SUMMARY REVIEW FOR REGULATORY ACTION

Date	2/20/08
From	Joel Schiffenbauer
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	22-029
Applicant Name	Hisamitsu
Date of Submission	8/17/08
PDUFA Goal Date	2/20/08
Proprietary Name / **Established (USAN) Name**	Salonpas
Dosage Forms / Strength	Patch; 10% Methyl Salicylate and 3% l-Menthol
Proposed Indication(s)	1. arthritis 2. backache 3. strains, sprains, bruises
Action/Recommended Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Fang; Porres
Statistical Review	Kim
Pharmacology Toxicology Review	none
CMC Review/OBP Review	Ochltree
Microbiology Review	none
Clinical Pharmacology Review	Zhang
DDMAC	
DSI	
CDTL Review	none
OSE/DMETS	pending
OSE/DDRE	
OSE/DSRCS	
Other	Hertz (DAARP)

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This submission is a complete response to a previous approvable letter.

The applicant submitted a 505b2 for OTC use of a topical patch product containing methyl salicylate [redacted] 10%) and menthol [redacted] 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 (GRASE) (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, lotions, or creams (but not patches) 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). In 2003 the FDA proposed a clarification to the monograph, by the exclusion of patches from the Final Monograph. There are no approved NDAs for methyl salicylate or menthol. b(4)

The subject of this NDA is a new formulation of Salonpas patch that contains only methyl salicylate [redacted] 10%) and l-menthol [redacted] 3%). b(4)

2. Background

To support clinical efficacy and safety, one pivotal Phase 3 trial, 5 dermal safety trials, and 6 in vivo PK trials were conducted. The studies determined 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 salicylate/salicylic acid, and menthol compared to respective ointment formulations defined by TFM, and PK data in male and female subjects. In the re-submission there is one single-dose PK study and no new efficacy and/or safety studies in the current submission dated August 17, 2007.

The original NDA was submitted on February 26, 2006 and received an approvable letter on December 7, 2006. The major deficiency was insufficient data to adequately support the proposed usage of the patch (one patch for eight hours per affected area with no more than two patches per affected area per day, [redacted]). The applicant was also requested to provide an assessment of symptoms of excess salicylate exposure, as well as a repeat PK study because of the unreliability of the data submitted in the original submission. A post action meeting took place on February 8, 2007. The Agency expressed concerns with the lack of data to support the b(4)

intended use of a single patch in the target population and requested multiple-dose data to support a safe and effective
dosing interval for repeated use and for the total duration of use. The Sponsor anticipated difficulties in identifying an acute pain condition that would have sufficient pain intensity lasting for days to allow for a multiple-dose evaluation.

On 8/17/08 the applicant submitted a complete response to the approvable letter. In that submission the applicant submitted a new PK study as requested in the approvable letter, as well as a re-analysis of the data from the single patch efficacy study to support the [redacted] dosing interval. They did not perform a new efficacy study. b(4)

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues. The applicant agreed to revise the label to state that any remaining patches should be discarded 14 days after the pouch is opened.

4. Nonclinical Pharmacology/Toxicology

No new information was submitted for this review cycle. Dr. Belinda Hayes performed the original review. She noted that the applicant should provide an exposure margin of the reproductive changes noted in the reproductive toxicology studies submitted in support of methyl salicylate but that this could be done post-marketing. This issue was addressed during the previous review cycle with Dr. Jacobson-Kram who commented that it was "reasonable to conclude that there is sufficient clinical experience to obviate the need for reprotoxicity studies." In addition, there is a warning on the label in regards to the use of this product during pregnancy and especially during the last trimester, because of the salicylate. See my previous review for additional comments.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

No information was submitted for review.

7. Clinical/Statistical-Efficacy

The results of the original efficacy and dermal safety studies have already been reviewed in detail in 2006 (see reviews by Drs. Fang, Porres and the dermatology consult; also see my review of the original submission). As part of the complete response to the approvable letter, the applicant presented a re-analysis the data from the original single patch efficacy study. This re-analysis purports to demonstrate that the dosing interval is [redacted] and that there is no residual effect as soon as the patch is removed. This argument is based on the fact that the differences in effect between the active patch and the placebo patch do not change over the interval from hours 9-12. b(4)

Dr. Fang the medical reviewer comments that "the Sponsor's re-analysis of efficacy data to show a duration lasting eight hours instead of 12 hours in the current submission is not considered acceptable and will not be reviewed here." The reader is referred to her review for additional details. She also comments "Assessing the median time to rescue medication can be problematic in studying mild to moderate acute non-surgical pain because in many studies, most patients do not ask for rescue or re-medication. The time-specific pain measurements for pain with movement, together with time weighted summation of pain scores and patient global assessment in Study E02, provided support of an 8-to12-hour duration of effect after eight hours of patch application. A multiple-dose efficacy study of fixed dosing regimens is not considered required for this application."

The statistical reviewer Dr. Kim, examined the post-hoc analysis performed by the applicant. He comments " several concerns arose.....However since the clinical team did not consider any re-analyses of single dose efficacy data to be useful in determining approvability of the drug, I did not further investigate my concerns."

In terms of this re-submission, the applicant proposes that the re-analysis of the data demonstrates that the patch, when removed at 8 hours carries no depot effect and that there is in fact no efficacy from hours 9-12 as demonstrated in the original study. The essence of the argument is that the placebo and treatment pain curves remain parallel from hour 8 onwards suggesting no further effect of treatment from the active patch, even after it is removed. In the applicants words " Dr. [redacted] [statistician] finds no treatment related pain relief is evidenced following patch removal." "Given these results the duration of the SALONPAS [redacted] has been established [redacted] and there is no statistically derived evidence for a lingering depot effect." However, this is an argument based on a statistical analysis, and not on clinical data, which should be the basis for any determination of dosing interval. Furthermore, the applicant's argument is hard to understand. The mechanism of action of this product is that of a counter-irritant. One would have to suppose that the irritant effect of the patch was completely obliterated with its removal at hour 8. This seems highly unlikely. Further, there are systemic levels of methyl salicylate and menthol remaining at hours 8-12 even after patch removal. While systemic levels do not necessarily correlate with local skin and soft tissue levels, it is likely that levels of active ingredients persist locally also. Taken together, it is likely that a clinical effect persists. Finally, if one were to accept the applicant's argument that the clinical effect is gone with removal of the patch, one would then have to say that with placement of the next patch, the time to onset of effect could be up to several hours. Based on b(4)

this, out of a 24 hour day, an individual would only be treated effectively for up to 10-12 hours (only effective therapy for 5-6 hours per patch placement and only 2 patches per day). Therefore, the applicant's re-analysis does not add to our understanding of the dosing interval for this patch. Although likely that the effect persists beyond hour 8, my recommendation is for the dosing interval for a single patch, to be 8-12 hours (see below for additional discussion). Allowing the patch to remain for up to 12 hours would provide a greater reassurance that efficacy persists through out the 12 hours and would allow for potentially round-the-clock pain relief.

8. Safety

The reader is referred to my review of the original NDA submission for a discussion of safety data. The reader is also referred to Dr. Porres original review as well as a Dermatology consult for the safety assessment. All of the formal dermal safety studies were reviewed with the original submission. This re-submission contains safety data from the single PK study and a review and update of post-marketing safety data.

The PK study submitted with the re-submission contributes little additional safety information. There were no deaths, serious AEs or discontinuations. There were adverse events that were mild in nature and all resolved without therapy.

The post marketing safety data demonstrates cases skin manifestations (contact dermatitis, burns) but there are no new signals that have not already been described in the original NDA review. There were 2 serious reports of salicylism, one involving the use of 20 patches per day and the other involving the use of oral salicylates.

Dr. Porres also provides the following comments:

In summary, the results of the multiple-dose (PK and dermatological safety) studies suggest the presence of a modest degree of irritation potential associated with the repeated use of both the active and placebo patch. The active patch was more irritating than the placebo patch, especially following prolonged skin contact for more than a few days. The skin irritation induced by the patches resolved with no need for topical treatment or other intervention. The results of the contact sensitization study did not suggest a sensitization potential of the product under the condition studied. The results of photoallergy study suggest photo sensitization to the inactive ingredients of the patch.

This reviewer assumes that most patients would discontinue treatment in clinical use if an application site reaction developed that would include any of the following: grade ≥2, marked glazing, cracking, fissuring, or petechia.

It shoild be pointed out that the original dermal safety studies included a study examining dermal safety using 2 patches every 8 hours for 5 days, as well as a study of a single patch for 23 hours for 21 days.

9. Advisory Committee Meeting

No advisory committee meeting was convened. These ingredients are not NMEs.

10. Pediatrics

There is no evidence provided in this submission to support the use of this patch in subjects below the age of 17 years.

b(4)

b(4)

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The applicant has been provided labeling comments. The label will include warnings for GI events similar to other OTC NSAID warnings due to the fact that methyl salicylate is a non-acetylated salicylate (NSAID) b(4)
However, based on the relatively low systemic levels of salicylate, and the fact that the risk for GI events, in particular, increases as the dose of a NSAID increases, but also because we do not know the true extent of the risk for GI bleeding, it was decided to include a GI bleeding warning (but not bold it), and comment that the chance of a bleed is small but higher if you have risk factors as listed in the label. For additional details see labeling comments by Dr. Tan.

The use of multiple names for the same patch (as requested by the applicant) was reviewed and the Division expressed concern that it could contribute to the use of multiple patches. However, there is precedent for allowing multiple names for products with the same ingredients, and the applicant agreed to put additional language on the PDP that reminds consumers to use only one at a time. Further, there does not appear to be a significant safety concern even if more than one patch is used at a time. Therefore, the use of multiple names is acceptable. However, the use of the phrase ——— will not be allowed for a patch.

The applicant has requested the name "Salonpas ———— ' DMETS had originally stated that use of the modifier ——— may be misleading ———— I agree and the applicant should add the modifier "pain" to the words ——— On the other hand DMETS recommends the use of the name Salonpas, without a modifier. As this product contains a different strength of methyl salicylate and menthol than other patches (and at this time it is the only patch with these ingredients to be approved), a unique modifier seems reasonable. There is also precedence for the use of modifiers with other OTC products (Advil Migrane, for example). Therefore, the name "Salonpas Pain Relief Patch" appears acceptable. b(4)

There are also concerns raised by a number of the elements in the PDP. ——— that states ——— implies that safety has been proven and this should not be allowed. Also, there is a statement ——— which also appears to be promotional. Further it implies that everyone will have ——— which is not the case. We should also request that the applicant remove this statement. Finally we have requested that the applicant add the ingredients to the PDP to inform consumers of the contents of the patch (also suggested by DMETS). b(4)

13. Decision/Action/Risk Benefit Assessment

The applicant proposes to use the patch for the relief of aches and pains associated with arthritis, sprains, strains, bruises and simple backache. The patch is applied for 8 hours followed by a second patch for 8 hours up to 2 patches per day for 3 days. Use of the patch ——— according to the proposed label, may potentially leave the consumer with 8 hours in which they are not treated. b(4)

However, the immediate question at hand is whether the data support the 8 hour dosing interval. The fact that no subject, even in the placebo group, asked for re-medication or rescue makes it somewhat problematic in defining a dosing interval, and forces us to rely on the pain measurement (curves) themselves for evidence of efficacy and determination of a dosing interval. However, examination of the pain curves provides support for a dosing interval that may be as long as 12 hours, since the curves remain separated up to that point. I agree with Dr. Fang that based on the pain intensity curves with movement, an 8-12 hour dosing interval is reasonable. Therefore, it also seems reasonable to recommend that the dosing interval be

labeled as one patch every 8-12 hours. Thus by allowing the patch to remain in place for up to 12 hours, the consumer would potentially have the flexibility to provide for round the clock analgesia. Other instructions to take the patch off at 8 hours and wait until 12 hours would not be easily conveyed to consumer in Drug Facts labeling. These dosing instructions are also more in line with OTC dosing for analgesics, where the dosing interval is often provided as a range, such as every 4-6 hours for ibuprofen, for example. The 12 hour dosing interval for this patch also allows for potential dosing throughout a 24 hour day, whereas the 8 hour dosing interval with up to 2 patches per day would not cover the 24 hour period and may leave some individuals in pain for 8 hours out of the 24 hour day.

In order to propose the 12 hour dosing interval we need to consider the safety profile for use up to 3 days. In terms of safety, the main adverse effect relates to the skin. Adequate safety data has been provided through the dermal safety studies. No one in these studies had skin reactions that did not resolve even when the patch was used for much longer than will be recommended on the label. Any reactions that did occur, usually just began at day 3 and tended to be mild in nature at that time. I agree with Dr. Porres that it is likely that any consumer developing a skin reaction would tend to just stop using the patch. Strains and sprains and bruises usually resolve quickly and often do not require prolonged therapy. Only for the backache and the arthritis indication would a consumer potentially use the product for longer than recommended. Again, any skin reactions would be observed by the consumer, and would likely lead to them removing the patch. In terms of safety, although we do not have specific safety data for two 12 hour patches per day for 3 days, I believe the safety data provided in the dermal safety studies (including a study of 2 patches every 8 hours for 5 days), and a limitation to use the patch for no more than 3 days (and the likelihood that the patch will be removed if a skin reaction occurs), more than provides for adequate safety data for two 12 hour patches a day for up to 3 days.

There are other safety concerns related to the ingredients that are not unique to this product. Since methyl salicylate is a NSAID it should have a GI warning on the label. However since it is a non-acetylated NSAID, it does not offer CV protection like ASA, and therefore should warning similar to all the other non-ASA NSAID. Although the systemic

. The same is true for the GI risk although there is some data that shows a higher risk for GI bleeding with higher doses. Therefore, the risk for GI bleeding is likely lower for this product than for oral NSAIDs. Based on this the label will include a modified GI warning ("there is a small risk...."; see label for specific language). b(4)

At this point it is also worth commenting on the model used to demonstrate efficacy. The applicant chose to use sprains/strains to establish efficacy. However as Dr. Fang notes, that when using models of pain such as this, the measure that has been traditionally used to establish the dosing interval, that is, time to rescue or re-medication, is not helpful in that very few, if any, subjects actually re-dose or ask for rescue medication. This appears to be the case for this product and the pain model chosen to establish efficacy. Therefore, in order to

establish a dosing interval we may wish to, going forward, advise applicants to use a more chronic or semi-acute model of pain such as acute backache or arthritis flare (OA) that may last longer than a single day. I believe that measures of dosing interval are more likely to be successfully obtained using these alternate models. Furthermore, these models will allow us to obtain multiple dose efficacy.

In terms of pediatric studies, PeRC recommended that the sponsor study children down to the age of 3, and I agree with this recommendation. However, recently another topical analgesic product was discussed at PeRC and the primary review division (DAARP) recommended studies down to the age of 8 due to the fact that sprains and strains rarely occur before that age. PeRC agreed with that approach. However the label for Salonpas not only includes sprains and strains but also includes bruises and arthritis, both of which may occur in young children, and so studies down to the age of 3 appear reasonable.

In terms of overall risk/benefit, Dr. Fang provided the following recommendations:

I recommend approval for the proposed use of one Salonpas® relief patch for [redacted] *followed by an additional 8-hour patch if pain persists, for up to two patches per day and for up to three days for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains based on clinical evidence in support of efficacy and safety.* b(4)

Dr. Porres recommended:

Upon review of the submitted safety data, the safety profile is acceptable. From the safety point of view, SALONPAS [redacted] *may be approved for OTC marketing.* b(4)

I agree with both of the reviewers. Therefore, it is recommend that the product be approved with dosing every 8-12 hours for up to 3 days, and to include the appropriate warnings (GI [redacted]) on the label.

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/s/

Joel Schiffenbauer
2/20/2008 02:39:56 PM
MEDICAL OFFICER

2/20/8

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products

DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR ACTION

DATE:	**February 19, 2008**
FROM:	**Sharon Hertz, M.D.**
SUBJECT:	**Deputy Director Summary Review**
NDA:	**22-029 (N000)**
APPLICANT:	**Hisamitsu Pharmaceutical Co., Inc.**
LETTER DATE:	**August 17, 2007**
PDUFA GOAL DATE:	**February 20, 2008** b(4)
PROPRIETARY NAME:	**Salonpas** [redacted]
ESTABLISHED NAME:	**10% Methyl Salicylate, 3% L-Menthol topical patch**
INDICATION:	**Aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains**
ACTION:	**Approval**

INTRODUCTION and BACKGROUND

This submission represents a complete response to an approvable action for this 505(b)(2) application in support of Salonpas [redacted] (FS-67), a combination topical patch, which contains methyl salicylate 10% and menthol 3% as the active ingredients. The active ingredients b(4)
in this product were reviewed in 1979 by an 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). However, the Tentative Final Monograph (TFM) for OTC External Analgesic Drug Products published by FDA in 1983 (48 FR 5852) provides for topically applied ointments, lotions or creams containing methyl salicylate in the range of 10%-60% and menthol in the range of 1.25%-16% individually or in combination, but does not include the dosage form of topical patch. Hence, a New Drug Application was required to obtain approval for marketing.

There are no approved NDAs for methyl salicylate or menthol. There are several products that contain these two drugs marketed under the TFM as over-the-counter (OTC) products under brand names that include BenGay, Icy Hot and Thera-Gesic.

It is known that topical exposure to methyl salicylate, a counter-irritant, results in redness, rash, warmth and irritation at the site, including rare cases of blistering, burning sensation, peeling, numbness, and changes in pigmentation. Excessive systemic exposure can result in the signs and symptoms of salicylate poisoning including dizziness, tinnitus, deafness, sweating, nausea, vomiting, headache and aspirin-induced asthma.

The original application consisted of two efficacy studies, five dermal safety studies, six clinical pharmacology studies and 13 nonclinical studies conducted under IND 62,735.

An approvable action was taken noting the following deficiencies:

1. Your single-patch study was not adequate to establish the dosing interval for your product, and thus cannot be labeled for consumer use. The data do not support use of a [redacted] dosing period [redacted]. Therefore to address these concerns you must perform an adequate and well-controlled study to define the duration of effect and to demonstrate efficacy and safety over the proposed duration of use for which the patch will be labeled. b(4)

2. Once you have established the appropriate dosing interval, determine the safety profile for your product for its intended dosing schedule. To address this you will need to collect safety data in the multiple-dose efficacy study described above.

3. Provide an assessment of symptoms of excess systemic salicylate exposure at the recommended dosing regimen.

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.

5. Low menthol and methyl salicylate assays were observed at 30 days when the pouch was not adequately closed. Therefore, revise your label to state that patches should be discarded 14 days after the pouch is opened. b(4)

In addition, it will be necessary for you to submit draft labeling revised as follows:

[redacted] b(4)

2. Your tradename "Salonpas [redacted]" is not an acceptable tradename and should be changed to your proposed tradename "Salonpas [redacted]." b(4)

The current submission seeks to respond to the listed clinical deficiencies based on a reanalysis of some of the original clinical, amended labeling recommendations and results from an additional pharmacokinetic study conducted in response to deficiency #4.

This application is for direct to over-the-counter marketing for this product. The responsibility for the clinical review was divided such that the efficacy review was assigned to the Division of Anesthesia, Analgesia and Rheumatology Products in the Office of Drug Evaluation II, while the safety review was assigned to the Division of Nonprescription Clinical Evaluation (DNCE) in the Office of Nonprescription Products. Dr. Joel Schiffenbauer, Deputy Director of DNCE and I are the signatory authorities for this application.

CHEMISTRY, MANUFACTURING AND CONTROLS

The CMC review was performed by Terrance Ocheltree, Ph.D. The product is a nonsterile patch for topical application of methyl salicylate and menthol for local efficacy. The active drug substances are combined with the adhesive and a cloth backing as on outer protective layer. The patch measures 7.1 cm by 10 cm in size with a total dose of [redacted] methyl salicylate and [redacted] mg *l*-menthol. Five patches are packaged per pouch [redacted] b(4)

During the first cycle, Dr. Ocheltree noted that the data to support a [redacted] use period for opened pouches were unacceptable due to low menthol levels. This was included as a deficiency in the approvable letter. The applicant has agreed to revise the label to state that the patches should be discarded 14 days after the pouch is opened. b(4)

Also, as per Dr. Ochletree's second cycle review, the following issues pending at the end of the first review cycle have been adequately addressed:

- GMP status recommendation by the Office of Compliance was entered into EES as "Acceptable" for the two drug substances and the drug product sites on December 18, 2006.
- The applicant has agreed to evaluate the process overages during the validation campaign for commercial scale production. They will make appropriate adjustments in the percent overage of drug substances as necessary during this campaign. An additional five lots will be monitored for further adjustments. A report of this work will be submitted to the FDA within six months of the NDA approval date.
- The applicant is developing a dissolution method in place of the originally proposed *in vitro* release method. The final method and supporting data will be provided to the FDA within six months of the NDA approval date.

Dr. Ocheltree concludes that the application is now suitable for approval from the CMC perspective.

PHARMACOLOGY AND TOXICOLOGY

There were no new nonclinical pharmacology and toxicology data in the current submission and no nonclinical outstanding pharmacology or toxicology issues. Dr. Belinda Hayes performed the original review. She noted that the applicant should provide an exposure margin of the reproductive changes noted in the reproductive toxicology studies submitted in support of methyl salicylate but that this could be done post-marketing. The findings from these studies suggested that this would be consistent with pregnancy category C. In an email exchange between Dr. Joel Schiffenbauer and Dr. David Jacobson-Kram dated December 18, 2006, the question of whether additional reproductive toxicology studies were needed was discussed (see the Addendum). Dr. Jacobson-Kram noted that he thought "it is reasonable to conclude that that there is sufficient clinical experience to obviate the need for reprotox studies" for methyl salicylate. The labeling b(4)
for an over-the-counter product would not normally include the pregnancy category, but the labeling does include the statement, "If pregnant or breastfeeding, ask a doctor before use during the first 6 months of pregnancy. Do not use during the last 3 months of pregnancy because it may cause problems in the unborn child or complications during delivery." The applicant did not perform pharmacology studies on methyl salicylate or *l*-menthol and is relying on articles submitted from the published literature. During the first review cycle, a number of nonclinical studies were submitted in support of the active drug substances and the drug product, in b(4)
particular, qualifying two novel excipients, styrene-isoprene-styrene (SIS) and [redacted].

BIOPHARMACEUTICS AND CLINICAL PHARMACOLOGY

The clinical pharmacology review was performed by Lei Zhang, Ph.D. All pharmacokinetic samples from studies conducted and submitted with the original application were analyzed at the b(4)
[redacted]. This site was found to have
multiple deficiencies following several FDA inspections. This lead to the following deficiency during the first cycle, as stated in the approvable letter:

> 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.

In response, the applicant submitted data from a new PK study, (Study 67-FS-15R). As noted by Dr. Zhang, the results of this study are considered acceptable and the data adequately describe the Cmax, Tmax, AUCt, and half-life for methyl salicylate, salicylic acid and l-menthol when four patches are applied. This is considered the maximal use condition. The following table is from Dr. Zhang's review.

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.

Also noted by Dr. Zhang, while there did appear to be higher l-menthol and methyl salicylate in men, this differences appears to behave been driven primarily by one outlier.

EFFICACY AND SAFETY

Dr. Christina Fang performed the efficacy review, Dr. Joseph Porres performed the safety review and Dr. Yongman Kim performed the statistical review for both the initial and second cycles of this application. Two clinical studies were submitted in support of efficacy in the original application along with five dermal safety studies. Based on discussions with the HFD-550 during development, an agreement was reached that efficacy must be supported by at least one successful efficacy study and that if positive results were clearly demonstrated in a single-patch study with a reasonable onset and duration to support the dosing recommendation, then no additional study would be required.

Efficacy

The results of two clinical efficacy studies were submitted in the initial application, a pilot study (FS-67-E01) and an efficacy study (FS-67-E02). Study FS-67-E01 was a double-blind, placebo-controlled, single-dose pilot study with an eight-hour application and 12-hour observation period that enrolled 48 adults with mild to severe muscle strain and pain on movement. The primary efficacy endpoint, SPID8 with movement, revealed a treatment difference that approached statistical significance (p=0.08) and several secondary endpoints demonstrated differences in favor of the active treatment. The pivotal efficacy study, Study FS-67-E02, was a single-dose,

12-hour, double-blind, placebo-controlled, multi-center efficacy study with a treatment period of eight hours and observation period of 12 hours. Two hundred and eight subjects with mild to severe muscle strain excluding the lower back and pain on movement of 50 to 75 on a 100mm VAS (excluding the lower back) were enrolled. The study showed a statistically significant difference between the FS-67 topical patch and the placebo patch in the summed pain intensity difference (SPID) with movement from baseline to Hour 8. The median time to rescue/re-medication was not identified in this study as patients did not request rescue medication. This efficacy data suggests the patch may be applied less frequently than an 8-hour interval and still provide adequate efficacy.

Based on the failure to adequately define the dosing interval using median time to remedication, and based on considerations of the potential for local skin reactions with use [redacted], additional data was requested. Rather than perform the requested additional efficacy study, the applicant reanalyzed their data and modified the proposed dosing instructions. The results of the applicant's reanalysis of the efficacy data from Study E02 suggest that the patch has an effect duration of only eight hours instead of 12 hours. This post hoc reanalysis was not considered an acceptable means of determining dosing interval and so was not reviewed in great detail. The new proposed dosing instructions [redacted] with no more than two patches per day, and use for no more than three consecutive days. b(4)

Safety

Dr. Fang reconsidered the safety data specifically evaluating the relationship between frequency and duration of exposure and frequency of adverse events. As can be seen in the following table from Dr. Fang's review, the PK study and the skin safety studies exposed subjects to a variety of patch durations including one daily 8-hour application for 14 days, every 8 hour application of two patches for four days, and daily 23-hour application for 21 days. These studies provide safety data on skin reactions from conditions that exceed the exposure of the proposed dosing.

Table 2
Summary of Multiple-Dose Exposures

Studies	Type	Multiple-dose exposure	# subjects exposed	# subjects in safety database
FS-67-122	PK	q8-h application of 2 patches x 13 applications	19	19
FS-67-011	Cumulative Irritation	Daily application of 23-hour patch x 21 days	38	37
FS-67-01	Cumulative Irritation	Daily application of 8-hour patch x 14 days	36	32
FS-67-02	Contact sensitization	24-h application 3x/wk x 3 wk followed by 24-h application once after a 2-wk rest (10 applications)	224	205
FS-67-11	Photoallergy	24-h application 2x/wk x 3 wk followed by 24-h application once after a 2-wk rest (7 applications)	32	28

Source: Table1 1 and 13 of the NDA Section 3.9, Clinical Data Summary.
Note: The exclusion of subjects from the safety database in these studies were due to various reasons other than AE, except one subject in study FS-67-02, who dropped out due to AE.

Skin reactions were assessed using the following scale:

Table 3

TABLE 25. ASSESSMENT OF APPLICATION SITE REACTIONS IN FS-67-E01	
Grade	Criteria
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Moderate erythema, readily visible; or minimal edema; or minimal papular response
3	Strong erythema; or erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site
A	Slight glazed appearance
B	Marked glazing
C	Glazing with peeling and cracking
F	Glazing with fissures
G	Film of dried serous exudate covering all or portion of the patch site
H	Small petechial erosions and or scabs
@	Additional comments as footnote

Reviewing the results of Study FS-67-011 in which subjects received a 23-hour application daily for 21 days, the following table from Dr. Fang's review shows that there were no cases of any substantial skin irritation of grade 3 or worse from the first three days of exposure.

Table 4
Number (%) of patients with skin irritation grade ≥3 and/or characterized by fissuring, exudate, petechiae, or required skipping patch application in 21-day cumulative irritation study FS-67-011

Treatment day	#patients (percentage) with skin irritation grade ≥3 and/or characterized by fissuring (F), exudate (G), petechiae (H), or required skipping patch application (X)			
	Active patch site		Vehicle patch site	
(n=37)	New onset	Cumulative	New onset	Cumulative
2nd	0	0	0	0
3rd	0	0	0	0
4th	1 (2.7%)	**1 (2.7%)**	0	0
5th	2 (5.4%)	3 (8.1%)	2 (5.4%)	2 (5.4%)
6th	3 (8.1%)	6 (16.2%)	1 (2.7%)	3 (8.1%)

Note: When a reaction requiring discontinuation (grade 3 or equivalent) occurred, the scores thereafter are the residual reactions remaining at the application site after patch removal.
Source: Table 14.2.1.12 in the original study report for Study FS-67-011 (also attached in Appendix)

Assessing grade 2 reactions or worse, as detailed in the following table modified from Dr. Fang's review, there were only a few cases with in the first three days. The grade 2 reaction of moderate erythema, possibly mild edema is easily recognizable and reversible.

Table 5
Number (%) of patients with skin irritation grade ≥2 and/or characterized by marked glazing, cracking, fissuring, petechiae, or required skipping patch application in 21-day cumulative irritation study FS-67-011

Treatment day	#patients (percentage) with grade ≥2 skin irritation and/or marked glazing (B), cracking (C), fissuring (F), petechiae (H) type skin irritation or required skipping patch application (X)					
	Active patch site			Vehicle patch site		
(n=37)	New onset	# actual case	Cumulative	New onset	# actual case	Cumulative
2nd	1 (2.7%)	1 (2.7%)	1 (2.7%)	1 (2.7%)	1 (2.7%)	1 (2.7%)
3rd	2 (5.4%)	3 (8.1%)	3 (8.1%)	1 (2.7%)	2 (5.4%)	2 (5.4%)
4th	2 (5.4%)	4 (10.8%)	**5 (13.5%)**	2 (5.4%)	3 (8.1%)	**4 (10.8%)**
5th	4 (10.8%)	8 (21.6%)	9 (24.3%)	2 (5.4%)	5 (13.5%)	6 (16.2%)
6th	4 (10.8%)	10 (27.0%)	13 (35.1%)	5 (13.5%)	11 (29.7%)	11 (29.7%)

As noted in Dr. Fang's review, Study FS-67-0122 was intended to assess local sin reactions and called for two patches to be applied to the subject's back every eight hours for more 13 consecutive applications, which amounts to more than 4 days of exposure. All 19 subjects in this study did have mild application site redness, but there were no serious skin reactions, and no reactions requiring patch removal or symptomatic treatment. Seven subjects did report episodes of mild site warmth or burning, all of which resolved within 30 minutes. There was one potential generalized allergic reaction during this study, this case was reviewed in detail by Dr. Porres.

LABELING

The applicant provided new dosing instructions, with no more than two patches per day, and use for no more than three consecutive days.

. Based on discussions with DNCE, it was felt that this could be challenging instructions to convey to patients via over-the-counter product labeling and could lead to confusion with patients leaving the patch on for 12 hours at a time. As demonstrated by the dermal safety studies, two 12-hour periods of application for three days of use does not present a safety problem. The dermal safety studies provide data that demonstrates that the safety data for skin irritation and adverse events under conditions comparable to wearing one patch for 12 hours twice daily for three days is adequately balanced by the evidence of efficacy. So, in order to simplify instructions for patients, the proposed dosing instructions were changed

b(4)

A full labeling review was conducted by Dr. Reynold Tan. As noted by Dr. Schiffenbauer, labeling was modified to include warning . As methyl salicylic acid is nonacetylated, the over-the-counter labeling for nonsteroidal anti-inflammatory drugs has also been added.

b(4)

however, as noted below under Pediatrics, the label has been modified . Additional changes have been made to the principle display panel .

During this review cycle, the applicant proposed three tradenames, [redacted], Salonpas Arthritis Pain, [redacted]. The use of [redacted] is not appropriate for this product and was rejected. The other two names were found acceptable, but the Division of Non-Prescription Clinical Evaluation raised the concern of different names possibly resulting in use twice as much product as intended. The applicant committed to adding language to the principle display panel reminding consumers not to do this. There is also precedence for over-the-counter products to carry more than one name. Additional discussions with the applicant has resulted in a request for use of the name [redacted]. DMETS had found the use of the modifier [redacted] to be possibly misleading. I think it is also potentially promotional. DNCE requested that the applicant use the name Salonpas Pain Relief Patch to clarify what relief is to be expected. While I do not feel that this is the best tradename, I think that patients will be able to quickly decide whether the product provides adequate relief and so, defer to DNCE on the acceptability of this name. b(4)

PEDIATRICS

As is common for over-the-counter drugs, [redacted] There were no pediatric patients included in the clinical studies and so labeling was modified [redacted]. b(4)

b(4)

[redacted]

DISCUSSION

This submission represents a Complete Response to Approvable action and includes new pharmacokinetic data, resolution of outstanding CMC concerns and amended labeling. There is sufficient data from the original efficacy and safety studies submitted in the initial application to

support approval of this product with the amended labeling. The assessment of efficacy for a topical over-the-counter product in a population with strains, sprains, bruises and pains due to arthritis is challenging. Patients often do not have a sufficient duration or intensity of pain to demonstrate a treatment effect that can separate the active treatment from placebo treatment. That there was a fairly robust separation from placebo in the efficacy studies is notable. The difficulty supporting the proposed dosing interval is also not unexpected in patients whose pain may not persist at sufficient intensity to warrant re-dosing. The safety data from the dermal safety studies support the proposed dosing of 8-hour to 12-hour applications of up to 2 patches in 24 hours for up to three days. As recommended by the Division of Nonprescription Clinical Evaluation, dosing instructions of 8 to 12 hours, no more than two patches per day and for up to three days may provide patients with the clearest understanding of how to safely use this product.

b(4)

Appears This Way
On Original

Addendum

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

David,

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

Joel

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

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

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

Dr. Jacobson-Kram,

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

Please see the e-mails below for additional explanations.

I appreciate your time. Thanks.

Joel Schiffenbauer

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

/s/

Sharon Hertz
2/20/2008 01:07:21 PM
MEDICAL OFFICER