CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-029

PROPRIETARY NAME REVIEW(S)

2 of 2

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 20, 2008
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From:	Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator Division of Medication Errors and Technical Support, HFD-420
Subject:	Proprietary Name, Label and Labeling Review
Drug Name(s):	[redacted] Salonpas Arthritis Pain [redacted] (Menthol and Methyl Salicylate) 3%/10% b(4)
Submission Number:	NA
Application Type/Number:	NDA 22-029
Applicant/applicant:	Hisamitsu Pharmaceutical Co., Inc.
OSE RCM #:	OSE 2007-2480, 2007-2482, 2008-213

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EXECUTIVE SUMMARY

DMETS Failure Modes and Effects Analysis (FMEA), identified a number of safety concerns surrounding the brand name extension of the Salonpas product line. First, the use of three different names for products containing the same active ingredients, strength and indication of use is misleading and may lead to concomitant administration and potential overdose. Secondly, the modifier [redacted] is unacceptable because [redacted]. Additionally, the modifiers, "Arthritis Pain" and [redacted] are unacceptable because these names misleadingly imply that the products are clinically different and can only be used for the specific treatment of arthritis pain or muscle pain, respectively. However, these are identical products. Lastly, expanding the already similar nomenclature among the Salonpas product line is concerning. The re-use of brand names needlessly complicates the identification of the active ingredients and self-selection of over-the-counter products. b(4)

Our Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion with other over-the-counter Salonpas products and could lead to medication errors. Detailed recommendations can be found in Section 6 of this review.

In summary, DMETS concludes that that the proposed proprietary names, [redacted] Salonpas Arthritis Pain, [redacted] are misleading and introduces an unacceptable source of confusion and risk of medication error. As such, DMETS objects to the use of the proposed proprietary names, [redacted] Salonpas Arthritis Pain, [redacted] and recommends that one proprietary name be submitted for consideration. Additionally, DMETS recommends that the proposed container labels and carton labeling be revised to provide adequate differentiation from other Salonpas products. When submitted, the proposed proprietary name and revised labels should be forwarded to DMETS for evaluation. b(4)

1 BACKGROUND

This review was written in response to a request from the Division of Nonprescription Clinical Evaluation for assessment of the proprietary names [redacted] Salonpas Arthritis Pain, and [redacted] regarding potential name confusion with other proprietary or established names. Container labels and carton labeling were also submitted and reviewed from a medication error perspective. b(4)

1.1 REGULATORY HISTORY

The Applicant submitted NDA 22-029 on 2/27/2006 for approval of their Salonpas patch product as the first NDA-approved OTC topical analgesic patch product. Patch products are still being considered for inclusion in the OTC topical analgesic monograph. The Applicant proposed the following trade names in the NDA application: [redacted] DMETS reviewed the proposed names in OSE consult # 06-0197/06-0197-1/06-0197-2 dated July 14, 2006 and found all three names to be unacceptable because of the ambiguous modifiers ([redacted]) which appeared to be promotional and misleading. However, against DMETS recommendations, the Division decided the name [redacted] was acceptable and conveyed this information to the Applicant in the Division's 12/27/2006 Approvable Letter. b(4)

The Applicant responded with four new proposed tradenames in a 1/8/2007 submission: [redacted] Without consultation with DMETS, the Division informed the Applicant that the name [redacted] was not acceptable because it did not differentiate the proposed product from existing Salonpas products and that the name [redacted] b(4)

[redacted] was also unacceptable as it misleadingly suggested product superiority. We are unsure as to the disposition of the names [redacted] b(4)

Subsequently, the Applicant submitted proposed Drug Facts labeling in a 7/25/2007 submission to address labeling deficiencies cited in the 12/27/2006 Approvable Letter. This 7/25/2007 submission referred to the product as [redacted]". The Division believed the choice of a tradename was resolved, because they had previously informed the Applicant that [redacted]' was an acceptable trade name. b(4)

On August 17, 2007 the applicant provided a complete response to the Approvable letter. Subsequently on November 16, 2007, the Applicant submitted a labeling amendment in which in which they proposed their intention of simultaneously marketing the same Salonpas patch product under the three trade names: [redacted], Salonpas Arthritis Pain and [redacted]. On December 3, 2007 the Division requested a DMETS review of the proposed trade names.

1.2 PRODUCT INFORMATION

The proposed products [redacted], Salonpas Arthritis Pain, [redacted] are pain relief patches containing menthol 3% and methyl salicylate 10%. They are over-the-counter transdermal products for the temporary relief of mild to moderate aches and pains of muscles and joints associated with strains, sprains, simple backache, arthritis, and bruises. The usual dose is to apply one patch to the affected area and leave into place for [redacted]. No more than two patches are to be used per day. In addition, patches should not be used for more than 3 consecutive days. The applicant proposes marketing the product in 5 patches, 15 patches and 5 patches. b(4)

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by DMETS medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. DMETS defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary names, [redacted], Salonpas Arthritis Pain, and [redacted], and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency. Since Salonpas is already marketed, DMETS also considered the appropriateness of the addition of the three modifiers, [redacted], "Arthritis Pain", [redacted]". Additionally, the modifiers were assessed for resemblance to any numbers, dosing instructions, or medical abbreviations. Furthermore, DMETS evaluated the appropriateness of the proposed modifiers, considered the potential for modifier's omission or interpretation, and verified that the modifiers do not appear on the error-prone abbreviation list maintained by the Institute of Safe Medication Practices (ISMP). b(4)

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

For the proprietary names, [redacted] Salonpas Arthritis Pain, [redacted] the medication error staff of DMETS search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.5). DMETS also conducts internal prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.3). b(4)

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.3). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMETS uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMETS considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

2.1.1 Search Criteria

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'S' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4 5]

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[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

[4] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[5] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artifical Inteligence in Medicine (2005)

2.1.1.1

[redacted]

b(4)

[redacted]

When searching to identify potential names that may sound similar t [redacted] the Medication Error Staff focused on the root word Salonpas and searched for names with similar number of syllables (3), stresses (Sa-LON-pas, SA-lon-pas, or sa-lon-PAS), and placement of vowel and consonant sounds. We also considered how the inclusion of [redacted] may change the sound of the name. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

2.1.1.2 Salonpas Arthritis Pain

To identify drug names that may look similar to Salonpas Arthritis Pain the Staff also considers the other orthographic appearance of the names on lined and unlined orders. Specific attributes taken into consideration of Salonpas Arthritis Pain include length of the name (21 letters), upstrokes (7, capital letters 'S', 'A', and 'P' and letters 'l','t', and 'h'), downstokes (one, letter 'p'), cross-strokes (two, letter 't'), and dotted letters (three, letter 'i'). Additionally, several letters in Salonpas Arthritis Pain may be vulnerable to ambiguity when scripted, including the letter 'S' may appear as 'G'; lower case 'a' appear as a lower case 'c', 'e', or 'u'; lower case 'l' may appear as lower case 't', 'b', 'd' or 'e'; lower case 'p' may appear as lower case 'g', 'f', 'q', 'j' or 'y', lower case 's' may appear as lower case 'n', letter A may appear as 'Cl' or 'U', letter 'r' may appear as 'n', letter 't' can appear as an 'x', letter 'h' can appear as letters, 'l', 'b', 'd', 'e' and letter 'i' can look like 'e'. As such, the Staff also considered these alternate appearances when identifying drug names that may look similar to Salonpas Arthritis Pain.

When searching to identify potential names that may sound similar to Salonpas Arthritis Pain, the Medication Error Staff focused on the root word Salonpas and searched for names with similar number of syllables (3), stresses (Sa-LON-pas, SA-lon-pas, or sa-lon-PAS), and placement of vowel and consonant sounds. We also considered how the inclusion of "Arthritis Pain" may change the sound of the name. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

2.1.1.3

[redacted]

b(4)

[redacted]

[redacted] b(4)

When searching to identify potential names that may sound similar to Salonpas Arthritis Pain, the Medication Error Staff focused on the root word Salonpas and searched for names with similar number of syllables (3), stresses (Sa-LON-pas, SA-lon-pas, or sa-lon-PAS), and placement of vowel and consonant sounds. We also considered how the inclusion of [redacted] may change sound of the name. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission. b(4)

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary names [redacted] Salonpas Arthritis Pain [redacted] the established name (menthol and methyl salicylate), proposed indication (temporary relief of mild to moderate aches and pains of muscles and joints associated with bruises, sprains, strains, simple backache and arthritis), strength (3%/10%), dose [redacted] frequency of administration (every 8 hours with maximum dose of 2 patches per day), route (transdermal) and dosage form of the product (patch). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration. b(4)

Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.4 Data base and information sources

The proposed proprietary names [redacted] Salonpas Arthritis Pain, and [redacted] were provided to the medication error staff of DMETS to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to [redacted] Salonpas Arthritis Pain, and [redacted] using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel. b(4)

2.1.1.5 CDER Expert Panel Discussion

An Expert Panel Discussion is held by DMETS to gather CDER professional opinions on the safety of the product and the proprietary names, [redacted] Salonpas Arthritis Pain, and [redacted] Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). b(4)

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 Prescription analysis studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Salonpas Arthritis Pain and [redacted] with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. A study was not conducted for [redacted], as DMETS typically only reviews the primary and secondary names an applicant submits. At the time the study was conducted we were under the impression that [redacted] was a tertiary name). The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners. b(4)

In order to evaluate the potential for misinterpretation of Salonpas Arthritis Pain and [redacted] in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the medication error staff. b(4)

Figure 1. Salonpas Arthritis Pain Study (conducted on January 3, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Outpatient Prescription: Salonpas Arthritis Pain #8 Apply 1 patch to affected area. Dlhr.	Salonpas Arthritis Pain Dispense #8 Apply 1 patch to affected area q 8 hours.
Inpatient Medication Order : Salonpas Arthritis Pain Apply 1 patch to affected area q 8h	

Figure 2. Salonpas Arthritis Pain Study (conducted on January 18, 2008)

Outpatient Presecription:	
3) Apply 1 patch to affected area q 8 hr	Apply one patch to the affected area every 8 hours
Inpatient Prescription Order:	
Apply 1 patch to affected area q 8 hrs	

b(4)

2.1.3 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMETS seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

[6] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Are the names [redacted] Salonpas Arthritis Pain, and [redacted] Arthritis Pain, [redacted] convincing similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for [redacted] Salonpas Arthritis Pain, and [redacted] be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review. b(4)

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

DMETS will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. DMETS identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug another drug product.

In the event that DMETS objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMETS will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while DMETS will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMETS will not object to the use of the proprietary name. If any of these conditions are met, then DMETS will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, DMETS contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMETS believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If DMETS objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. DMETS is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMETS to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMETS may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[7]

Because DMETS staff analyze reported misuse of drugs, DMETS staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMETS uses FMEA and the principles of human factors to identify potential sources of error with the proposed product

[7] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on November 16, 2007 the following labels and insert labeling for DMETS review (see Appendices G, H and I for images):

- Container: 5 patches, 5 patches, 5 patches
- Carton: 5 patches, 15 patches, 5 patches

2.3 ADVERSE EVENTS REPORTING SYSTEM (AERS)

Since the Salonpas product line is currently marketed in the United States marketplace, DMETS conducted a search of the FDA *Adverse Event Reporting System* (AERS) for Salonpas related medication errors. AERS was searched using the verbatim entry "Salon%" with MedDRA High Level Group Terms "Medication Errors" and the Preferred Term "Pharmaceutical Product Complaint".

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Data base and information sources

In total, 9 products were identified as having some similarity to the name [redacted] Salonpas Arthritis Pain, an[redacted]

b(4)

Seven of the nine names were thought to look and sound similar to [redacted] Salonpas Arthritis Pain, ar[redacted] include: Salonpas Patch, Salonpas Hot Patch, Salonpas Gel Patch, Salonpas Gel, Air Salonpas Spray, Salonsip Aqua-Patch and Salonpas Muscle Mousse. Two additional names (Gabapentin and Salagen) were thought to look similar to [redacted] Salonpas Arthritis Pain, and [redacted]

[redacted]

Additionally, it was determined that the proposed proprietary names contain the U.S. Adopted Name (USAN) stem, "sal-". The USAN Council has designated the stem "Sal-" to indicate a drug that is contains salicylic acid derivative. The stem is appropriate because this product contains methyl salicylate.

3.1.2 CDER Expert panel discussion

The Expert Panel reviewed the pool of names identified by DMETS staff (see section 3.1.1, above), and no additional names were thought to have orthographic similarity to [redacted] Salonpas Arthritis Pain, and [redacted] . and have the potential for confusion. DDMAC was unable to provide comments on the proposed trade names [redacted] "Salonpas Arthritis Pain", and [redacted] " as these are over-the-counter drug products.

b(4)

3.1.3 Prescription analysis studies

3.1.3.1 Salonpas Arthritis Pain

A total of 36 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About 11% of the participants (n=4) interpreted the name correctly as "Salonpas Arthritis

Pain" with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurred in the outpatient written study, with the first letter 'a' reported as 'e' and 'o', the letter 'n' reported as 'r' and the letter 'l' reported as 't'. In the written and verbal prescription studies, the letter 'S' was misinterpreted as a 'C' by two respondents. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.3.2 [redacted]

A total of 34 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About 15% of the participants (n=6) interpreted the name correctly as '[redacted]' with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurred in the outpatient prescription study, with the first letter 'a' reported as 'o' and the last letter 's' reported as 'x'. In the verbal prescription study the letter 'S' was reported as a 'C' by two respondents. In the inpatient prescription study, the letter 'S' was misinterpreted as a 'G' by one respondent, and two respondents omitted the modifier completely and interpreted the name as only Salonpas. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies. b(4)

3.1.4 Safety evaluator risk assessment

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look similar t[redacted]; Salonpas Arthritis Pain, and [redacted]

As such, a total of 9 names (which included the Salonpas product line (7) and 2 additional names) were analyzed to determine if the drug names could be confused with [redacted] Salonpas Arthritis Pain, and [redacted] and if the drug name confusion would likely result in a medication error. b(4)

This analysis determined that the name similarity between [redacted] Salonpas Arthritis Pain, a[redacted] and one name, Salonpas Muscle Mousse, was unlikely to result in medication errors since Salonpas Muscle Mousse has been discontinued by the manufacturer (Appendix C).

For two of the names (Gabapentin and Salagen), FMEA determined that medication errors were unlikely because the products do not overlap in strength or dosage with [redacted] Salonpas Arthritis Pain, and [redacted] and have minimal orthographic and/or phonetic similarity to the proposed products. Additionally, Gabapentin and Salagen are available by prescription only (Appendix D).

The remaining names of concern are the Salonpas product line (Salonpas Patch, Salonpas Hot Patch, Salonpas Gel Patch, Salonpas Gel, Air Salonpas Spray, and Salonsip Aqua-Patch). This product line was analyzed to determine if the similar appearance and sound of the drug names could lead to confusion with the proposed products and if the drug name confusion would likely result in a medication error. We also analyzed how the proposed modifiers would allow for proper identification among the already marketed products. The product characteristics of these products are listed Appendix E.

Additionally, we considered if the proposed modifiers had similarity in spelling and pronunciation to other drug names. These names are listed in Appendix F. Although there is some overlap with the modifiers of these products, all of the products listed in Appendix F are orthographically and phonetically different from the proposed products. The listed products either contain a different root name or additional descriptors which help to differentiate them from [redacted] Salonpas Arthritis Pain, and [redacted] Additionally, the modifiers [redacted] "Arthritis Pain" and "[redacted]" were not found to resemble any numbers, dosing instructions, b(4)

or medical abbreviations. Furthermore, [redacted] "Arthritis Pain" and [redacted] do not appear on the error-prone abbreviation list maintained by the Institute of Safe Medication Practices (ISMP). b(4)

Additionally, the proposed name "Salonpas" contains the U.S. Adopted Name (USAN) stem "sal-". Use of the stem "sal-" in the proprietary names Salonpas is consistent with the USAN Council definition of this stem.

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels and carton labeling identified several potential sources of medication errors.

The carton labeling does not provide sufficient information on the principle display panel, such as the dosage form, active ingredients and corresponding pharmacological category that would distinguish this product from the currently marketed Salonpas product line.

The container label and carton labeling do not contain the route of administration on the principle display panel.

The net quantity is bolded. In addition, the net quantity of the Salonpas Arthritis Pain container label states 5 patches, whereas the carton labeling states 15 patches.

The labels and labeling contain promotional phrases, misleading phrases as well as information that is not useful. Furthermore, information regarding how to effectively apply [redacted] /Arthritis Pain [redacted] and how to safely discard the patches are not clear and/or missing from the labels and labeling. b(4)

The proprietary name is not presented in the same size, color or font. In addition, the established name does not appear on the principle display panel.

The principle display panel on the carton labeling contains many prominently displayed and distracting pictures.

The packaging does not match the maximum allowable amount. For example, the maximum is two patches per day for 3 days, yet the carton provides a net quantity of 15 patches. In addition, unused patches must be discarded 14 days after opening.

The labels and labeling do not contain information regarding when it is safe to resume using Salonpas again, if a patient has used it for the maximum 3 days (i.e. can they restart treatment after 2 days, 3 days, etc).

3.3 ADVERSE EVENTS REPORTING SYSTEM (AERS)

This search did not retrieve any cases of postmarketing confusion with the nomenclature, labels, or labeling of the Salonpas product line.

4 DISCUSSION

The proposed products [redacted] Salonpas Arthritis Pain, and [redacted] will be an extension to the currently marketed over-the-counter Salonpas product line. These products all use the family trade name "Salonpas" with various descriptors to distinguish the products (see Appendix E). Additionally, the currently marketed products and the proposed products share individually or in combination the same active ingredients (menthol, methyl salicylate, camphor, and/or capsaicin) at different concentrations. Furthermore, all currently marketed products share the same indication of use as the three proposed products. Based on the use of the family trade name, product similarities and overlaps, DMETS has safety concerns with the continued use of the brand name extension b(4)

"Salonpas" because this practice has proven to be unsafe. As it relates to this review, the use of the proposed proprietary names [redacted] Salonpas Arthritis Pain, and [redacted] extends the Salonpas trade name to three new products with the same active ingredients with different concentrations as the currently marketed Salonpas gel. We note the proposed three products are identical in ingredients, concentration and indication of use. b(4)

Brand name extension is a term used to describe the reuse of a well-known, successful proprietary name to introduce a new product that may contain an active ingredient different from the active ingredient in the original product.[8] In the United States, there are more than 1,000 active ingredients used in the 100,000 products that are marketed over-the-counter,[9] and medication safety experts have noted that the reuse of brand names needlessly complicates the identification of the active ingredients and self-selection of over-the-counter products.[10] More recently, in an FDA Advisory Committee Meeting that addressed similar brand name confusion among cough and cold products, the committee noted that the marketing of products with multiple ingredients and current product labeling is confusing and both lead to issues with the safe use of the products by the consumer. [11] Brand-name extension products have been associated with patient and practitioner confusion with respect to the product's ingredients, strength, and concentration and this confusion has led to medication errors in which the wrong product or dose was administered or the product was used in a contraindicated manner or in combination with a product with similar or the same active ingredients. These errors can stem from the similarity of product names, and overlapping product characteristics coupled with the low level of awareness or knowledge of the product profile by healthcare professionals and patients. Additionally, other visual cues such as similar product packaging and storage location increase the risk of name confusion and subsequent error.

The Salonpas proprietary names (specifically the descriptors) imply to patients and healthcare practitioners that there are unique clinical differences among the products in the Salonpas product line (i.e., currently marketed and proposed). Although there may be some differences in the active ingredients and concentration/strength depending upon the product chosen, all of these products have the same indication of use. Patients will likely not understand that the majority of the products contain the same and/or overlapping ingredients with similar or the same concentrations. This may increase the risk of a patient selecting and using multiple Salonpas products concomitantly, resulting in overuse and/or overdose. For example, if a patient is suffering from both arthritis pain and muscle pain and decides to treat them both at the same time; the patient may use two products [redacted] and Salonpas gel) concomitantly because they are unaware that the two products contain the same active ingredients (e.g. menthol and methyl salicylate). Furthermore, a patient could sequentially use each of the products thinking they are using two different products, but ultimately be using the same active ingredient for over a week. In either case the patient is at risk for concomitant administration of the same active ingredients which can lead to overdose and potentially to methyl salicylate toxicity including death depending upon the product used. Additionally, without knowing that all the products are essentially the same, a patient may choose Salonpas gel or [redacted] after the unsuccessful use of [redacted] or any combination within Salonpas product line and continue to have treatment failure. Thus, DMETS is unsure if the benefit of adding another three product names to this product line with the same indication of use outweighs the potential risk of confusion resulting from this brand name extension. b(4)

[8] United States Pharmacopeia. OTC Names: An Invitation to Err? Quality Review, 1996 Volume 54.

[9] Consumer Healthcare Products Association (CHPA): "Facts and Figures About OTCs," 2001. Accessed on 6/13/2007 at: http://www.chpa-info.org/ChpaPortal/PressRoom/Statistics/OTCFactsandFigures.htm

[10] ISMP, USP

[11] Joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee October 18-19, 2007.

With regard to the specific modifiers, [redacted] and Arthritis Pain, DMETS considers these names misleading as they imply that the products are clinically different and can only be used for the specific treatment of arthritis pain or muscle pain, respectively. However, these are identical products. Thus neither of these modifiers will be appropriate for the proposed Salonpas product indicated for the temporary relief of mild to moderate aches and pains of muscles and joints associated with bruises, sprains, strains, simple backache and arthritis. Similarly with regards to the proposed modifier [redacted] the Office of New Drug Quality Assessment (ONDQA) reviewer for this application related via email that the common practice in ONDQA is to not allow the use of [redacted] for patches, as by their nature, almost all patches are [redacted] so the distinction does not need to be made and can be confusing. Even with the removal of [redacted] from the name, the modifier [redacted] is misleading to patients and healthcare practitioners because it implies that the duration [redacted] than the other Salonpas products. DMETS believe this is misleading as all Salonpas products [redacted] however the maximum dosing for this product is only 2 patches per day. Therefore this modifier is also unacceptable. b(4)

The creation of three new proprietary names for the same active ingredient adds unnecessarily to the growing number of proprietary names in the Salonpas product line. This proliferation of numerous proprietary names may increase the likelihood of occurrence of medication errors resulting in patient injury from potential overdose due to confusion and concomitant administration of these products.

Additionally, DMETS notes that the proposed modifier incorporates the U.S. Adopted Name (USAN) stem, "sal-" in the (brand name) proprietary name Salonpas. From a safety perspective, DMETS has concern with the inclusion of a USAN stem in the proprietary names. USAN stems are used by the USAN Council as the building blocks of nonproprietary names. The stems are intended to provide practitioners with meaningful, informative designations which indicate members of a related group of drugs. USAN stems may allow shared characteristics (such as pharmacologic action) to be identified from the nonproprietary name, and thus enhance the safe use of medications. When stems are incorporated into proprietary names the effect of the efforts is lessened. DMETS does not believe that the FDA should permit the use of USAN stems in proprietary names. While this concern may not direct consequences to the use of Salonpas from a mediation errors standpoint, the issue does have broad implication to the safe use of medications in general since it detracts from the Council's efforts to communicate meaningful information to practitioners via nonproprietary nomenclature.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, DMETS believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners, and, in this case, the data submitted by the Applicant from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, DMETS recommends that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

Additionally, we note a safety concern between the proposed products and the currently marketed Salonpas gel. The proposed products contain the same active ingredients as Salonpas gel. However, the

products are different with respect to dosage form (gel vs. transdermal patch), product strength (7%/15% vs. 3% /10%) and maximum duration of treatment (3 days vs. 7 days). It is counter intuitive to both consumers and healthcare practitioners that the product with the higher strength has a longer duration of treatment than the proposed product with a lower strength (shorter duration of treatment). Most consumers/healthcare practitioners will assume that the higher strength product will have a shorter duration of treatment and the lower strength product a longer duration of treatment. Thus, most patients will likely choose the higher strength product because they feel it is more effective than the lower strength product. In fact this may not be the case. We note the gel is not an approved product and there may be some pharmacokinetic reason as to why the gel has a higher strength and longer duration of therapy. However, DMETS cannot comment on this issue. Overall we believe that these two products should not be co-marketed together.

4.1 LABEL AND LABELING RISK ASSESSMENT

Our FMEA analysis of the container labels and carton labeling identified several sources of medication error. We noted areas that are promotional, duplicative, and lack sufficient prominence which can make them vulnerable to misinterpretation. These types of deficiencies are well known contributing factors to medication errors. What will further impact these potential Failure modes is the fact that most practitioners and patients will not be aware of the introduction of these products.

The labels and labeling of the three products look identical. In fact, the Applicant uses identical layouts on each product. The same large patch on the center of the principle display pane, body illustrations and promotional statements in the same location and the same colors make the products difficult to distinguish from one another and can lead to selection errors. The Applicant's presentation of the trade names, [redacted], Salonpas Arthritis Pain, and [redacted] appears in a different size, color, and font. For easier readability of the proprietary name, the entire name should be presented in the same size, same color, and same font. In addition, the most prominent information on the principle display panel should be the proprietary name, established name, strength, dosage form and pharmacological category. However these pieces lack prominence because the three large graphics of the body illustrations and the patch are larger and distract from this essential information and does not leave room to collectively present this information on the principle display panel. Displaying the proprietary name, established name, strength, dosage form and pharmacological category in a collective manner is important as it would help consumers differentiate between the proposed product and other products in the Salonpas product line. Although these improvements will enhance the readability of the label/labeling; this is a low leverage approach to minimizing the expected errors from the introduction of brand extension noted above.

b(4)

The principle display panel contains promotional, misleading, and unnecessary statements that could be removed to allow more room for important information. The statement [redacted] is promotional and misleading as it implies that everyone who uses [redacted] Salonpas Arthritis Pain [redacted] will have an increase in their activity level. Additionally, the phrase [redacted] is also misleading as the directions state [redacted] The phrase [redacted] implies that this product [redacted] the currently marketed Salonpas products; however, the currently marketed products [redacted] Furthermore, the label and labeling contain other unnecessary phrases such as "minty scent", [redacted] and "comfort stretch" which do not convey any useful information and thus adds clutter to the principal display panel. Although the statement [redacted] may be accurate at this time, the Applicant has no way of knowing if other Applicants or Applicants are in the process of submitting an application for patch approval. Therefore, this statement is misleading. Lastly, the words [redacted] appear on the principle

b(4)

display panel of the [redacted] however, these indications differ from those in the Uses section within Drug Facts.

Our analysis of the [redacted] and Salonpas Arthritis Pain carton labeling, contain the statement [redacted]. This distinction does not need to be made and it is not in compliance with recommendations from the Office of New Drug Quality Assessment (ONDQA). Allowing this phrase on the principle display panel of [redacted] and Salonpas Arthritis Pain implies that [redacted] Salonpas products or may be misinterpreted to mean the product [redacted] b(4)

We also noted other information that is absent from the labels and labeling or not prominently displayed. The route of administration does not appear on the container labels or carton labeling. Additionally, detailed instructions on how to apply the patch appear on the back panels, whereas the illustrations appear on the side panels. These illustrations and steps should appear together otherwise the reader has to look in two different places to find application instructions. Keeping the illustrations with the text offers a better comprehension and understanding of the application instructions. Finally, the directions on the back panel do not appear to ensure that patients remove a patch prior to applying another patch.

The packaging configuration for the Salonpas Arthritis pain carton labeling has a net quantity of 15 patches, which is incongruent with the usual dosage of this product. The directions of use state: "do not use the patches for more than 3 consecutive days" and [redacted] The sponsor should package the Salonpas patches in a size that is congruent with the proposed frequency (no more than 2 per day) and duration of treatment (no more than 3 days). If in fact a patient can restart Salonpas after stopping treatment for a specified time, then the applicant can modify the statement to accommodate this time frame. However, if patients should contact their physician after a single treatment trial of Salonpas then this information should be included also. b(4)

5 CONCLUSIONS

The FMEA identified a number of safety concerns surrounding the brand name extension using Salonpas and utilizing three different trade names for an identical product. The Proprietary Name Risk Assessment findings indicate that the proposed names, [redacted] Salonpas Arthritis Pain, or [redacted] appears vulnerable to name confusion that could lead to medication errors with other Salonpas products and be misleading in and of themselves. As such, DMETS objects to the use of the proprietary names, [redacted] Salonpas Arthritis Pain, or [redacted] for this product. To decrease the risk of patient harm, the Applicant must not be allowed to simultaneously market the same product using three different trade names. b(4)

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

6 RECOMMENDATIONS

We recommend the revisions below be implemented in the interest of minimizing user error and maximizing patient safety. DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Cherye Milburn, Project Manager, at 301-796-2084.

6.1 COMMENTS TO THE DIVISION OF NONPRESCRIPTION CLINICAL EVALUATION

Based upon our assessment of the proposed proprietary name, labels and labeling, DMETS has identified areas needed of improvement. We have provided recommendations below for your consideration, and request that the recommendations and comments in section 6.2 be forwarded to the Applicant.

1. DMETS objects to the use of the proprietary names [redacted] Salonpas Arthritis Pain, or [redacted] because of our safety concerns with simultaneously marketing the same product under three different proprietary names. b(4)

2. DMETS does not recommend that the presentation of information and design of the proposed container labels and carton labeling be approved. The current proposed labels introduce vulnerability to confusion with other Salonpas products that could lead to medication errors. If modified labels are requested and submitted, please forward these labels to DMETS for evaluation.

6.2 Comments To the Applicant

DMETS concludes that that the proposed proprietary names, [redacted] Salonpas Arthritis Pain, or [redacted], and labels and labeling introduces unacceptable sources of confusion and risk of medication error. b(4)

Our analysis identified a number of safety concerns surrounding the use of three different names for the same active ingredients. We also identified problems with the use of the modifiers, [redacted] "Arthritis Pain", and [redacted] As such, DMETS objects to the use of the proprietary names, [redacted] Salonpas Arthritis Pain, or [redacted] for this product.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

A. Modifiers

1. Using three different modifiers to describe the same product is misleading. Their use implies each product has some unique effectiveness, when in reality, they all have the same active ingredients, are dosed the same and have the same indications of use. These uses should be marketed under one product name and all uses should appear on the principle display panel.
2. The modifier [redacted] is unacceptable because all patches are considered [redacted] However, this product can be used two times a day. b(4)

3. We consider the modifiers [redacted] and Arthritis Pain, misleading as they imply that the products are clinically different and can only be used for the specific treatment of arthritis pain or muscle pain, respectively. However, these are identical products. b(4)

B. Container labels/Carton Labeling

1. Present the proprietary name, dosage form, active ingredients, and corresponding pharmacological category on the principle display panel in the following manner on all labels and labeling.

Salonpas Patch

Contains:

Menthol 3%.....Topical analgesic

Methyl salicylate 10%.....Topical analgesic

2. Ensure the proprietary name in its entirety (name and modifier) is presented in the same size, color and font.
3. Include the route of administration on the principle display panel.
4. De-bold the net quantity statement.
5. Delete the promotional statement [redacted]
6. In the directions section, revise the third and fourth statement to read: [redacted] b(4)
7. Provide detailed directions regarding how to apply the patch beneath each illustration.
8. Delete the phrase "minty scent".
9. Include the statement: [redacted] b(4)
10. Please comment on the discrepancy of the net quantity of the Salonpas Arthritis Pain container labels (5 patches) and the carton labeling (15 patches).

C. Carton Labeling

1. See Section 6.2.1 Comments 1 thru 9.
2. Delete or decrease the prominence of the body graphics and the patch graphic on the principle display panel.
3. Delete the statements "comfort stretch". [redacted]
4. Delete the words: [redacted]
5. [redacted] b(4)
6. On the Salonpas Muscle Pain and Salonpas Arthritis Pain Cartons, delete the statement [redacted]

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7. REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. Micromedex Integrated Index (http://weblern/)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

3. Phonetic and Orthographic Computer Analysis (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for DMETS, FDA.

4. Drug Facts and Comparisons, online version, St. Louis, MO (http://weblern/)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

5. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

6. Division of Medication Errors and Technical Support proprietary name consultation requests

This is a list of proposed and pending names that is generated by DMETS from the Access database/tracking system.

7. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

8. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. WWW location http://www.uspto.gov.

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (http://weblern/)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. Natural Medicines Comprehensive Databases (http://weblern/)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. Stat!Ref (http://weblern/)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. Lexi-Comp (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

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APPENDICES

Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMETS also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMETS will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, DMETS also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstokes Downstrokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication

Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses for Salonpas Arthritis Pain

Outpatient Prescription	Voice Prescription	Inpatient Medication Order
Salergas Arthritis Pain	Celonpos arthritis Pain	Salonpas Arthritis Pain
Salenpas Arthritis Pain	Salonpas Arthritis Pain	Salonpar Arthritis Pain
Serytenpus Arthritis Pain	Solan plus arthritis pain	Celonpos Arthritis Pain
Salenpas Arthritis Pain P		Salonpin Arthritic Pain
Serlenpas [???] Arthritic		Solopac Arthritis Pain
Salonpas Arthritis Pain		Salonpas Arthritic Pain
Sertenpas Arthritis Pain		Salonpace arthritis Pain
Salerpas (or Salenpas)		Sal?? arthritis patch
Salerpas Arthritis Pain		Salonpac Arthritis Pain
Salenpas Arthriris Pain		Salopac Arthritis Pain
Serlenpus Arthritis Pain		Salonpac Arthritis Pain
Serlenpas Arthritis Crear		?
Serlenpers Arthritis Pain		Salopac Arthritis Pain
Sarlenpas Arthritis Pain		Salspac
Sutinpas Arthritis Pain		Salonpas arthritis Pain
Salenpus Arthritis Pain		
Salenpas Arthritis Pain		

Appendix B:

CDER Prescription Study Responses for [redacted] b(4)

Outpatient Prescription	Voice Prescription	Inpatient Medication Order
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	)	Salonpas
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	b(4)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Appendix C: Products withdrawn from the market with no generic equivalent product available.

Proprietary Name	Similarity to Salonpas	Year Product withdrawn by the Applicant
Salonpas Muscle Mousse	Look and Sound	Information not available.

Appendix D: Products with no numerical overlap in strength and dose

[redacted]/Salonpas Arthritis Pain [redacted] (Menthol/Methyl Salicylate)	b(4)	3%/10%	**Usual dose:** **The usual dose in to apply one patch to the affected area and [redacted] No more than two patches are to be used per day. In addition, patches should not be used for more than 3 consecutive days.** b(4)
Product name with potential for confusion	**Similarity to Proposed Proprietary Name**	**Strength**	**Usual Dose (if applicable)**
Gabapentin	Look and Sound	100 mg, 300 mg, 400 mg, 600 mg, 800 mg, 250 mg/5 mL	Postherpetic neuralgia: Initiated as a single 300 mg dose on day one, 600 mg/day on day 2 (divided twice daily), and 900 mg/day on day 3 (divided 3 times daily). Dose can be titrated as needed for pain relief to a daily dose of 1800 mg (divided 3 times daily) Epilepsy: 900 mg to 1800 mg/day given in divided doses (3 times a day).
Salagen	Look and Sound	5 mg; 7.5 mg	Head and neck cancer patients: Initial dose is 5 mg three times a day. Dosage should be titrated according to therapeutic response and tolerance. The usual dosage range is up to 15-30 mg per day. Sjogren's Syndrome patients: 5 mg taken four times a day

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Appendix E: Names that Look and Sound Like [redacted] Salonpas Arthritis Pain and [redacted] b(4)

Product	Established name, Dosage form (s)	Usual adult dose*
b(4) [redacted] Salonpas Arthritis Pain and [redacted]	**Menthol 3%** **Methyl salicylate 10%** **Transdermal patch**	**The usual dose in to apply one patch to the affected area [redacted]; No more than two patches are to be used per day. In addition, patches should not be used for more than 3 consecutive days.** b(4)
Salonpas (includes Salonpas Large)	Menthol 5.7% Methyl salicylate 6.3% Camphor 1.2% Transdermal patch	Apply to the affected area not more that 3 to 4 times daily for 7 days. Remove patch from the skin after at most 8 hour's application.
Salonpas Hot	Capsaicin 0.025% Transdermal patch	Apply to the affected area not more that 3 to 4 times daily for 7 days. Remove patch from the skin after at most 8 hour's application.
Salonpas Gel Patch	Menthol 1.25% Capsaicin 0.025% Transdermal gel patch	Apply to the affected area not more that 3 to 4 times daily for 7 days. Remove patch from the skin after at most 8 hour's application.
Salonpas Gel*	Menthol 7% Methyl salicylate 15% Topical	Apply to the affected area not more that 3 to 4 times daily for 7 days. Remove patch from the skin after at most 8 hour's application.
Air Salonpas	Menthol 3.2% Methyl salicylate 1.75% Camphor 3% Topical Spray	Spray onto affected area no longer than 3 seconds. Do not use more than 5 times daily for not more than 7 days
Salonsip Aqua-Patch	Menthol 1.25% Transdermal Patch	Apply to the affected area not more that 3 to 4 times daily for 7 days. Remove patch from the skin after at most 8 hour's application.
*Contains same active ingredients as proposed products		

Appendix F: Modifiers that Look and Sound Like [redacted] Arthritis Pain and [redacted]

b(4)

Proposed Proprietary Name		Dosage Form	Active Ingredient
[redacted]	[redacted]	[redacted]	[redacted]
Salonpas Arthritis Pain	•Arthritis Pain Relief Rub •Tylenol Arthritis Pain [redacted] Relief Caplet •Walgreens Arthritis Pain Relief [redacted] Caplet •Arthritis Pain Relief Cream		
[redacted]	[redacted]		

b(4)

Appears This Way On Original

6 Page(s) Withheld

_____ Trade Secret / Confidential

8 Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Proprietary Name Review*____

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/s/

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