CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-195 & 22-207

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

MEMORANDUM

To: **Lisa Basham, MS**
Division of Anesthesia, Analgesia, and Rheumatology Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **March 6, 2008**

Re: **Comments on draft labeling for morphine sulfate oral solution and tablets**
NDA 22-195 and 22-207

We have reviewed the proposed label for morphine sulfate oral solution and tablets (FDA version received 3/4/08) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- Throughout the FPI, the product is sometimes call "morphine" and sometimes "morphine sulfate." Please review and decide if one should be used throughout or if there are reasons to use both in certain situations.

- Other than on the product title line in Highlights, generic names for drugs are not usually capitalized in the text. Please consider revising throughout the labeling text.

- The main section headings in the Full Prescribing Information (e.g., "1 Indications and Usage") should not have a period after the numbers. Please delete throughout the label, including Contents.

- The cross-references in the Full Prescribing Information (FPI) do not follow the preferred formatting. The preferred presentation is to reference the main section name, with the appropriate subsection number in parentheses [e.g., "*See Clinical Pharmacology (12.3)*" and not "*See Pharmacokinetics (12.3)*"]. Additionally, the entire cross-reference should be italicized and entirely surrounded by brackets. Please correct throughout the label.

- If, after revisions have been made, Highlights and Contents do not all fit on one page, we prefer that Highlights appear on page one and that Contents appear in its entirety on page 2, rather than being split between pages.

HIGHLIGHTS

- Within each section of Highlights, there should be no white space separating the section title from the first line of text underneath, but there should be an extra hard return at the end of a section before the next section title.

- *"Morphine Sulfate Oral Solution and Morphine Sulfate Tablets (Morphine Sulfate Oral Solution) SOLUTION for ORAL use"*

  An extra hard return should be inserted before this line to separate it from the initial required paragraph, "These highlights do not..."

  There is no need to include the "established name" in parentheses for a product without a tradename. It can read simply,

  Morphine Sulfate Oral Solution and Morphine Sulfate Tablets

  For oral formulations, it is not necessary to include "for oral use" if deemed redundant.

  The controlled substance schedule should also be added to the end of this line.

- *"Initial U.S. Approval: 1987"*

  The initial U.S. approval date should reflect the first time any morphine product was marketed, regardless of the salt or dosage form.

Dosage and Administration

- *"Caution in patients with hepatic failure or renal insufficiency. (8.8, 8.9)"*

  We suggest being more specific here with the language, saying to start with low doses and then titrate and monitor carefully.

  Please change "insufficiency" to "impairment, the preferred term.

  Additionally, please consider if the warning about use in renal/hepatic impairment should appear in "Dosage and Administration" or in "Use in Specific Populations" in Highlights. It currently appears in both places. In general, the same concept should not be presented twice in Highlights.

Contraindications

- We note that the Contraindications section in the FPI includes one about hypersensitivity. Is this a demonstrated reaction or is it theoretical. We note that such reactions are not discussed anywhere else in the label. If this contraindication is appropriate to include, it must appear in both Highlights and the FPI. If it is not, then it should be deleted from both sections.

- We note that the FPI section also includes patients with hypercarbia. All contraindications listed in the FPI must be included in Highlights.

Warnings and Precautions

- The topics discussed in this section should be in decreasing order of importance. We recommend reviewing the Warnings and Precautions section in the FPI first to ensure proper ordering. Then, you can decide how many of them warrant inclusion in Highlights.

- The preferred presentation for this section is to state the risk, followed by a colon, and then describe any further details and how to manage it (as is done under "Drug Interactions" in Highlights). We can assist with revisions.

Adverse Reactions

- We recommend streamlining this section to read:

  Most common adverse reactions seen on initiation of therapy: constipation, nausea, somnolence, lightheadedness, dizziness, nausea, vomiting, sweating, dysphoria, and euphoria. (6.1)

- [redacted]

b(4)

Drug Interactions

- In the bullet about MAOIs, there is no need to capitalize "Oxidase" and "Inhibitors."

Use in Specific Populations

- *"Geriatric: Dose selection should be cautious, usually starting at the low end of the dosing range. (8.1)"*

  Please change "Geriatric" to "Geriatric patients."

  The cross-reference should be to section 8.5, not 8.1.

- See comment above about proper placement for renal/hepatic dosing recommendations.

Revision Date

- A line for the "revision date" must be added to the end of Highlights. It should be entirely bolded, right-justified within the right column, and should read:

  Revised: XX/2008

CONTENTS

- Once the FPI has been finalized, the Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.

- The main numbered section titles (e.g., 1 Indications and Usage) should be bolded in Contents. The numbered subsections should remain unbolded.

- As noted above, please delete the periods after the main section numbers.

FULL PRESCRIBING INFORMATION

2.1 Individualization of Dosage

- *"As with any opioid drug product, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience."*

  We recommend streamlining this sentence by deleting "it is necessary to."

- Because labeling now has numbered sections and subsections, we recommend that the list now numbered 1-7 use bullets instead of numbers to avoid confusion.

- We recommend reversing the order of the final two paragraphs in this section. This change will keep all the dosing/titrating/monitoring information together, and then conclude with the importance of communication between physicians and patients.

- [redacted] b(4)

2.2 Initiation of Therapy in Opioid-Naïve Patients

- *"Patients who have not been receiving opioid analgesics should be started on morphine sulfate in the following dosing range:*

Morphine Sulfate Oral Solution: 10 to 20 mg every 4 hours as needed for pain.
Morphine Sulfate Tablets: 15 to 30 mg every 4 hours as needed for pain."

We recommend indenting the two lines of dosing recommendations for ease of reading.

- *"This dose can then be adjusted to an acceptable level of analgesia taking into account the pain intensity and side effects experienced by the patient."*

  We recommend using a different term for "side effects," which is not generally used in labeling.

2.3 Conversion from Parenteral Morphine or Other Non-Morphine Opioids (Parenteral to Oral) to Morphine Sulfate

- The title for this subsection does not seem entirely accurate. Should it be (changed text underlined):

  Conversion from Parenteral Morphine or Other Non-Morphine Opioids (Parenteral <u>or</u> Oral) to <u>Oral</u> Morphine Sulfate

- The last subsection discussed conversion from these products to controlled-release oral morphine. It seems unusual to include instructions on how to switch to another product in a label. Should this remain in the label? Wouldn't it be more appropriate in the controlled-release morphine labels? In addition, the section title does not include this topic. Therefore, if these instructions remain in the label, either the title for 2.3 should be revised or this topic should have its own numbered subsection.

2.4 Maintenance of Therapy

- Please consider if this paragraph needs its own subsection or if it would fit better coming at the end of section 2.1.

3 Dosage Forms and Strengths

- The regulations require that this section of the FPI describe the appearance of the product (e.g., tablet color, imprinting, solution color). Please note that this information is also required to appear under How Supplied/Storage and Handling.

- We recommend indenting the two lines in this section that begin with "Morphine Sulfate" for ease of reading.

4 Contraindications

- As noted under Highlights, please consider if the hypersensitivity contraindication should remain in the label. If it does, a second sentence should be added here describing the type and nature of the observed reactions (e.g., "Observed reactions have included...").

- *"Morphine Sulfate is contraindicated in patients with respiratory depression in the absence of resuscitative equipment and in patients with acute or severe bronchial asthma or hypercarbia"*

  We recommend separating these into separate contraindications as was done in Highlights.

5 Warnings and Precautions

- As noted above, please ensure that the warnings/precautions are presented in decreasing order of importance.

5.1 Respiratory Depression

- *"Respiratory depression is the chief hazard of Morphine Sulfate."*

  Is there a better term we can use here for "chief hazard"? "Primary risk" or something similar? "Chief hazard" seem unusual for labeling.

5.4 Head Injury and Increased Intracranial Pressure

- We suggest changing this section title to "Use in Head Injury..." for clarity.

5.5 Hypotensive Effect

- b(4)

5.6 Gastrointestinal Effects

- b(4)

  Because this is the morphine label, we suggest that this sentence read, "Administration of morphine may obscure..."

  Please add an "s" to the end of "condition."

Special Risk Groups

Appears This Way On Original

b(4)

- *"Morphine Sulfate should be administered cautiously and in reduced dosages in patients with severe renal or hepatic insufficiency, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients."*

  In this sentence (and throughout the label), please change "insufficiency" to "impairment," which is the preferred term for labeling.

6 Adverse Reactions

- The [redacted] can be deleted, leaving all the text to appear directly under the main section title.

- *"Other less frequently observed side effects expected from opioid analgesics, including morphine include:"* b(4)

  Please change "side effects" to "adverse reactions."

7 Drug Interactions

- As with "Warnings and Precautions," drug interactions should be presented in decreasing order importance. Please review to ensure proper ordering. If any changes are made here, they must also be made in Highlights and Contents.

7.1 CNS Depressants

- [redacted] b(4)

  Please consider rewording this sentence to clarify if we mean to "use with caution and at reduced doses" for morphine or for the concomitant CNS depressants.

7.4 Cimetidine

- *"Concomitant administration of morphine and cimetidine has been reported to precipitate apnea, confusion, and muscle twitching in an isolate report."*

  Should "isolate" be "isolated" in this sentence?

7.7 P-Glycoprotein (PGP) Inhibitors

- Please delete the colon at the end of the section title.

- *"Based on the literature, it appears that PGP inhibitors such as quinidine increase the absorption/exposure of morphine by about two fold."*

  Please consider revising to, "Based on published reports, PGP inhibitors (e.g., quinidine) may increase the..."

8.1 Pregnancy

- Per SEALD's recent discussions with the Maternal Health Team, they suggest focusing the pregnancy section on the following information:

    - Summary statement of the most clinically relevant bottom line based on the data available.
    - Description of available human data.
    - Brief summary of available animal data described in terms of species exposed, equivalent human doses, and maternal, fetal, and offspring outcomes. If deemed important for labeling, a fuller description of the non-clinical data can be presented in section "13.2 Animal Toxicology and/or Pharmacology" under a subsection entitled, "Reproductive Toxicology Studies."

- Please refer to CFR 201.57(c)(9)(i)(A)(3) for required statements for Category C drugs.

- b(4)

  This sentence should be moved up within the section. As written, it appears to be part of the "Nonteratogenic Effects" section, when it really applies to the entire pregnancy section.

8.3 Nursing Mothers

- Please see the labeling regulations at CFR 201.57(c)(9)(iii) for required language in this section.

Sections 8.7 to

- These sections under "Use in Specific Populations" should summarize the clinically relevant information (e.g., the need for dose adjustments) about use of the drug in these subpopulations. Details of pharmacokinetic studies should be moved to "12.3 Pharmacokinetics." Please consider revising. b(4)

- Please change the title of to "Renal Impairment."

9 Drug Abuse and Dependence

- The PLR regulations require the following subsections in "Drug Abuse and Dependence":

  9.1 Controlled Substance
  9.2 Abuse
  9.3 Dependence

  Please revise this section (and Contents) accordingly.

b(4)

12.1 Mechanism of Action

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b(4)

This paragraph is nearly identical to information that appears in the Overdose section. Please consider the proper placement for this information, perhaps summarizing it in one section and keeping the more detailed discussion in another. We try to avoid using redundant language in labeling as much as possible.

12.2 Pharmacodynamics

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b(4)

We recommend deletion of this sentence. It gives advice on general clinical management, not pharmacodynamic information.

12.3 Pharmacokinetics

- *"Administration of the 30 mg Morphine Sulfate Tablet and 30 mg of Morphine Sulfate Oral Solution Q6H for 5 days resulted in a comparable 24-hour exposure (AUC)."*

  In this sentence under the "Steady-State" subheading, please replace "Q6H" with "every 6 hours." When possible, Latin abbreviations for dosing regimens should not be used in labeling.

•

b(4)

16 How Supplied/Storage and Handling

- *"Morphine Sulfate Oral Solution is a green solution available in two strengths as follows:"*

  This introductory sentence could be somewhat confusing given that three formulations of the solution are listed below. One must read very carefully to recognize that two of the formulations have the same concentration of morphine. Please consider if this section could be presented more clearly.

b(4)

  We recommend deletion of this sentence because it is unnecessary and does not generally appear in labeling.

17 Patient Counseling Information

- We recommend replacing the numbers in this list with bullets

Revision Date

- The revision date appearing at the end of the label should be deleted. The date that appears at the end of Highlights is intended to replace this.

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

/s/

Iris Masucci
3/11/2008 01:58:34 PM
DDMAC REVIEWER

Laurie Burke
3/13/2008 03:56:54 PM
INTERDISCIPLINARY

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:	March 13, 2008
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia, and Rheumatology Products
Thru:	Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Felicia Duffy, RN, BSN, Safety Evaluator Division of Medication Errors and Technical Support
Subject:	Label and Labeling Review for Morphine Sulfate
Drug Name(s):	Morphine Sulfate Tablets Morphine Sulfate Oral Solution
Application Type/Number:	NDA 22-207 NDA 22-195
Submission Number:	N/A
Applicant:	Roxane
OSE RCM #:	2007-1786-1 2007-1808-1

1 INTRODUCTION

This memorandum is in response to the Applicant's February 27, 2008, labeling amendment in response to comments provided in a Discipline Review Letter from the Agency dated February 26, 2008.

2 MATERIAL REVIEWED

Revised container labels and carton labeling submitted on February 27, 2008.

3 RESULTS

Upon reviewing the revised labels and labeling, we note that the Applicant did not remove the [redacted] from the labels and labeling. b(4)

Additionally, the Applicant name and logo still appear prominent on the labels and labeling.

4 DISCUSSION

The Applicant has not revised the labels and labeling as requested in our February 6, 2008, review. The areas not revised are the [redacted] Applicant name and logo. Additionally, there was discussion with the Division about discontinuing availability of the 20 mg/10 mL unit-dose cup. b(4)

[redacted] b(4)

4.2 APPLICANT NAME AND LOGO

We asked the Applicant to decrease the prominence of the Applicant's name and delete the logo on the carton and container labels, since the logo is distracting and the Applicant name appears almost as prominent as the proprietary name. This information is also contained in the [redacted] discussed above, specifically on the unit-dose container labels. The Applicant's response was that they decreased the prominence of the logo and their address, and that other companies include their logo as well. Additionally, the Applicant mentioned that at a minimum the label must include the company address in accordance with 21CFR 201.1. We agree that the address needs to be provided, but we did not request removal of the company name, just the logo. We acknowledge that the Applicant may have decreased the prominence of their name and logo b(4)

on the unit-dose container labels but this revision is negligible because as noted above, the highlights this information giving it greater prominence.

b(4)

4.3 PACKAGE SIZE

The Division of Medication Error Prevention had an internal meeting with the Division of Analgesia, Anesthesia, and Rheumatology Products on February 27, 2008. During the meeting, there was discussion about the necessity of having unit-dose cups of Morphine Sulfate oral solution in two strengths (10 mg/5 mL and 20 mg/10 mL) based on our concerns that the two cups could be confused with one another. The discussion led towards removing the 20 mg/10 mL strength. We concur that not marketing the 20 mg/10 mL unit-dose cup will help avoid confusion with the 20 mg/5 mL strength in bulk bottles and the two unit-dose cups.

5 CONCLUSIONS

Despite the Applicant's rationale

the Division of Medication Error Prevention does not believe that their reasons outweigh the risks of confusion leading to medication error that may occur due to the similarity in appearance of the labels within the Roxane product line. To minimize the potential for errors, and to improve readability, we recommend implementation of the container label and carton labeling revisions outlined below.

b(4)

The Division of Medication Error Prevention would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy our division on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Darrell Jenkins, Project Manager, at 301-796-0558.

6 RECOMMENDATIONS

b(4)

3. Discontinue the availability of the 20 mg/10 mL unit-dose cups for the oral solution.

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/s/

Felicia Duffy
3/13/2008 08:38:55 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/13/2008 10:04:49 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/13/2008 11:00:50 AM
DRUG SAFETY OFFICE REVIEWER

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 6, 2008
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia, and Rheumatology Products
Thru:	Kellie Taylor, PharmD, Team Leader Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Felicia Duffy, RN, BSN, Safety Evaluator Division of Medication Errors and Technical Support
Subject:	Morphine Sulfate Labeling Review
Drug Name(s):	Morphine Sulfate Tablets Morphine Sulfate Oral Solution
Submission Number:	N/A
Application Type/Number:	NDA 22-207 and NDA 22-195
Applicant/Applicant:	Roxane Laboratories
OSE RCM #:	2007-1786 and 2007-1808

CONTENTS

EXECUTIVE SUMMARY

DMETS reviewed the carton and container labels, insert labeling, and postmarketing data for Morphine Sulfate and identified several areas that contribute to medication errors. Medication errors pertinent to the labels and labeling of Morphine Sulfate tablets and oral solution were primarily related to the similar labeling and packaging of these products to others within Roxane's product line.

Product similarities may be improved upon increasing the readability of pertinent information presented on the labels, deleting non-pertinent information, differentiating the strengths, and distinguishing the NDC numbers on the labels and labeling.

We also recommend deleting the modifier [redacted] from the labels and labeling as it is not in compliance with USP, and to educate patients and practitioners of the labeling change. For full recommendations, we refer you to section 5 of this review. b(4)

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products to evaluate the container label, carton and insert labeling for Morphine Sulfate Tablets, Morphine Sulfate [redacted] Tablets, and Morphine Sulfate Oral Solution. b(4)

1.2 REGULATORY HISTORY

These NDAs are for marketed unapproved drugs (Morphine Sulfate Tablets and Morphine Sulfate Oral Solution). These drugs have been marketed with the proposed labeling since the 1987. The Applicant now proposes NDAs for Morphine Sulfate Tablets and Morphine Sulfate Oral Solution.

1.3 PRODUCT INFORMATION

Morphine Sulfate is an opioid analgesic indicated for the relief of moderate to severe acute and chronic pain where use of an opioid analgesic is appropriate. Dosing regimens should be individualized taking into account the patient's prior analgesic treatment experience.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring. For managing chronic pain, Morphine Sulfate is on the third step of the WHO three step analgesic ladder and is of most benefit when a constant level of opioid analgesia is used as a platform from which break-through pain is managed.

The usual adult oral dose in patients without a proven tolerance to opioids is as follows:

Morphine Sulfate Oral Solution: 10 mg to 20 mg every 4 hours or as directed by physician.

Morphine Sulfate Tablets: 15 mg to 30 mg every 4 hours or as directed by a physician.

For opioid naïve patients, the dose should be increased conservatively until achievement of a balance between analgesia and opioid side effects. When the patient no longer requires therapy

with Morphine Sulfate, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Morphine Sulfate is currently supplied as an oral solution in unit dose cups of 10 mg/5 mL and 20 mg/10 mL, and in bulk bottles of 20 mg/5 mL (100 mL and 500 mL bottles). Morphine Sulfate is also is supplied as 15 mg and 30 mg tablets.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMETS medication error staff to conduct a label, labeling, and/or packaging risk assessment for a product that is currently marketed (see 2.1 AERS and DQRS selection of cases and 2.2 Carton and Container Labels). The primary focus of the assessments is to identify and remedy potential sources of medication errors. 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 ADVERSE EVENT REPORTING SYSTEM (AERS) AND DRUG QUALITY REPORTING SYSTEM (DQRS) SELECTION OF CASES

Because Morphine Sulfate has been marketed since 1987, DMETS conducted a search of the Adverse Event Reporting System (AERS) and Drug Quality Reporting System (DQRS) databases to determine if any medication errors are associated with the product packaging and labeling. The MedDRA Higher Level Terms (HLT) "Maladministration", "Medication Errors NEC", "Overdoses", and the Preferred Terms (PT) "Pharmaceutical Product Complaint", and verbatim substance name "Morphine Sulf%", and active ingredient "Morphine Sulfate" were used as search criteria. Since Morphine Sulfate was manufactured by Boehringer Ingelheim and Roxane Laboratories, the following advanced product criteria were also used to narrow the search: Manufacturers name, valid manufacturer "Boehr%" (sender of ISR and reported applicant holder), and "Roxa%" (sender of ISR and reported applicant holder). In addition, DQRS was searched for similar reports with Roxane's Morphine Sulfate (tablets and oral solution).

The cases were manually reviewed to determine if a medication error occurred. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. DMETS reviewed the cases within each category to identify factors that contributed to the medication errors.

2.2 CARTON AND CONTAINER LABELS

For this product, the Applicant submitted on June 7, 2007, the following labels and insert labeling for DMETS review (see Appendices A through F for images):

- Blister Label: 15 mg, 30 mg
- Container Label: 15 mg, 30 mg, 10 mg/5 mL, 20 mg/5 mL, —
- Carton Labelling: 15 mg, 30 mg
- Prescribing Information- package insert (no image)

b(4)

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

Additionally, the Applicant submitted on January 29, 2008, a diagram of the dosing cup (see Appendix G for image).

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) AND DRUG QUALITY REPORTING SYSTEM (DQRS)

The FDA Adverse Event Reporting System (AERS) and the Drug Quality Reporting System (DQRS) was searched on September 25, 2007, for all postmarketing safety reports of medication errors associated with Morphine Sulfate (see Appendix J for a sample representation of narratives).

A total of 64 cases involving Morphine Sulfate were retrieved. After manual review of the cases, 14 cases were determined not to involve a medication error. These cases mainly described adverse events related to the correct use or intentional misuse of Morphine Sulfate (e.g., intentional overdose). Of the 64 medication error cases retrieved with Morphine Sulfate, 34 of these cases were pertinent to the Roxane product line or Roxane's Morphine Sulfate tablets and oral solution. The remainder of the cases involved methadone, Roxane products, or a concentrated morphine sulfate oral solution (Roxanol), which is not the subject of this NDA submission. The following table depicts the types of errors in which the cases were categorized:

Table 1: Morphine Sulfate medication errors categorized by type

Type of Error	# of Cases (n=64)	*Deaths (n=8)
Medication errors pertinent to this review		
Roxane product line errors	13*	1
Immediate-release vs. Extended-release confusion (tablets)	10	
Roxanol concentrate vs. Morphine Sulfate oral solution	4*	1
Oral Solution strength confusion	4	
Wrong Route of Administration	3*	1
Medication errors Not pertinent to this review		
Adverse Events	14	
Roxanol Overdoses (concentrated Morphine Sulfate oral solution)	8*	5
Roxanol and Roxicodone confusion	8	
* Deaths occurred in these categories		

There were a total of 8 deaths associated with Morphine Sulfate. The breakdown of deaths is as follows: Roxanol overdoses (n=5), Roxanol concentrate oral solution vs. Morphine Sulfate immediate-release oral solution confusion ((n=1), Roxane product line error (n=1), and wrong route of administration (n=1). Additional adverse events include prolonged hospitalization.

The contributing factors in some of the reports relevant to this review were indicated in the narratives, or noted in review of the cases. They are described in detail below. As additional information, other results of medication errors not relevant to this review are in Appendix I.

3.1.1 Roxane product line errors (n=13):

These errors include medication errors that occurred within the Roxane product line. Product line errors occurred between the following products marketed by Roxane: Roxanol oral solution vs. Methadone oral solution (n=3), Oramorph SR extended-release tablets vs. Meperidine tablets (n=2), Roxanol oral solution vs. Demerol syrup (n=2), Roxanol oral solution vs. Roxicet oral solution (n=2), Morphine Sulfate tablets vs. Codeine tablets (n=1), Oramorph SR 15 mg tablets vs. Oramorph SR 30 mg tablets (n=1) and Oramorph SR extended-release tablets vs. Roxicet tablets (n=1). There was also an additional case that described concern of a potential error between Roxane's Morphine Sulfate, Codeine, Oxycodone, and Hydromorphone tablets due to the similar labeling and packaging of the products.

The majority of the aforementioned cases indicated the contributing factors as similar packaging and/or labeling, similar tablet appearance, and similar names (Roxicet/Roxanol).

One death did occur in an 8 year old female who was administered Roxanol oral solution instead of Demerol syrup. The cause of the error was not indicated.

Since these errors are not specific to the morphine products for this submission, they will be included in a future postmarketing surveillance review pertaining to Roxane product line errors.

3.1.2 [redacted] vs. Extended-release tablets (n=10):

A total of ten medication errors involved confusion between Roxane's Morphine Sulfate tablets and Morphine Sulfate extended-release tablets (MS Contin and Oramorph SR). The contributing factors of these errors included look-alike packaging, [redacted] b(4)

3.1.3 Roxanol concentrate vs. Morphine Sulfate oral solution (n=4):

There were four cases of confusion with Roxanol concentrate (20 mg/mL) and Morphine Sulfate oral solution (10 mg/5 mL and 20 mg/5 mL). In one case, the data entry technician chose the wrong product (20 mg/mL instead of 20 mg/5 mL) in the computer, and the pharmacist did verify the order with the product prior to dispensing the medication; the outcome of the error was death. The remaining errors were attributed to similar concentrations of Roxanol and Morphine Sulfate oral solution, and the lack of a warning to check the concentration. DMETS reviewed the currently labeling for Roxanol, and it is noted that there is now an alert in red on the Roxanol label stating that it is concentrated and to check the dose carefully.

3.1.4 Oral solution strength confusion (n=4):

The medication errors between Roxane's Morphine Sulfate oral solution 10 mg/5 mL, 20 mg/5 mL, and [redacted] occurred as a result of similar packaging, labeling, and shelf storage proximity. One case also indicated that the error occurred because of a lack knowledge with respect to the fact that Morphine Sulfate oral solution is available in two different strengths. b(4)

3.1.5 Wrong route of administration (n=3):

Two cases pertained to the administration of Morphine Sulfate oral solution via the wrong route: subcutaneously and via central line. No harm was reported in either of these cases. In the third

case, Roxanol oral solution was administered intramuscularly. Although the patient was terminal, the certificate of death did indicate morphine toxicity.

3.2 CARTON AND CONTAINER LABELS

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

3.2.1 Morphine Sulfate Tablets

DMETS notes the blister label, and carton and container labels contain "[redacted] on all of the labels, this is not consistent with USP dosage form nomenclature. b(4)

The product strength is small and difficult to read on the blister label. Additionally, the strengths may be difficult to differentiate as the blister labels are all in black and white for both strengths.

Only the numerical portion of the strength is highlighted and not unit of measure (mg) in conjunction with the product strength on the blister label.

The [redacted] on the blister label is more prominent than the product strength which may cause confusion.

The barcode on the blister label takes up a lot of space at the bottom of the blister, which gives less prominence to the other pertinent information on the label.

The middle portion of the NDC numbers are very similar since they vary by only one digit (-0235- versus -0236-) on the carton and container labels.

The entire proprietary name on the carton and container labels does not appear on the same horizontal plane. The first portion of the name is on one line, and the second portion of the name is on the line below the first.

b(4)

The product strength appears small in comparison to the [redacted] statement on the principle display panel of the carton and container labels.

The Applicant's logo at the bottom of the principle display panel is distracting, and the Applicant's name is almost as prominent as the proprietary name on the carton and container labels.

On the carton labeling, the net quantity statement includes [redacted]. b(4)

3.2.2 Morphine Sulfate Oral Solution

The middle portion of the NDC numbers are very similar since they vary by only one digit (-0235- versus -0236-) on the unit-dose and bulk bottle container labels.

The entire proprietary name on the carton and container labels does not appear on the same horizontal plane. The first portion of the name is on one line, and the second portion of the name is on the line below the first on both unit-dose and bulk bottle container labels.

The Applicant's logo at the bottom of the principle display panel is distracting, and the Applicant's name is almost as prominent as the proprietary name on the carton and container labels.

The product strength on the unit-dose container labels are difficult to differentiate b(4)

The strength is less prominent on the unit-dose label.

The usual adult dose statement on the bulk bottle label is misleading since the dose is individualized. b(4)

3.2.3 Package Insert

The Description section of the insert does not clearly describe the appearance of the morphine sulfate oral solution.

3.3 DOSING CUP

The Applicant provided a diagram of the proposed dosing cup (see Appendix G). The size of the dosing cup is 30 mL with graduation marks at 5 mL, 10 mL, 15 mL, and 20 mL.

4 DISCUSSION

When evaluating the postmarketing cases concerning Morphine Sulfate, a number of medication errors were identified including strength confusion of the oral solution and confusion between extended-release and immediate-release formulation of the tablets. These errors resulted in either an overdose or an underdose.

Our analysis of the medication error cases and the product labeling identified several areas of risk that DMETS believes the Applicant can help to minimize through labeling (see section 4.1).

4.1 CARTON AND CONTAINER LABELS FOR MORPHINE SULFATE TABLETS AND ORAL SOLUTION

In review of the carton and container labels, we identified two areas where improvements could be made for both dosage forms.

DMETS notes the blister label, and carton and container labels contain on all of the labels. This terminology is not a defined dosage form in the USP. We acknowledge that Roxane has marketed the unapproved morphine sulfate tablets on the . However, products do not need to be qualified, and approval of the modifier would not be in accordance with USP standards, and would set negative precedence for the Agency. Furthermore, the modifier which may be confused when scripted. b(4)

We also have concern that when practitioners see products labeled as through confirmation bias, they may make the cognitive connection that the product is . Therefore, by approving the modifier practitioners may inadvertently dispense or administer the product thinking that it is e. Additionally, the inconsistency of labels specifying would create confusion among practitioners and potentially increase the risk of medication errors, since it is not customary for products to be labeled as .

DMETS believes the overall risks associated with the continued use of will outweigh the risk associated with the removal of the modifier. The Applicant will need to alert and educate practitioners about the change to help mitigate the risk since these morphine products have been out for an extended period of time. b(4)

Additionally, the only difference between the NDC's of Roxane's Morphine Sulfate tablets (15 mg tablet and 30 mg) and Morphine Sulfate oral solution (10 mg/5 mL and 20 mg/5 mL) is the third digit in the middle portion of the NDC number. Specifically, Morphine Sulfate tablets 15 mg and Morphine Sulfate 30 mg are only one digit off (-0235- versus -0236-) similar to Morphine Sulfate oral solution 10 mg/5 mL and 20 mg/5 mL (-0237- versus -0238-). The closeness of these numbers may potentially be missed upon verification. Distinction between NDC numbers is another method that may be used to minimize medication errors with Roxane's Morphine Sulfate products. Ideally, we believe that different strength of morphine should have uniquely distinctive NDC numbers between the Morphine Sulfate strengths. However, as this product has been marketed for some time, we acknowledge that the re-assignment of new, more unique NDC numbers would be problematic and could interfere with barcoding systems that rely on these codes. However, to improve the readability of the NDC numbers, the middle portion of the NDC numbers should be presented in tall man format and bolded in order to increase its prominence (e.g, 0054- **0235**- 25).

4.1.1 Morphine Sulfate Tablets

When evaluating the labels and labeling of the tablet dosage form, we noticed several areas that make the labels vulnerable to error. The first area of concern noted was the presentation of the product strength. The product strength on the blister label is small and difficult to read. The strengths may be difficult to because the entire blister card for both strengths are in black and white (see Appendix A). Additionally, only the numerical portion of the strength is highlighted without the unit of measure in conjunction with the product strength (e.g., **15** mg rather than **15 mg**) which is visually distracting. Furthermore, the barcode takes up a lot of space at the bottom of the blister, which increases crowding of the remaining information on the blister label. It is important that patients and practitioners are able to clearly differentiate between the product strength, especially due to the potentially harmful effects of this narcotic. Highlighting both the numeral and the unit of measure of the product strength will help to improve the readability of the strength. Improvement can be made to the layout and presentation to help improve overall readability and decrease risk of medication errors (see section 5). Relocating the barcode from the bottom to the side of the blister will allow more space on the blister to increase the prominence of the product strength. In addition to increasing the product strength, differentiating the strengths by using the same colors used on the container labels may be helpful in minimizing medication errors between the two strengths.

The second area of concern is the . used on the blister label. The on the blister label is more prominent that the product strength. Using may cause confusion especially when the overlaps with an actual product strength. The Institute for Safe Medication Practices (ISMP) reported that a nurse mistakenly identified a 10 mg tablet as a 20 mg tablet when using a product by Roxane that came in a unit-dose package that uses a (see Appendix H for article). We find this not very useful since the unit-dose tablets are not always removed in sequence, and it is potentially dangerous if the strength is confused with the . This will likely happen with 30 mg unit-dose tablet at . where the 30 mg tablet may be confused as a 15 mg tablet which would result in an overdose. b(4)

The third area of concern is the layout and placement of the proprietary name. On the container labels and carton labeling of the tablets, the proprietary name (Morphine Sulfate) is difficult to read because it is not presented in its entirety on the same horizontal plane. The first half of the

[2] ISMP-Acute Care Medication Safety Alert, Volume 13, Issue 2, January 31, 2008

name appears on the first line, and the second of the name appears on the next line. Dividing the proprietary name decreases its readability and may increase its potential for confusion with other proprietary names (see Appendices B and C).

b(4)

On the carton labeling and container labels, the Applicant's logo at the bottom of the principle display panel is distracting and appears almost as prominent as the proprietary name. The most prominent information on the principle display panel should be the proprietary name, established name, and product strength. The Applicant name and logo are not essential in dispensing and/or administering the drug product.

4.1.2 Morphine Sulfate Oral Solution

Similar to the Morphine Sulfate tablets, the proprietary name (Morphine Sulfate) is difficult to read on the container labels of the oral solution because it is not presented in its entirety on the same horizontal plane. The first half of the name appears on the first line, and the second of the name appears on the next line. Dividing the proprietary name decreases its readability and may increase its potential for confusion with other proprietary names.

Additionally, the product strength on the unit-dose container labels are difficult to differentiate . Despite the fact that the mg/mL concentration is the same, the strengths should still be adequately differentiated from one another. This may minimize the risk of selection errors.

b(4)

4.1.3 Package Insert

The Description section of the package insert does not clearly describe that the color of the 10 mg/5 mL and 20 mg/5 mL are blue-green. This may be helpful in differentiating the product from concentrated Morphine Sulfate oral solution (20 mg/mL) which is clear.

4.1.4 Dosing Cup

DMETS is unable to ascertain if increment markings or print on the cup is clear or in ink. Post-marketing experience has indicated that it is difficult to read clear lettering or markings on a clear cup. Ink on clear cups provides for improved readability. This is especially important when working with narcotics which can be harmful if dosed incorrectly.

The Applicant indicates that the dosing cup will be included in the carton packaging for the 100 mL and 500 mL bulk bottles, which will be available in concentrations of 10 mg/5 mL and 20 mg/5 mL. The total volume of the dosing cup is 30 mL. Therefore, if the dosing cup if filled to the top (30 mL), a patient may potentially received a 120 mg dose from the 20 mg/5 mL bottle. This dose may be fatal. Although the package insert indicates that dosing may be individualized, the usual adult dose in patients without proven tolerance is 10 mg to 20 mg (5 mL ———) every 4 hours of Morphine Sulfate oral solution. This dosing cup configuration is inconsistent with the recommended dosing. The excess total volume of this dosing cup increases the risk of overdoses with Morphine Sulfate, especially if the cup is difficult to read. A dosing cup with a smaller volume that is more consistent with the recommended dosing may decrease the risk of overdose with these opioid solutions. b(4)

5 CONCLUSIONS AND RECOMMENDATIONS

DMETS recommends the label and labeling recommendations outlined below be implemented to improve differentiation between the two strengths, and to increase the prominence of pertinent information on the container labels and carton labeling of both Morphine Sulfate tablets and oral solution.

We acknowledge that Roxane has marketed the unapproved morphine sulfate tablets ——— . However, ——— products do not need to be qualified, and approval of the modifier ——— would be not be in accordance with USP standards, and would set negative precedence for the Agency. Furthermore, the modifier ——— may be confused as when scripted. DMETS believes the overall risks associated with the continued use of " ——— " will outweigh the risk associated with the removal of the modifier. The Applicant will need to alert and educate practitioners about the change to help mitigate the risk since these morphine products have been out for an extended period of time. b(4)

5.1 COMMENTS TO THE DIVISION

DMETS would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed.

Based upon our assessment of the labels and labeling, and the review of postmarketing medication error reports, DMETS has identified areas needed of improvement. We have provided recommendations in section 5.2 and request this information be forwarded to the Applicant.

Please copy DMETS on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Darrell Jenkins, Project Manager, at 301-796-0558.

5.2 COMMENTS TO THE APPLICANT

5.2.1 General Comment for Tablets and Oral Solution

Delete from the labels and labeling. It is not approved USP nomenclature for the dosage form. b(4)

5.2.2 Blister Label: Morphine Sulfate Tablets

1. Increase the prominence of the product strength. If possible further differentiate the strengths by using the same colors used on the container labels.
2. When highlighting the strength (15 mg and 30 mg), include the unit of measure (mg), not just the numerical portion of the strength (15 and 30) in the box or color block.
3. Delete the on each blister. It is more prominent than the strength thus your eye is drawn to this initially. This may cause confusion with the strength.

Delete b(4)

4. Relocate the barcode to the side of the blister to allow more space to increase the prominence of the product strength.

5.2.3 Container Label and Carton Labeling: Morphine Sulfate Tablets

1. Use tall man format for the middle portion of the NDC number (e.g., 0054-**0235**-25).
2. Relocate "Sulfate" juxtapose to Morphine so the proprietary name is on the same line (e.g., Morphine Sulfate).
3. b(4)
4. Increase the prominence of the product strength.
5. Delete the Applicant's logo. If this is not achieved then at a minimum, decrease the prominence of the Applicant name (Roxane Laboratories) and logo.
6. On the carton, revise the net quantity statement as: 4 cards x 25 tablets each.

5.2.4 Unit-Dose Container label: Morphine Sulfate Oral Solution

1. Use tall man format for the middle portion of the NDC number (e.g., 0054-**0235**-25).
2. Relocate "Sulfate" juxtapose to Morphine so the proprietary name is on the same line (e.g., Morphine Sulfate).
3. Increase the prominence of the product strength.
4. Differentiate the strengths (10 mg/5 mL) by using contrasting colors, boxing or some other means. The entire strength (including the unit of measure) should b(4)

be highlighted if such measures are employed. If contrasting color is use, use another color other than blue in order to avoid confusion with the 20 mg/5 mL strength.

5. b(4)

6. Delete the Applicant's logo. If this is not achieved then at a minimum, decrease the prominence of the Applicant name (Roxane Laboratories) and logo.

5.2.5 Container Label: Morphine Sulfate Oral Solution 100 mL and 500 mL Bulk Bottles

1. Use tall man format for the middle portion of the NDC number (e.g., 0054-**0235**-25).
2. Relocate "Sulfate" juxtapose to Morphine so the proprietary name is on the same line (e.g., Morphine Sulfate).
3.
4. Delete the usual adult dose statement since the dose is individualized. b(4)
5. Delete the ——— that appears beneath the product strength.
6. Increase the prominence of the product strength.
7. Delete the Applicant's logo. If this is not achieved then at a minimum, decrease the prominence of the Applicant name (Roxane Laboratories) and logo.

5.2.6 Package Insert

In Description section of the package insert, in addition to the ingredients listed, DMETS recommends clearly describing the appearance of the morphine sulfate oral solution.

5.2.7 Dosing Cup

1. Decrease the total volume of the dosing cup to more appropriately reflect the recommended dosing.
2. Ensure the markings and print on the dosing cup is in ink for improved readability.

8 Page(s) Withheld

_____ Trade Secret / Confidential

2 Draft Labeling b(4)

_____ Deliberative Process

Withheld Track Number: Proprietary Name Review____

Appendix I: Results of medication errors with Morphine Sulfate not specifically related to this submission

Roxanol overdoses (n=8):

Roxanol is concentrated Morphine Sulfate oral solution (20 mg/mL). Reporters described errors with Roxanol as a result of incorrect directions for use on the label, the bottle was labeling incorrectly, bottle size not is consistent with dose, inadvertent overdose, and misread dropper and difficult to read marking on bottle (packaging design error). Out of the eight overdoses, five errors resulted in death.

Roxanol and Roxicodone confusion (n=8):

Errors between Roxanol and Roxicodone have been attributed to similar packaging, bottle size, identical strengths, similar names, and proximity on pharmacy shelves. No adverse events were reported between these two products.

Appendix J: Morphine Sulfate Medication Errors

Source/ISR/ DQRS/USP #	FDA Receipt Date	Age/ Sex	Type of Error	Outcome/ Description	Narrative Excerpt
Roxane Product Line Errors					
FDA control # 1522654	9/26/1994	8 y.o. F	Wrong Drug	Death	Pt underwent T&A removal on Prescribed Demerol and antibiotic. Pharmacist substituted Roxanol for Demerol. Initially 1 tsp given to child (complained of bad taste). On her father mixed 2 tsp Roxanol in soda; it was consumed throughout that day. Child found dead in bed in the am of
ISR 4207350-2	10/08/2003	unknown	Wrong Drug	Not reported	Dispensed Roxanol instead of Demerol liquid as prescribed.
ISR 3519543-8	06/19/2000	unknown	Wrong Drug	No sequelae	Responding to an order for Methadone intensol , the pharmacist mistakenly dispensed Roxanol Concentrated Solution (morphine sulfate) Roxanol 2 was subsequently administered by nursing personnel to 2-3 patients before the error was discovered by nursing personnel. There was no patient sequelae.
ISR 3498706-4	05/11/2000	unknown	Wrong Drug	No adverse events	Administration of Roxanol instead of Methadone. No adverse effect, however, analysis revealed product package and labeling similar.
ISR 4164278-4	08/07/2003	N/A	Wrong Drug	No adverse events	Packaging and appearance of methadone 10 mg tab & morphine sulfate 30 mg tab is very similar and are kept typically close together. This has potential for fatal medication error (dispense morphine when Rx is for methadone). Methadone pt. typically take up to 7 tabs qid here (ie, 210 mg immediate release morphine if erroneously substituted).
ISR 5391345-X	07/17/2007	48 y.o. F	Wrong Drug	Hospitalization	Pharmacist dispensed Morphine30 mg instead of Codeine 30 mg. To complete a prescription pharmacist took bottle from stock and misread label Root Cause Analysis: A prescription was initially filled for 80 tablets of Codeine Sulfate 30 mg on or about with 100 tablets to be filled later. The balance to be picked up when reordered for stock. This initial filling was verified through our automated counting machine. The second portion or owed balance of the prescription was filled incorrectly. There is no evidence to support that any technicians were involved, although Pharmacist on duty usually works with one technician. The new stock bottle of Codeine Sulfate 30 mg tablets (Roxane brand) was placed on the shelf directly next to the bottle of Morphine Sulfate 30 mg tablets (Roxane brand). The two bottles look identical having the same size, same color and same label color. The Morphine was inadvertently taken from the shelf and was used to fill the 100 tablet balance of the codeine prescription. This part of the prescription was never verified by the verification and counting unit. It was signed off as prescription complete by the pharmacist on duty and picked up on by the visiting nurse. Patient was admitted to hospital on Patient was admitted again to the hospital on and was discharged on The incident was reported to Pharmacy Manager on by the visiting nurse. Primary diagnosis of patient was Morphine overdose, secondary HTN, bipolar disorder and asthma. Internal Analysis: The pharmacy was adequately staff on There were 2 pharmacy technicians actively working in the pharmacy area and 2 other

b(6)

b(6)

					technicians in the pharmacy in addition to pharmacist. The nurse working for a local agency that has multiple patients as our customers came in to collect the balance of medication from a previously partially filled prescription. It appears that the pharmacist on duty in an effort to provide faster service to the nurse did not follow established procedures. There is no evidence that a technician working in the area was involved in completion of the prescription. No technician has any knowledge of the incident, of working with the nurse in question or of the patient on that day. The pharmacist has no memory of this particular event, however only his initials are on the completed pick up slip. There is no record of the prescription being counted or verified in the counting/verification unit. Bypassing the procedures meant that 1 person took the medication off the shelf, transferred the medications to a pharmacy bottle, labeled the bottle, put it in a bag and gave it to the nurse. Patient was hospitalized. The new stock bottle of Codeine Sulfate 30 mg tablets (Roxane brand) was placed on the shelf directly next to the bottle of Morphine Sulfate 30 mg tablets (also Roxane brand). The two bottles look identical having the same size, same color and same label color. The Morphine was inadvertently taken from the shelf and was used to fill the 100 tablet balance of the Codeine prescription.
ISR 4117210-3	05/22/2003	90 y.o. F	Wrong Drug	Nausea, vomiting, decreased respiratory rate	This 90yo female patient was admitted with intractable pain and cervical disc disease. She had been receiving Demerol 15-20mg IV on a q2h prn schedule. This order was changed to 100mg orally q4h prn. When a dose of pain medication was requested, 2 tablets of MS Contin 100mg were administered rather than 2 tablets of Demerol 50mg. The patient developed nausea with vomiting. Over the next few hours the respiratory rate decreased from 20 to 16, the blood pressure increased to 220/60, and the patient experienced some precordial chest discomfort.
ISR 3779857-3	08/20/2001	unknown	Wrong Drug	No adverse events	The reporter needed to report an error that was made at our hospital partly due to similar packaging. They were both Roxane unit dose CII medications. An Oramorph 15mg tablet was given for a Meperidine 50mg tablet.
ISR 4623591-4	03/30/2005	unknown	Wrong Drug	Not reported	The packaging of Oramorph SR and Roxicet is so similar that medication errors have occurred. The medications are packaged in five, 5 by 5 strips covered with a brown wrap with a white design. Also, both tablets are white and round and look similar.
ISR 4097999-2	04/25/2003	unknown	Wrong Drug	Hospitalization	Pharmacist dispensed Roxanol Solution on a prescription written for Roxicet Solution. The incorrect medication was administered to the patient which resulted in the hospitalization of the patient. Pharmacist states that at the time of the incident it was the practice of the pharmacists at this facility to review the patient's profile prior to dispensing medications. He explained that the prescription volume made it impossible to review patient profiles " in the traditional fashion". The volume also made it difficult to provide quality patient care. This was a mail order pharmacy which was described by the pharmacist as a "volume-driven business. "
ISR 4568954-0	01/31/2005	24 y.o. M	Wrong Drug	Sedation	Physician ordered Roxicet liquid 1-2 tsp q 4 h prn pain. (Roxicet = Oxycodone and acetaminophen). At 6 am nurse picked up Roxanol liquid (morphine sulfate 20 mg/mL) from pharmacy. Patient given 10 mL of Roxanol 200 mg morphine).
ISR 4657679-9	05/21/1995	unknown	Wrong Drug	No adverse events	Our nursing department reviewed medication errors over the last two years. Concluded errors made with Roxane products because the tablets and packaging all look the same. Four drugs specifically mentioned: (1) Morphine 15 mg} oral tablets (2) Codeine 300 mg } oral tablets

b(4)

					(3) Oxycodone 5 mg } oral tablets (4) Hydromophone 4 mg } oral tablets NDC 0054-4394 I am passing this on as information to FDA and to manufacturer. No adverse event have been reported as a result , but errors have occurred.
ISR 3563833-X	08/17/2000	unknown	Wrong Drug	Not reported	The patient was given 30mg Oramorph not 15mg Oramorph.
vs. Extended-release Confusion (Tablets)					
ISR 3507518-4	06/05/2000	Unknown	Wrong Drug	Not reported	The controlled medication is available on the nursing unit as Floor stock. The patient was on both morphine and morphine (for break-through pain). The pharmacy ordered both products from Roxane labs. The look-a-like packaging cause the patient to receive the wrong morphine product more than once.
ISR 4072063-7	03/12/2003	74 y.o. F	Wrong Drug	No adverse events	Because of the shortage of MS Contin (lavender color), our pharmacy ordered morphine 30 mg from Roxane (white tablet) (NDC# 0054858J24). the wholesaler sent the pharmacy morphine 30mg NDC#00054858324. Unfortunately, the pharmacist who accepted the medication upon arrival to the pharmacy did not notice the mistake. For 3 weeks the error went unnoticed by the other dispensing pharmacists and nurses administering the morphine. Six patients were affected. Once the mistake was noticed charts of patients affected were reviewed and no adverse events were noticed or documented in the chart.
ISR 4806793-3	10/21/2005	unknown	Wrong Drug	No adverse events	We have a medication error which has packaging issues. I ordered morphine 30 mg RNP from our wholesaler. We were sent morphine 30 mg RNP from the wholesaler, manufacturer Roxane. Pharmacy did not notice the error and dispensed to nursing narcotic drawer. A patient received 9 tablets out of 10 sent. The error was discovered when a different pharmacist was asked to bring more, and he noticed ' on the outside of the package. The problem is the unit dose packaging does not indicate only the outside of the package. It does have an NDC number, but nursing has no way of verifying the product Part of the error was that we do not stock product, only , so neither pharmacy nor nursing staff had any reason to question, we saw 30 mg and assumed Note that the patient , who received 2 tabs per dose, order was MS Contin 60 mg po bid, did not suffer any harm. She did not c/o pain early, was not overly sedated, there was no indication that she got anything but . Packaging does not indicate
ISR 4623531-8	06/06/1996	47 y.o. F	Wrong Drug	Naloxone required later in the day	Nurse meant to give patient Morphine sulfate table 30 mg for pain, but gave the product by mistake. The packaging is very similar. Naloxone required later in the day.
ISR 4181165-6	09/04/2003	N/A	Wrong Drug	Not reported	Labeling and packaging of the and morphine are similar enough to cause the products to be mistaken for each other- especially in facilities where physician orders, formularies, etc. are written generically- not by brand names.
ISR 4889417-9	01/20/2006	N/A	Wrong Drug	No adverse events	Confusion regarding the labeling of morphine 15 mg tablets. The brand name for morphine is The brand name is very well marked. However, the generic version, available from the hospital pharmacy, is only labeled as morphine 15 mg by Roxane NDC # 00054-8582-24. This caused confusion during the nursing night shift. This product was in a bag labeled from the pharmacy as

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					Pharmacy verified that the medication was correct the next morning. Better labeling would remedy this situation.
ISR 4695530-1	06/05/2005	N/A	Wrong Drug	No adverse events	Roxane's Morphine 15 mg tablets -#25- indicate that they are on the outside package but do not state this on the unit dose packages, leading to confusion with other morphine products.
ISR 4111229-4	05/12/2003	56 y.o. M	Wrong Drug	No adverse events	MS CONTIN 15 MG GIVEN INSTEAD OF MORPHINE SULFATE
ISR 5052793-0	07/14/2006	68 y.o. M	Wrong Drug	Not reported	Physician ordered MS Contin 30mg bid. Nurse administered Morphine Sulfate 30mg Tabs x2 doses. e not delineated on individual UD package labeling.
Roxane Concentrate vs. Morphine Sulfate Oral Solution					
ISR 4020194-X	12/06/200	74 y.o. F	Wrong Drug	Death	(1) Received a fax prescription for Roxanol 20mg/5cc "Give 1 cc q 2H prn distress". The Data Entry Technician picked the wrong product from the computer system (Roxanol 20mg/1cc). The online review pharmacist did not catch the error. The label along with the prescription proceeded to the control room. The dispensing pharmacist did not catch the error and the medication was dispensed. The nursing home nurse did not verify her physicians order with the product received and the patient received 8 doses.
ISR 3135359-9	09/28/1998	unknown	Wrong Drug	Pt slept all day	Roxanol 20mg/ml was in a Pyxis as Morphine Elixir 10mg/5ml and morphine and morphine concentrate 20 mg/ml order was for Morphine Elixir 15ml prior to treatment (which was twice daily) Nurse removed and gave 15ml (300mg) of Morphine concentrate instead of liquid for 2 doses. Patient fortunately suffered no permanent disability; only adverse effect was that the patient slept all day.
ISR 3466622-X	03/02/2000	88 y.o. F	Wrong Drug	Death	RESIDENT IN END-STAGE RENAL FAILURE HAD NO EFFECTIVE PAIN MEDS (TYLENOL ONLY) DR CALLED GIVING ORDER FOR ROXANOL. ORDER CALLED INTO PHARMACY TO STAT OVER MEDICATION; PHARM SENT OVER MORPHINE SULFATE 5CC=10MG. (2HRS LATER MED MATH, PERFORMED , 5CC GIVEN AT 830 PM. AT 7AM NURSES COUNTED NARCS AND STATED 5CC ROXANOL GIVEN (125 X DOSE PRESCIBED) WHEN ACTUALLY THIS WAS NOT SO: WOMAN DIED 12 1/2 HRS LATER & RUMORS SPREAD OF NURSE KILL RESI
ISR 4762164-X	09/06/2005	41 y.o. M	Wrong Drug	Possible withdrawal	Because of short staffing this particular day of our cold/flu season, RX was entered, filled and dispensed incorrectly. The more diluted form of morphine was dispensed instead. patient may have experienced withdrawals Prescription entered into the system incorrectly, drugs with similar concentrations, pharmacy too busy
Oral Solution Strength Confusion					
ISR 4453748-7	02/24/1994	N/A	Wrong Drug		PHARMACIST CALLED TO EXPRESS CONCERN OVER THE APPEARANCE OF THESE TWO PRODUCTS. THE SOLUTION IS THE SAME COLOR, THE BOTTLES ARE THE SAME SIZE AND THE LABELING IS THE SAME COLOR AND TYPE. THE ONLY DIFFERENCE IS THE STRENGTH. A MEDICATION ERROR ALMOST OCCURRED BECAUSE OF THIS EXTREME SIMILARITY. THE NDC NUMBER OF THE 10 MG/5ML IS 0054-3785-63 AND THE 20 MG/5 ML IS 0054-3786-63.

b(4)

ISR 4585538-9	01/07/2005	45 y.o. M	Wrong Drug	No adverse events	On Thursday, January 6th at approximately 9:30 Am I received a message from the Outpatient Pharmacy that the narcotic count was off. I went up to the pharmacy to investigate the discrepancy and noticed that the Morphine10mg/5cc was over by 480cc and the Morphine 20mg/5cc was under by 480cc. There was only one prescription filled on [redacted] for Morphine solution and that was for Patient X. The prescription was for Morphine 10mg/5cc #480cc with directions: Take 1 tablespoonful (15ml) by mouth every 2 hours as needed for pain. Since the inventory was incorrect, I came to the conclusion that the wrong strength of Morphine was dispensed to this patient. I immediately called the patient, I spoke to his wife and informed her of this error. She had not yet opened that bottle and did not give any to the patient. Since the patient was on his way to Connecticut, where they live, they were unable to return to the Pharmacy. I instructed her to give her husband 1 and 1/2 teaspoonful instead of 1 tablespoonful. She was aware that the medication came in both strengths and received the 20mg/5cc before. She completely understood that she would have the cut the dose in half for the patient. She was very grateful that I had discovered this error and was able to follow up with the family. I informed her that an incident report would be filled out and I would also report this error to USP-national data bank. I notified the prescribing Physician of the error at 4:10Pm the same day. Contributing Factors: Both bottles are made by Roxane Laboratories and the packaging looks exactly the same. The stock bottle did not follow the Prescription to the checking station. The bottles were placed next to each other on the shelf. Corrective Action: When a pharmacist is checking prescriptions the stock bottle must always follow the prescription to the checking station. The Pharmacist can then compare the stock bottle to the label. The bottles will be separated on the shelves. To distinguish between the 2 bottles, an extra colored label will be placed on the 20mg/5cc to note the strength.
ISR 4517499-2	01/25/1998	unknown	Wrong Drug	Lack of pain relief	Rx written for [redacted] 20 mg/cc. RPh filled Rx with [redacted] 20mg/5cc. Patient's caregiver called pharmacy to complain about lack of pain relief. Patient called to say did not get 'dropper' (had previously had [redacted] 20 mg/cc and had used a dropper).
ISR 5119320-0	10/02/2006	N/A	Wrong Drug	No adverse event	The institution, a hospital, was carrying two concentrations of morphine sulfate oral solution with very similar packaging [redacted] 10 mg/5 ml ,5 ml) both made by the same manufacturer , Roxane (R). Mistakes were made by pharmacists in both dispensing from the narcotic vault and also accepting ordered inventory into the narcoltic vault due to similar appearance. A review of the narcotic inventory revealed a discrepancy in the 10 mg/5ml. 5ml strength. On review it was discovered that [redacted] type was "checked -in" into the narcotic inventory by mistake. Once the mistake was discovered, it was identified as a potential error and it was decided that the institution would only carry the 10 mg /5 ml , 5 ml formulation and to no longer order the [redacted] type. Mistakes were made by pharmacists in both dispensing from the narcotic vault and also accepting ordered inventory into the narcotic vault due to similar appearance. A review of the narcotic inventory revealed a discrepancy in the 10 mg/5ml, 5 ml strength. On review it was discovered that [redacted] type was "checked-in" into the narcotic inventory by mistake. The institution, a hospital, was carrying two concentrations of morphine sulfate oral solution with very similar packaging [redacted] and 10 mg/5ml) both made by the same manufacturer, Roxane (R).

b(6)

b(4)

b(4)

Wrong Route of Administration					
ISR 3109227-2	07/28/1998	92 y.o. M	Wrong Route of Administration	Death	Patient was to receive 4 mg Roxanol oral, nurse gave the patient 2 mL IM (40 mg, 10-fold overdose via the intramuscular route). Patient was expected to die before being administered the Roxanol and the family had been called. The Certificate of Death listed the immediate cause of death as Alzheimer's Disease, organic brain syndrome, respiratory and renal failure, and morphine intoxication.
ISR 3507439-7	06/01/2000	44 y.o. F	Wrong Route of Administration	No adverse events	PT was in IMCU; Pt had chest tubes; + MD was then to remove C.T. He gave order for M.S. 6mg IV NOW Nurse (RN) went into pyxis, + withdrew container of Morphine Sulfate for ORAL use; Drew it up after opening foil lid container, Diluted w/ NS + injected into central line. Error discussed immediately, Pt. observed closely, pt remained ok. Rx. notified who contacted company- Roxane.
ISR 3179787-4	01/12/1999	unknown	Wrong Route of Administration	Redness at injection site	Medication order for morphine 4 mg subcutaneously every 2 hours as needed. LPN retrieved oral morphine solution (10mg/5 ml) from narcotic cabinet. Drew up 4 mg(2ml) into syringe with needle. Administered the oral solution subcutaneously.

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

/s/

Felicia Duffy
2/6/2008 04:19:05 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
2/6/2008 05:16:47 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/6/2008 05:19:54 PM
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REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Division of Anesthesia, Analgesia and Rheumatology Products

Application Number: Original NDAs 22-195 and 22-207

Name of Drug: Morphine sulfate oral solution (10 mg/5 mL and 20 mg/5 mL) and tablets (15 gm and 30 mg)

Sponsor: Roxane Laboratories

Material Reviewed:

Submission Date(s): NDA 22-195: June 8, 2007 (BL)
NDA 22-207: July 27, 2007

Receipt Date(s): NDA 22-195: June 11, 2007 (BL)
NDA 22-207: July 30, 2007

Submission Date of Structure Product Labeling (SPL): June 8, 2007 (NDA 22-195) and July 27, 2007 (NDA 22-207)

Type of Labeling Reviewed: Labeling submitted in WORD and SPL; WORD version reviewed.

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the firm's proposed labeling.

Highlights

- The highlights limitation statement must read as follows: **These highlights do not**

include all of the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. The word "use" is missing from the latest version.

- The "Initial U.S. Approval" date should list the year in which FDA initially approved the new molecular entity of morphine, the active ingredient in this product. For new formulations, the original date of approval of the active ingredient is used, even if the labeling does not refer to older formulations. Therefore, 2007 is not correct for the initial US approval of morphine. The firm should revise this date accordingly.

- Under Indications and Usage, if the drug is a member of an established class, the concise statement under this heading must identify the class as follows: "(Drug) is a (name of class) indicated for (indications(s))." In this case, the statement should read, "Morphine Sulfate is an opioid analgesic indicated for the relief of moderate to severe acute and chronic pain."

- Under Dosage and Administration, the referenced sections are incorrect for the statement, "Caution in patients with hepatic failure and renal insufficiency." The referenced sections should read: b(4)

- In the Contraindications section, only known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug) should be listed. If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction. You may wish to consider removing the statement, "Morphine Sulfate is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product."

- The Adverse Reactions section does not include the incidence rate (21 CFR 201.57(a)(11).

- In The Adverse Reactions section, the company has referenced a general link to a company website. A general website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It will not provide a structured format for reporting [See 21 CFR 201.57 (1)(11)].

- In The Use in Specific Populations section, the referenced sections in the FPI are incorrect.

- The revision date will be edited to the month/year of application approval. In the mean time, it should be left blank.

- A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]. There is no line separating the Contents from the FPI.

Contents

- Pregnancy and Labor and Delivery should be in section 8 (Use in Specific Populations), rather than section 13 (Nonclinical Toxicology).

Full Prescribing Information

- In the Contraindications section, only known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug) should be listed. If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction. You may wish to consider removing the statement, "Morphine Sulfate is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product."

- There is an Adverse Events subheading under Adverse Reactions. It is not recommended that adverse reactions be referred to as adverse events.

- Cross referencing throughout the label contains both the section and the subsection headings. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]*. In addition, the cross references are in capital letters. Capital letters or bolded print should not be used.

Recommendations

A letter conveying the above deficiencies and asking that the firm please address the identified deficiencies/issues by re-submitting revised labeling should be issued. Following the first team labeling meeting, it was determined that it would be appropriate for the applicant to combine the package inserts for the two formulations of morphine sulfate into one. This will be conveyed in the letter, as well. This updated version of labeling will be used for further labeling discussions.

Reviewed by: Lisa Basham, Regulatory Project Manager

Supervisory Comment/Concurrence: Parinda Jani, Chief, Project Management Staff

Drafted: LB 11/8/07
Revised/Initialed: PJ 11-21-07
Finalized: LB 12-5-07
CSO LABELING REVIEW OF PLR FORMAT

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

/s/

Lisa Basham
12/5/2007 01:45:19 PM
CSO

Parinda Jani
12/5/2007 02:24:14 PM
CSO