

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201517Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 201517	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A		
Established/Proper Name: Morphine Sulfate Oral Solution		
Dosage Form: Oral Solution		
Strengths: 20 mg/mL		
Applicant: Lannett Holdings, Inc.		
Date of Receipt: December 23, 2010		
PDUFA Goal Date: June 23, 2011		Action Goal Date (if different):
Proposed indication(s)/Proposed change(s): The relief of moderate to severe acute and chronic pain in opioid-tolerant patients		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Morphine Sulfate Oral Solution, 20 mg/mL, Roxane Laboratories, Inc., NDA 22195 (also S-002)	Pharmacology, toxicology and human clinical trial data (human clinical efficacy and safety other than bioavailability)

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The Sponsor conducted a Bioavailability/Bioequivalence study on morphine 20 mg/mL oral solution.

Study No. MRN-P9-644: Single Dose Crossover Comparative Bioavailability Study of Two Oral Solutions of Morphine 20 mg / mL vs 20 mg / 5 mL In Healthy Male and Female Volunteers Following the Administration of a 20 mg Dose / Fasting and Fed States

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Morphine Sulfate Oral Solution	NDA 22195	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

Morphine Sulfate Oral Solution, NDA 22195

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

When the Sponsor met with the Agency in July 2009, the filing of this NDA application was considered for a different strength of morphine sulfate solution (20 mg/mL); at that time the Agency agreed with the Sponsor's use of the approved 4 mg/mL (20 mg/5 mL) morphine sulfate solution as a reference for a 505(b)(2) application. (NDA 22-195 approved in March 2008). However, between the time of that meeting and the time the sponsor submitted this application (between July 2009 and March 2010), the Agency approved a 20 mg/mL morphine sulfate solution (supplement to NDA 22-195 approved in January 2010), and this product was used as a component in the bridging BA study.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including*

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): morphine sulfate solution 20 mg/mL

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If **“YES”** and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If **“NO”** or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): morphine sulfate solutions 20 mg/5 mL and 20 mg/mL. ER capsules, tablets, ER tablets + generics, injectables + generics are also pharmaceutical alternatives to the proposed product.

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If **“NO”**, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

DIANA L WALKER
06/23/2011

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

PATIENT LABELING REVIEW

Date: April 28, 2011

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Addiction Products
(DAAAP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide, and
Patient Instructions for Use)

Drug Name (established name): Morphine Sulfate Oral Solution (20mg/ml)

Application Type/Number: NDA 201517

Therapeutic Class: Opioid Analgesic
(optional)

Applicant: Lannett Holdings, Inc.

OSE RCM #: 2010-653

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU)

2 BACKGROUND

On February 26, 2010, Lannett Holdings, Inc. submitted a New Drug Application (NDA) for Morphine Sulfate Oral Solution (20 mg/mL). Morphine Sulfate Oral Solution (20 mg/mL) is a highly concentrated formulation indicated for the relief of moderate to severe acute and chronic pain in opioid tolerant patients. Morphine Sulfate Oral Solution is available in 10 mg per 5 mL, 20 mg per 5 mL and 20 mg per mL concentrations, however only the 20 mg/mL concentration is indicated for opioid tolerant patients. Lannett has only submitted an NDA for the 20 mg per mL concentration.

On November 1, 2010 DRISK submitted a review of the Medication Guide for Morphine Oral Solution (20 mg/ml). On December 10, 2010 the Agency issued a Complete Response Letter to Lannett Holdings. On December 23, 2010 Lannett Holdings submitted a Class 2 Resubmission. This review is a focused review and only highlights the revisions that DRISK recommended in our review dated November 1, 2010.

3 MATERIAL REVIEWED

- Draft Morphine Sulfate Oral Solution (20mg/ml) Medication Guide (MG), and Patient Instruction for Use (IFU) received on December 23, 2010 and sent to DRISK on April 12, 2011.
- Draft Morphine Sulfate Oral Solution (20mg/ml) prescribing information (PI) received December 23, 2010 and sent to DRISK on April 12, 2011.

4 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- completed a focused review based on DRISK's review submitted on November 1, 2010
- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

5 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG and IFU are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

22 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

STEVE L MORIN
04/28/2011

LASHAWN M GRIFFITHS
04/29/2011



**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: April 1, 2011

To: Bob Rappaport, Director
Division of Anesthesia and Analgesia Products

Through: Melina Griffis, R.Ph., Team Leader
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

From: Anne Tobenkin, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Morphine Sulfate Oral Solution

Application Type/Number: NDA 201517

Applicant/sponsor: Lannett Pharmaceuticals

OSE RCM #: 2011-1139

EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Lannett Pharmaceutical's Morphine Sulfate Oral Solution (NDA 201517) on October 20, 2010 in which we made recommendations regarding the proposed container labels and carton labeling (See Appendices B and C). In the submission dated December 21, 2010, the Applicant submitted their revised labels and labeling addressing DMEPA's requested changes. Additionally, DMEPA conducted an AERS search of the currently approved Oral Morphine Solution (Roxane, NDA 022195) labels and labeling in order to determine if confusion during the drug use process has resulted in medication errors.

After comparing the recommendations in OSE review # 2010-656, dated October 20, 2010, to the revised labels and labeling and analysis of the AERS case identified in the AERS search, DMEPA has two additional recommendation to the Applicant; to specify that the product is to be dispensed with the 'enclosed', calibrated syringe and to include, if space permits, a 'for oral use only' statement on the calibrated syringe.

1 MATERIALS REVIEWED

The FDA Adverse Event Reporting System (AERS) database search conducted on March 9, 2011 used the following search criteria for reactions: Reaction terms; High Level Group Term (HLGT) "Medication Errors", the High Level Term (HLT) "Product Label Issues" and the Preferred Term (PT) "Product Quality Issues". The search criteria used for Products was verbatim substance search "Morphine Sulfate 20mg/mL%". Date limitations were set based upon the most recent AERS search which focused on the revised labels for concentrated Morphine Sulfate Oral Solution which occurred September 2010. A manufacturer limitation was also set based upon the revised labels which only pertain to Roxane laboratories. This limitation was set because DMEPA provided the label and labeling recommendations for Roxane labels and will also recommend the similar label and labeling revisions for this NDA. This search was narrowed in order to detect any new problems related to the revised labels and labeling so that they can be corrected for this product's labels.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors related to accidental exposures, intentional overdoses, etc.) were excluded from further analysis.

DMEPA also reviewed our recommendations regarding the Morphine Oral Solution labels and labeling evaluated in OSE review # 2010-656 dated October 20, 2010.

2 RESULTS

The following sections summarize our evaluation of the relevant AERS case and container label and carton labeling analysis for Morphine Oral Solution, 100 mg/5 mL (20 mg/mL).

2.1 AERS

A total of six reports were retrieved in the AERS search (See Appendix A), however after excluding cases as described in Section 1, only one case involved a wrong route medication error in which a patient was administered the oral concentrated solution via the subcutaneous route into the deltoid muscle by a family member. It was reported that the patient normally received the same dose via the oral route however she was having difficulty taking the oral dose and therefore it was administered subcutaneously. The case did not provide further information regarding the error or what syringe was used to inject the Morphine oral solution subcutaneously.

2.2 LABEL AND LABELING

Analysis of the labels and labeling in conjunction with the previous DMEPA Morphine label and labeling review (OSE Review # 2010-656) determined that all recommendations have been adequately implemented. However, due to the postmarketing wrong route error, we evaluated the Roxane Morphine Oral Solution container label. We found it does not display the statement 'For Oral Use Only', however the Lannett Morphine Oral Solution container labels and labeling communicate that the medication is for oral administration by including the route of administration in the name, 'Morphine Sulfate Oral Solution' on the principal display panel, in addition to a message on the 'Pharmacist/Nurse/Patient: For Oral Use Only' on the side panel (or flag label). Therefore, DMEPA has no further recommendations concerning this error and Lannett's labels and labeling. However, DMEPA recommends that an additional statement on the actual syringe, 'for oral use only' be included to warn patients the syringe is for oral administration only.

Additionally, the ONDQA reviewer, notified DMEPA that two statements (b) (4) on the container label and carton labeling required further investigation to determine their validity. The ONDQA reviewer disagreed with the statements because; (b) (4)

We concur with ONDQA in that the Applicant must provide data to support these statements and defer to ONDQA expertise for analysis of the submitted data. Additionally, reference to the calibrated syringe should state, 'Dispense only with the enclosed calibrated syringe', (b) (4) so that the dispensing pharmacist is aware that there is a specific syringe that should be used, (b) (4)

3 CONCLUSIONS

After our AERS analysis and comparing the recommendations in OSE review # 2009-556 to the revised labels and labeling provided by the Applicant, DMEPA has two additional

comments. We recommend that the Applicant include a statement on the oral syringe which reads, 'for oral use only' and to revise the syringe statement presented in conjunction with the storage statement, (b) (4) to specify the syringe that is enclosed with the product. Additionally, we defer to ONDQA regarding their concerns with the following statements (b) (4) and (b) (4) and concur that the Applicant should submit data to support these statements.

If you have further questions, or need clarification please contact, Danyal Chaudhry, Project Manager, Team Leader, at 301-796-3813.

3.1 COMMENTS TO THE APPLICANT

1. Include a statement on the oral syringe, 'for oral use only' which communicates the route of administration
2. Revise the calibrated syringe statement that is presented in conjunction with storage recommendation (b) (4) to read, '.....Dispense only with the enclosed, calibrated syringe'

4 REFERENCES

1. Reviews

OSE Review # 2010-656, dated October 20, 2010; Morphine Sulfate Oral Solution;
Crandall, Anne.

APPENDICES

Appendix A: AERS Results

ISRNUM	CK	CSENUM
6962666	1	7570923
7043082	3	7627911
7058700	3	7638270
7076723	5	7652000
7106114	X	7670944
7133172	9	7690268

Appendix B: Container Labels

30 mL Container



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/s/

ANNE CRANDALL
04/01/2011

MELINA N GRIFFIS
04/01/2011

CAROL A HOLQUIST
04/01/2011



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 10, 2010

To: Bob Rappaport, M.D., Director
Division of Anesthesia and Analgesia Products

Through: Michael Klein, Ph.D., Director
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 201-517** Morphine sulfate oral solution
Indication: relief of moderate to severe acute and chronic pain where an opioid analgesic is appropriate. The 20 mg per mL concentration is indicated for use in opioid-tolerant patients only.
Dosages: oral solution 20 mg/ml
Company: Lannett Holdings Inc.

Materials reviewed: NDA 201-517 is located in EDR
Previous PIND 105,256 (April 20, 2009)

This memorandum responds to the DAAP consult regarding abuse potential of morphine sulfate oral solution 20 mg/ mL by Lannett Holdings, Inc. The sponsor has submitted NDA 201,517 for the currently marketed, but unapproved, morphine sulfate product to bring it into voluntary regulatory compliance. This NDA is submitted as a 505(b)(2) application. The Reference Listed Drug is an approved product, morphine sulfate oral solution 20 mg/5 mL, NDA 22,195 (approved March 17, 2008; formulation 20 mg/mL was approved January 25, 2010) by Boehringer Ingelheim Roxane Laboratories Inc.

This formulation due to its high concentration of morphine sulfate is only for patients who are opioid-tolerant.

The submission includes a CMC section and one comparative PK study (MRN-P9-644) which is a bridging study to Roxane's already approved 20 mg/5 mL formulation. The study assessed relative bioavailability of Lannett's product to Roxane's product under fasted conditions and effect of presence of high-fat, high-caloric meal on Lannett's product. The Lannett product was approvable from a Clinical Pharmacology perspective.

The sponsor has no questions specific for CSS, but DAAP requests input from CSS regarding this NDA.

Background:

Morphine sulfate has been used for over a century as an analgesic. Morphine sulfate is listed as a Schedule II narcotic in the Controlled Substances Act.

The sponsor has marketed concentrated products of morphine sulfate oral solutions under the generic name morphine sulfate; however, they were unapproved products.

This product of morphine sulfate oral solution 20 mg/ml will have the same indication, dosage, and route and duration of administration as the previously marketed, but unapproved drug products.

Recommendation (to be relayed to the Sponsor)

1. Conduct routine pharmacovigilance of this drug and report all cases of potential abuse, misuse or overdose (intentional or unintentional and leading to death). Submit a summary of analysis in two years of all available data (including DAWN and AERS) from the US market for this formulation of morphine sulfate oral solution and relevant information on drug diversion.

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/s/

ALICJA LERNER
11/10/2010

LORI A LOVE
11/10/2010

MICHAEL KLEIN
11/10/2010

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

PATIENT LABELING REVIEW

Date: November 1 , 2010

To: Robert Rappaport, MD, Director
Division of Analgesics and Anesthetics Products (DAAP)

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management (DRISK)
LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management
Barbara Fuller, RN, MSN, CWOCN
Patient Labeling Reviewer
Division of Risk Management

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide and Patient Instructions for Use) and Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name (established name): Morphine Sulfate Oral Solution (20mg/mL)

Application Type/Number: NDA 201517

Therapeutic Class: Opioid Analgesic
(optional)

Applicant: Lannett Holdings, Inc.

OSE RCM #: 2010-653

1 INTRODUCTION

This review is written in response to a request by the Division of Analgesics and Anesthetics Products (DAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG), Patient Instructions for Use (PIFU), Proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for Morphine Sulfate Oral Solution (20 mg/mL).

DRISK conferred with DMEPA and DMEPA deferred to DRISK to provide review comments on patient labeling.

2 BACKGROUND

On February 26, 2010, Lannett Holdings, Inc. submitted a New Drug Application (NDA) for Morphine Sulfate Oral Solution. Morphine Sulfate Oral Solution (20 mg/mL) is a highly concentrated formulation indicated for the relief of moderate to severe acute and chronic pain in opioid tolerant patients. Morphine Sulfate Oral Solution is available in 10 mg per 5 mL, 20 mg per 5 mL and 20 mg per mL concentrations, however only the 20 mg/mL concentration is indicated for opioid tolerant patients. Lannett has only submitted an NDA for the 20 mg per mL concentration.

Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if DAAP would like a meeting with DRISK to discuss these comments before sending to the Applicant.

3 MATERIAL REVIEWED

- Draft Morphine Sulfate Oral Solution Prescribing Information (PI) received February 26, 2010, revised by the Review Division throughout the current review cycle and received by DRISK on October 14, 2010.
- Draft Morphine Sulfate Oral Solution Medication Guide (MG) and Instructions for Use (IFU) received on February 26, 2010, revised by the Review Division throughout the review cycle and received by DRISK on October 14, 2010.
- Proposed Morphine Sulfate Oral Solution Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on March 26, 2010.
- Approved Morphine Sulfate Oral Solution MG and IFU comparator labeling dated January 25, 2010, sponsored by Roxane Laboratories, Inc.

4 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU, document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU, is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU is consistent with the approved comparator labeling where applicable

In our review of the Proposed REMS and REMS Supporting Documents, we have:

- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS as proposed by the Applicant.

Please note, the timetable for submission of the assessment is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments do not need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to the Division of Analgesics and Anesthetics Products (DAAP):

Our annotated MG and IFU is appended to this memo (Appendix A Marked Copy, Appendix B Clean Copy). Any additional revisions to the PI should be reflected in the MG.

Comments to Lannett Holdings, Inc.:

See the appended Morphine Sulfate Oral Solution REMS proposal (Appendix C of this memo) for track changes corresponding to comments in this review.

a. GOAL

Your proposed goal for Morphine Sulfate Oral Solution is acceptable.

b. Your Medication Guide Distribution plan is acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CDR 208.24 is more appropriate for the REMS Supporting Document

See our editorial comments on this section of the Proposed REMS (see Appendix C)

c. Your Timetable for Submission of Assessments is acceptable.

We have some editorial comments in this section of the proposed REMS.

d. Regarding your REMS Assessment Plan: t.

(b) (4)

[Redacted text block containing multiple paragraphs of information, all obscured by grey bars.]

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/s/

BARBARA A FULLER

11/01/2010

DRISK review of Morphine Sulfate Oral Solution MG-REMS

CLAUDIA B KARWOSKI

11/01/2010

concur

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: October 29, 2010

To: Diana Walker – Regulatory Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

From: Twyla Thompson – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: **DDMAC Draft Medication Guide Comments
NDA 201517 Morphine Sulfate Oral solution CII**

DDMAC has reviewed the proposed Medication Guide for Morphine Sulfate Oral Solution CII submitted for DDMAC review on July 14, 2010.

The following comments are provided using the updated Medication Guide sent via email on October 27, 2010 by Diana Walker. DDMAC's comments on the proposed product labeling (PI) have been issued under separate cover. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

TWYLA N THOMPSON
10/29/2010

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: October 27, 2010

To: Diana Walker – Regulatory Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 202517 Morphine Sulfate Oral solution CII

DDMAC has reviewed the proposed product labeling (PI), and the Carton and Container label for Morphine Sulfate Oral Solution CII submitted for DDMAC review on July 14, 2010.

The following comments are provided using the updated proposed PI sent via email on October 27, 2010 by Diana Walker. DDMAC's comments on the proposed Medication Guide will be provided under separate cover. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

MATHILDA K FIENKENG
10/27/2010

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

Date: October 20, 2010

Application Type/Number: NDA 201517

To: Bob Rappaport, MD, Director
Division of Anesthesia and Analgesia Products

Through: Melina Griffis RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Anne Crandall, PharmD., Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Morphine Sulfate Oral Solution, 100 mg/5 mL (20 mg/mL)

Applicant/sponsor: Lannett Pharmaceuticals

OSE RCM #: RCM 2010-656

CONTENTS

EXECUTIVE SUMMARY	1
1 BACKGROUND.....	1
1.1 Product Information.....	1
1.2 Regulatory History.....	1
2 METHODS AND MATERIALS	2
2.1 FDA Adverse Event Reporting System (AERS) Database.....	2
2.2 Label and Labeling.....	2
3 RESULTS AND DISCUSSION.....	2
4 CONCLUSIONS AND RECOMMENDATIONS	4
4.1 Comments to the Applicant.....	4
APPENDIX A.....	4

EXECUTIVE SUMMARY

This review evaluates the proposed container labels, carton and insert labeling for NDA 201517, Morphine Sulfate Oral Solution, 20 mg/mL, submitted by the Applicant, Lannett Pharmaceuticals, on February 25, 2010 for areas in design that can potentially lead to medication errors.

Our review noted the lack of prominence of the product strength which may result in confusion with other concentrations of morphine sulfate oral solutions, including those that are less concentrated. Although this manufacturer does not market a less concentrated version, it is important that we ensure these labels don't get confused with other morphine labels that are in the market place. Thus, we recommend increasing both the prominence of the 20 mg/mL statement and removing unnecessary information from the principle display panel so that more attention is given to strength, the Medication Guide statement and instructions on how to use the oral dosing device. These label and labeling recommendations for this Morphine Sulfate Oral Solution are consistent with recommendations that were implemented for another Morphine Sulfate Oral Solution product of the same concentration

1 BACKGROUND

This review responds to a request from the Division of Anesthesia and Analgesia Products for assessment of the container labels, carton and labeling, contained in the NDA 201517 submission for Morphine Sulfate Oral Solution, 20 mg/mL, dated March 23, 2010, for medication error potential.

1.1 PRODUCT INFORMATION

Morphine Sulfate Oral Solution (20 mg/mL) is a highly concentrated formulation indicated for the relief of moderate to severe acute and chronic pain in opioid tolerant patients. Morphine Sulfate Oral Solution is available in 10 mg per 5 mL, 20 mg per 5 mL and 20 mg per mL concentrations, however only the 20 mg/mL concentration is indicated for opioid tolerant patients. Lannett has only submitted and NDA for the 20 mg/mL concentration.

The usual dose of Morphine Sulfate Oral Solution is 10 mg to 20 mg by mouth every 4 hours as needed. Morphine Sulfate Oral Solution will be available in three different volumes; 30 mL, 120 mL and 240 mL bottles, and will include an oral delivery device in the carton. Morphine Sulfate Oral Solution is stored at room temperature.

1.2 REGULATORY HISTORY

As part of FDA's attempt to bring marketed, unapproved drugs into compliance, Lannett Pharmaceuticals submitted an NDA for Morphine Sulfate Oral Solution (20 mg/mL). This is the second concentrated Morphine Sulfate Oral Solution product that was submitted as an NDA. The first was submitted by Roxane Pharmaceuticals and was approved in January 2010.

Morphine Sulfate Oral Solution, 20 mg/mL, is a concentrated formulation which has been involved with medication errors concerning confusion between the 20 mg/mL and 5 mg/mL Morphine Sulfate Oral Solutions available in the market place. A Dear Healthcare Professional letter was distributed in 2001 to mitigate this type of error. This letter warned of the potential for error between the two products and recommended that prescribers include both the intended mg dose as well as the corresponding volume in mL [0.75 mL (15 mg)] to help the pharmacist and/or nurse differentiate between the two products.

DMEPA completed a label and labeling review¹ of Roxane's Morphine Sulfate Oral Solution and Morphine Sulfate Tablets in 2008, which included post marketing analysis of medication errors that occurred between Morphine Sulfate oral solutions that varied in strength. One medication error occurred

¹ OSE review #2007-1808. Morphine Sulfate Oral Solution Labeling Review. Felicia Duffy. February, 2008.

when the 20 mg/mL strength was mistaken for the 20 mg/5 mL strength and resulted in death. Although this review did not recommended label and labeling changes specifically for the concentrated Morphine Sulfate Oral Solution, DMEPA was able to provide label and labeling recommendations based upon the analysis of the errors which were communicated to the Roxane when they submitted the concentrated Morphine Sulfate Oral Solution NDA at a later date.

Roxane implemented the DMEPA label and labeling recommendations for Morphine Sulfate Oral Solution, 20 mg/mL, in January 2010. These label and labeling revisions were highlighted in a communication to practitioners via an article in ISMP, entitled “A new look for Morphine Sulfate 100 mg per 5 mL (20 mg/mL) Oral Solution”².

2 METHODS AND MATERIALS

DMEPA evaluated the proposed container label and carton labeling of the proposed product as well as those of Roxane which was the first concentrated Morphine product to be approved.

We also conducted a search of the Adverse Event Reporting System for all medications errors that involved the Roxane concentrated morphine product. The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors related to accidental exposures, intentional overdoses, etc.) were excluded from further analysis.

2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The FDA Adverse Event Reporting System (AERS) database search conducted on August 4, 2010 using the following search criteria.

Reaction terms; High Level Group Term (HLGT) “Medication Errors”, the High Level Term (HLT) “Product Label Issues” and the Preferred Term (PT) “Product Quality Issues” were used as search criteria for Reactions. The search criteria used for Products was verbatim substance search “Morphine Sulfate 20mg/mL%”. Date limitations were set based upon the most recent label and labeling revisions for concentrated Morphine Sulfate Oral Solution which occurred January 2010. A manufacturer limitation was also set based upon the revised labels which only pertain to Roxane laboratories. This limitation was set because DMEPA provided the label and labeling recommendations for Roxane labels and will also recommend the same label and labeling revisions for this NDA. This search was narrowed in order to detect any new problems related to the revised labels and labeling so that they can be corrected for this product’s labels.

2.2 LABEL AND LABELING

Using Failure Mode and Effects Analysis³ (FMEA) DMEPA evaluated labels and labeling. This review focuses on the labels and labeling submitted as part of the NDA Application dated March 23, 2010 submissions (see Appendix A).

3 RESULTS AND DISCUSSION

No new cases of medication errors were detected in our AERS search, however a recent article, prompted by errors reported to ISMP associated with the oral dosing device of Roxane’s Morphine Sulfate Oral Solution, was published in the Institute of Safe Medication Practices (ISMP) Medication Safety Alert,

² Institute for Safe Medication Practices. ISMP Medication Safety Alert!. Volume 15, Issue 3. February 11, 2010.

³ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

Acute Care Newsletter⁴. This article cited errors that have occurred in institutions due to confusion related to the plunger of the oral dosing device for morphine sulfate oral solution, 20 mg/mL. The device described in the article is the same device that is proposed for use in this NDA 201517. The dispensing end of the plunger is pointed, rather than flat, which was specifically designed to provide low residual syringe volume after the drug has been administered to the patient. This pointed tip pushes out all of the solution and which leaves very little solution in the dead space, however this pointed tip has resulted in confusion because practitioners are unsure where to measure the liquid; from the end of the plunger tip or from the widest part of the plunger, located above the tip. See picture below:

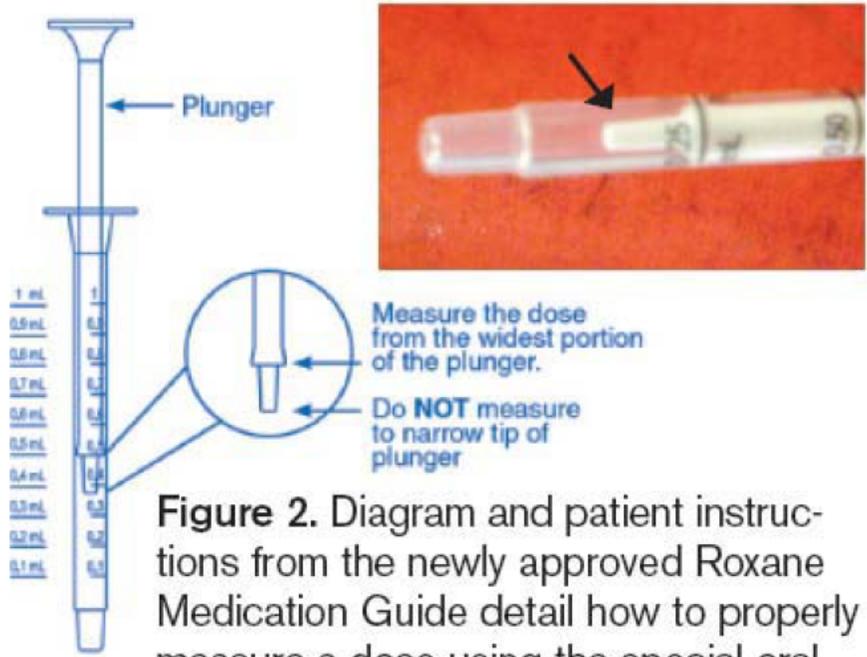


Figure 2. Diagram and patient instructions from the newly approved Roxane Medication Guide detail how to properly measure a dose using the special oral dispenser.

The correct measurement is obtained when using the widest portion of the plunger. When the pointed tip is used to measure the dose, the end result is an overdose as this provides more than the prescribed amount. The concern with this device design was considered in the Roxane review. Roxane stated they had no post-marketing problems with the syringe use in other countries, therefore a design change was not requested and the explicit directions for use were placed in the insert. Therefore, the same instructions for use need to be included in the proposed products labels as well.

This type of diagram or picture can instruct exactly how to properly measure the correct dose and may be especially useful if placed in both the Medication Guide for patients and the container label and carton labeling to ensure that each bottle has instructions for the dosing device available for either a practitioner or patient.

Additionally, the oral dosing device contains a statement; (b) (4) which is inconsistent with the Morphine Sulfate oral solution formulation and dosing instructions. This oral dosing device will be dispensed with an oral formulation (b) (4). Removing the word (b) (4) from the oral dosing device can mitigate this confusion and instruct patients regarding the proper route of administration.

⁴ Institute for Safe Medication Practices. ISMP Medication Safety Alert!. Volume 15, Issue 6. April 22, 2010.

Additionally other areas of the labels and labeling need revisions such as increasing the prominence of the strength 100 mg/5 mL and highlighting statements to ensure better differentiation from the less potent Morphine Sulfate Oral Solution, 20 mg/mL and updating the labels and labeling to display the Medication Guide statement. These recommendations are further explained in Section 4 below.

4 CONCLUSIONS AND RECOMMENDATIONS

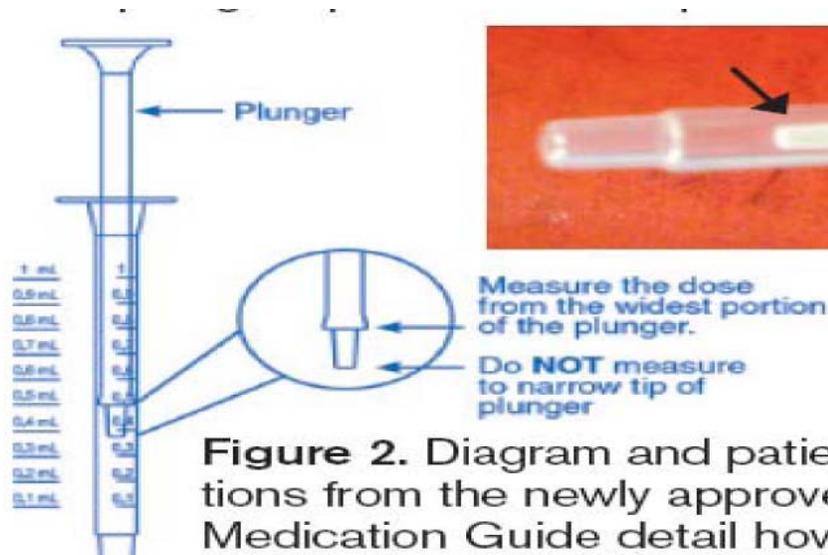
Our evaluation of the proposed container labels, carton and insert labeling, and the oral dosing device, noted areas of needed improvement in order to minimize the potential for medication errors. Specifically, improved instructions for use of the dosing device and improved product differentiation between morphine concentrations. We request the recommendations for the container labels and carton labeling in Section 4.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Abolade Adeolu, at 301-796-4264.

4.1 COMMENTS TO THE APPLICANT

A. Oral Dosing Device

1. Medication errors described in a recent article which discussed confusion related to the oral dosing device used for concentrated Morphine Sulfate Oral Solution. The device involved in these errors is the same device that was submitted in your application. The plunger is all white and pointed and has caused confusion because practitioners are unsure if the dose should be measured from the narrow tip or the widest part of the plunger. These types of errors have resulted in overdose. We recommend adding a picture or diagram of the syringe and plunger with explicit instructions indicating what part of the plunger is used for measuring doses to mitigate this type of error. This picture or diagram should be included on the container label and the carton labeling (and retained in the Medication Guide). See picture below:



APPEARS THIS WAY ON ORIGINAL.

2. Remove the word, (b) (4) from the oral dosing device.

B. Container Labels (30 mL, 120 mL and 240 mL bottle)

1. Principal Display Panel

- a. Revise the presentations of strengths so that the 100 mg per 5 mL is more and the 20 mg/mL statement so that it is less prominently displayed and appears in parenthesis underneath the 100 mg per 5 mL statement. Additionally, a large color box should stretch across the principle display panel which highlights the name and strength. This color should be chosen to ensure that it is visually well differentiated from the other morphine sulfate oral solution concentration because of the multiple similarities between the products, i.e. name, bottle shape and size.
- b. Remove the statement [REDACTED] (b) (4) and replace with “Only for use in patients who are opioid tolerant”. This statement should appear in a box below the strength statements.
- c. Remove the statement, [REDACTED] (b) (4) and replace it with the Medication Guide statement: “Pharmacist: Must dispense the enclosed Medication Guide to each patient”.
- d. Revise the [REDACTED] (b) (4) statement so that it only displays the quantity “120 mL”.
- e. Add a statement to the principal display panel that alerts patients, caregivers and practitioners to always use the oral dosing device provided to measure each dose of Morphine Sulfate Oral Solution.

2. Side Panel

- a. See comment A1
- b. Remove the [REDACTED] (b) (4) statement on the side panel and replace with 100 mg per 5 mL so that the strength is consistently displayed throughout the label and labeling.
- c. Remove all of the text which appears under the title “Pharmacist/Nurse/Patient” and replace with a succinct description of how to properly measure a dose with the provided dosing device.
- d. Revise the dispense statement, the usual dose statement, and the storage statement on the **30 mL** bottle so that they appear horizontally oriented [REDACTED] (b) (4) which will result in increased readability.

C. Carton Labeling (30 mL, 120 mL and 240 mL)

1. Principle Display Panel

- a. See comments A1 and B1a through B1c.

2. Back Panel

- a. See comments A1, B2a and B2b.
- b. The back panel and principal display panel should mimic one another in the presentation of information which will ensure that the vital information regarding strength, opioid tolerance and Medication Guides are communicated regardless of which direction the carton is facing.

3. Side Panels

- a. See comment A1 (diagram can be placed on either back panel OR side panel).
- b. Add a statement which alerts practitioners that the carton contains both the morphine sulfate bottle and an oral dispenser.
- C. See comment B1e.

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/s/

ANNE CRANDALL
10/21/2010

MELINA N GRIFFIS
10/21/2010

CAROL A HOLQUIST
10/21/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201517 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Morphine Sulfate Oral Solution Dosage Form: Oral Solution Strengths: 20 mg/mL		
Applicant: Lannett Holdings, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: February 26, 2010 Date of Receipt: March 1, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: January 1, 2011		Action Goal Date (if different): December 10, 2010
Filing Date: April 30, 2010		Date of Filing Meeting: April 15, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7		
Proposed indication(s)/Proposed change(s): The relief of moderate to severe acute and chronic pain in opioid-tolerant patients		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s):				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	XX			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	XX			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	XX			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		XX		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	XX			Requested a Small Business User Fee Waiver, but is not eligible
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment								
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	XX			Advice was given that the Sponsor could file as a b2. Right before they filed, another product was approved, but they filed as b2 anyway. It was decided to go forward with the b2 instead of the RTF.								
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		XX										
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>		XX										
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:		XX										
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration								
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration									
<i>If there is unexpired, 5 year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3 year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>												
Exclusivity	YES	NO	NA	Comment								
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		XX										
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			XX									
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		XX										

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		XX		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			XX	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	XX			
Index: Does the submission contain an accurate comprehensive index?	XX			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	XX			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i> March 18, 2010	XX			Abuse Liability Assessment not included, but scheduling proposal is included
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				

Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature? <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	XX			
Are all establishments and their registration numbers listed on the form/attached to the form?	XX			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?		XX		Patent Certification was submitted
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? <i>Forms must be signed by the APPLICANT, not an Agent.</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	XX			
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	XX			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>) <i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i> <i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	XX			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			XX	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		XX		Sponsor was told in pre-IND/NDA meeting that Pediatric studies would be required, depending on the proposed indication. The Sponsor submitted a request for Full Waiver. However, this application does not trigger PREA.
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		XX		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	XX			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	XX			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		XX		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>		XX		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	XX			
Is the PI submitted in PLR format?	XX			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			XX	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	XX			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	XX			
REMS consulted to OSE/DRISK?	XX			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	XX			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		XX		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 1, 2009 <i>If yes, distribute minutes before filing meeting</i>	XX			As a PIND, no IND was opened.
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		XX		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 15, 2010

BLA/NDA/Supp #: 201517

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Morphine Sulfate Oral Solution

DOSAGE FORM/STRENGTH: Oral Solution, 20 mg/mL

APPLICANT: Lannett Holdings, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): The relief of moderate to severe acute and chronic pain in opioid-tolerant patients

BACKGROUND: This is a 505(b)(2) application for a currently marketed, unapproved drug.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Diana Walker	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Robert Shibuya		Y
Clinical	Reviewer:	Robert Shibuya	Y
	TL:	N/A	
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Sheetal Agarwal	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	N/A	
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carlic Huynh	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Art Shaw	N
	TL:	Danae Christodoulou	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	TBD	N
	TL:	TBD	N
OSE/DMEPA (Carton & Container)	Reviewer:	Anne Crandall	Y
	TL:	Carlos Menas-Grillasca	N
OSE/DRISK (REMS)	Reviewer:	Steve Morin and John Hubbard	N
	TL:	Sharon Mills	N
Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:	N/A	

Other reviewers	Angelica Dorantes, Biopharm Alicja Lerner, CSS	N N
Other attendees	Sharon Hertz, Deputy Division Director Sally Loewke Abolade Adeolu, RPM, OSE Cheryle Milburn, RPM, OSE	Y Y Y Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: No Clinical Studies, only bioequivalence studies. Clinical Pharmacology will consult DSI for BioPharm inspections.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Will not request inspections from DSI</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: Deficiency for the DMF</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Deficiency for the DMF</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: TBD	
21st Century Review Milestones (optional): Mid-Cycle = July 15, 2010 Wrap-Up = October 18, 2010 Labeling Comments and PMRs due to Sponsor November 5, 2010 Action Goal Date = December 10, 2010 PDUFA Date = January 1, 2011	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): CMC and Nonclinical <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74 – To be sent by May 15, 2010
<input checked="" type="checkbox"/>	Other – Request Dosing device samples from the Sponsor to go to CMC, DMEPA, and Clinical disciplines.

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201517	ORIG-1	LANNETT HOLDINGS INC	morphine sulfate oral solution 20 mg/mL

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

/s/

DIANA L WALKER
04/22/2010