CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201517Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	201517/000
Applicant Name	Lannett Holdings, Inc.
Date of Submission	December 23, 2010
PDUFA Goal Date	June 23, 2011
Proprietary Name / **Established (USAN) Name**	NA/Morphine Sulfate Oral Solution
Dosage Forms / Strength	Oral solution/ 100 mg per 5 mL (20 mg per mL)
Proposed Indication(s)	For the management of moderate to severe acute and chronic pain in opioid-tolerant patients.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Pharmacology Toxicology Review	Carlic Huynh, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review/OBP Review	Arthur B. Shaw, Ph.D.; Prasad Peri, Ph.D.
Microbiology Review	Bryan S. Riley, Ph.D.; Stephen E. Langille, Ph.D.
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D.; Suresh Doddapaneni, Ph.D.
DDMAC	Mathilda K. Fienkeng; Twyla N. Thompson
DSI	N/A
CDTL Review	Sharon H. Hertz, M.D.
OSE/DMEPA	Anne Crandall, Pharm.D., Melina Griffis, R.Ph.; Carol Holquist, R.Ph.
OSE/DDRE	N/A
OSE/DRISK	Steve L. Morin, Ph.D.; LaShawn Griffiths, R.N., MSHS-PH, B.S.N.; Barbara Fuller, R.N., M.S.N., CWOCN; Claudia Karwoski, Pharm.D.
Controlled Substance Staff	Alicja Lerner, M.D., Ph.D., Lori Love, M.D., Ph.D., Michael Klein, Ph.D.

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Signatory Authority Review Template

1. Introduction

The applicant has submitted a response to a Complete Response (CR) action taken on December 10, 2010. The CR was a result of deficiencies identified for the drug substance and at the drug product production site. The application is relying on the results of one pharmacokinetic study and on the Agency's prior findings of safety and efficacy for Morphine Sulfate Oral Solution (Roxane, NDA 22-195), 20 mg/ 5 mL to support this 505(b)(2) application. Please refer to my Summary Review for Regulatory Action dated December 10, 201 for details of the first cycle review (Appendix.)

In this submission, the applicant has addressed the first cycle deficiencies. No new clinical efficacy or safety studies, nonclinical studies, or clinical pharmacology studies were submitted.

2. Background

Numerous unapproved narcotic analgesics are currently marketed, many under the mistaken belief that, as very old products, it was not necessary for applications to be submitted for review under the Drug Efficacy Study Implementation to support continued marketing of these products. The current application is for a product that has been marketed, although previously unapproved, morphine sulfate oral solution.

Morphine was isolated from opium as early as 1806. Opiate receptors were first identified in the early 1970's followed by the discovery of the first endogenous opiate-like substance, enkephalin. The existence of mu, delta and kappa sub-types of opiate receptors was also confirmed in the 1970's. Morphine, along with most of the clinically used opioids, is relatively selective for the mu receptor and it is through the mu receptor that it exerts its clinical effects.

3. CMC/Device

The deficiencies identified during the first review cycle and cited in the action letter were:

FACILITY INSPECTIONS
During a recent inspection of the Lannett Company, Inc., 9001 Torresdale Avenue, Philadelphia, PA, 19136-1514, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRODUCT QUALITY

DMF [redacted] for morphine sulfate held by [redacted] was found deficient and the holder notified on December 2, 2010. Satisfactory resolution of this deficiency is required before this application may be approved.

The drug substance is supplied by [redacted] under DMF [redacted]. A DMF deficiency letter for DMF [redacted] was filed in DARRTS on September 14, 2010 and was not addressed prior to the PDUFA goal date for the original review cycle. The manufacturing information, specifications and stability data in the DMF were found acceptable in a review dated April 1, 2011 and as of June 8, 2011, this site was found to be acceptable from a CGMP point of view.

The drug product is an oral liquid manufactured by Cody Laboratories. The excipients are compendial. As noted by Dr. Shaw:

> A statistical analysis of the stability data support an expiration date of [redacted] months based on an acceptance criterion of NLT [redacted] for sodium benzoate, [redacted] However a statistical analysis of the stability data support an expiration date of eighteen months based on an acceptance criterion of NMT [redacted] for a novel degradant eluting at Relative Retention Time (RRT) [redacted] The degradant has been identified but not qualified. In order to grant a longer expiration date, that impurity would have to be qualified.

The applicant has included an oral dosing syringe to ensure accurate dosing by patients and caregivers.

I concur with the conclusions reached by the chemistry reviewer that there are no outstanding issues precluding approval and I concur with an expiry of 18 months.

4. Nonclinical Pharmacology/Toxicology

There were no nonclinical pharmacology or toxicology deficiencies from the first review cycle and no new nonclinical data were submitted for review.

5. Clinical Pharmacology/Biopharmaceutics

There were no clinical pharmacology or biopharmaceutics deficiencies from the first review cycle and no new clinical pharmacology data were submitted for review.

6. Product Quality Microbiology

A microbiology review by Dr. Riley found that the applicant had not submitted test methods and acceptance criteria to demonstrate that the product is free of *Burkholderia cepacia* and a request was sent to the applicant. The following was requested of the applicant:

> Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

The applicant responded by submitting revised specifications for the drug substance and the drug product with a test for B cepacia. The applicant also included validation studies for the B. cepacia test method. Dr. Riley concluded that the validated test procedure appears adequate to isolate B. cepacia fro the drug product. The preservatives and low pH are also likely to prevent microbial contamination.

I concur with the conclusions reached by the product quality microbiology reviewer there are no outstanding product quality microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

No new clinical safety or efficacy data was submitted in support of this application. The applicant is relying on the Agency's prior findings for morphine sulfate oral solution, NDA 22-195.

8. Safety

No new clinical safety or efficacy data was submitted in support of this application. To improve the safety and accuracy of dosing, an oral dosing syringe was requested by FDA and added by the applicant. While this NDA contains only one concentration of morphine oral solution, there are other morphine oral solutions marketed with different concentrations (NDA (b) (4), 20 mg per 5 mL and 10 mg per 5 mL). Therefore, the applicant was told that a medication guide was required to ensure that patients were alerted to the need for care when administering a dose of this product. Labeling changes include a boxed warning to alert prescribers to the risk for medication errors as follows:

(b) (4)

In addition, the indication for this product, for the management of moderate to severe acute and chronic pain in opioid-tolerant patients, reflects that the 100 mg per 5 mL (20 mg per mL) concentration of morphine sulfate poses greater risks for overdose and should be reserved for use in patients who require doses that cannot be adequately accommodated with 20 mg per 5 mL and 10 mg per 5 mL concentration oral solutions.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this NDA. Morphine sulfate is a long established analgesic and the formulation proposed does not present any novel issues or concerns.

10. Pediatrics

As this application does not represent a change in active ingredient, dosage form, route of administration, indication or dosing regimen, the requirements under the Pediatric Research Equity Act were not applicable.

11. Other Relevant Regulatory Issues

The Controlled Substances Staff was consulted and had the following recommendation:

> 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.

505(b)(2) Regulatory Pathway
The question of evaluating this application as a 505(b)(2) as opposed to an ANDA has been discussed. The concentration of sorbitol contained in Lannett's morphine sulfate 100 mg per 5 mL (20 mg per mL) product is high enough that there is a theoretical possibility that doses of morphine sulfate oral solution at or in excess of 300 mg total dose may result in a different relative morphine exposure than doses below 300 mg. The potential effect of sorbitol on morphine sulfate absorption is based on the effects of sorbitol concentration on ranitidine, a

BCS class 3 drug. However, the BCS classification of morphine sulfate oral solution is not clear, and therefore, it is not clear if this concern is relevant for morphine sulfate.

One approach to determining whether there is an effect of the sorbitol concentration on the absorption of morphine would be to perform a pharmacokinetic. Performing such a study with a dose of 300 mg of immediate-release morphine, even with naltrexone blockade, poses an unacceptable level of risk for opioid toxicity. Therefore, given that such a study is impracticable, at this time we do not believe that bioequivalence can be effectively investigated, nor can Lannett's product be AB rated to Roxane's morphine sulfate oral solution 100 mg per 5 mL (20 mg per mL). Additionally, because such a bioequivalence study cannot be performed, this product is not appropriate as an ANDA; approval requires a clinical judgment on whether this drug is safe and effective for use.

The question of whether the effects of sorbitol on morphine absorption at doses of 300 mg poses safety concerns must then be considered. Patients receiving morphine sulfate doses at 300 mg (e.g., 300 mg orally every 4 hours) or higher are encountered infrequently in clinical practice. They represent a group of patients that are highly opioid tolerant. A difference in morphine absorption based on the amount of sorbitol contained in Lannett's morphine sulfate oral solution would not be expected to place patients at risk. Therefore, there is no need for specific labeling to address this.

Lannett cited NDA 22195 as a listed drug. There are no patents or exclusivity associated with the-is listed drug.

12. Labeling

The labeling, instructions for use, and medication guide has been reviewed by DRISK, DMEPA and DDMAC. Recommended changes to the package insert, medication guide and container and carton labels were implemented.

The changes to the labeling, in particular the addition of boxed warnings, improved dosing and administration instructions, and the addition of an oral syringe for dosing and the accompanying instructions for use are expected to improve the safe use of this product.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment

There is adequate evidence for efficacy and safety of Morphine Oral Solution for use in adults.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

None

Appendix

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA # Supplement #	201517/000
Applicant Name	Lannett Holdings, Inc.
Date of Submission	March 1, 2010
PDUFA Goal Date	January 1, 2011
Proprietary Name / Established (USAN) Name	NA/Morphine Sulfate Oral Solution
Dosage Forms / Strength	Oral solution/ 100 mg per 5 mL (20 mg per mL)
Proposed Indication(s)	For the management of moderate to severe acute and chronic pain in opioid-tolerant patients.
Action/Recommended Action for NME:	Complete Response

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5 Pages have been Withheld in Full -- as duplicates of the pages included in the Medical Review dated 12/10/10 -- immediately following this page.

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/s/

SHARON H HERTZ
06/23/2011