

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201517Orig1s000**

**CHEMISTRY REVIEW(S)**

# **Chemistry Review Cover Sheet**

**NDA 201517**

**Morphine Sulfate Oral Solution**

**Arthur B. Shaw, Ph.D.**

**ONDQA/DNDQA3/DAAAP**

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## Chemistry Review Data Sheet

1. NDA 201517
2. REVIEW #4
3. REVIEW DATE: June 11, 2011
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Document</u>	<u>Document Date</u>	<u>Comment</u>
Original	2010-02-26	
Filing Letter	2010-05-17	Request for stability info, safety of excipients, (b) (4) and container-closure
IR Letter (e-mail)	2010-05-20	Request for sample dosing device
Amendment	2010-06-23	Response to 17-May-2010 letter (b) (4) and c-c
Amendment	2010-07-01	Response to 17-May-2010 letter Excipients
Amendment	2010-07-09	Response to 17-May-2010 letter Photostability data
IR Letter (e-mail)	2010-07-12	Request for info regarding preservatives
IR Letter (e-mail)	2010-07-13	Request for info regarding delivery volume
Amendment	2010-07-14	Response to 12-Jul-2010 IR
Amendment	2010-07-15	Response to 13-Jul-2010 IR
Amendment	2010-07-20	Response to 17-May-2010 letter Stability data
Quality Micro Review	2010-09-01	Issues regarding testing for Burkholderia
Chem. Review #1	2010-09-20	Many issues
Discipline Review Letter	2010-09-17	See Chem Review #1
Amendment	2010-10-25	CFR citations for packaging
Amendment	2010-11-12	Response to DR letter
Amendment	2010-12-03	Response to DR letter micro issues
Amendment	2010-12-03	Updated stability
Pharm/tox review	2010-11-04	(b) (4) not genotoxic
Chem Review #2	2010-12-07	Minor issues DMF (b) (4) deficient
General info and advice letter	2010-12-08	See Chem review #2
Complete Response Letter	2010-12-10	Inspection issues and DMF issues. Other CMC from 2010-12-08 letter not included as approvability issues
Resubmission	2010-12-23	Responds to all comments
IR Letter	2011-04-05	Request revision of tables to conform to revision in text
Amendment	2011-04-07	Response to 2011-04-05 IR
IR Letter	2011-04-19	Request for Placebo samples
Amendment	2011-04-19	Placebo samples

Amendment	2011-05-02	(b) (4)
Biometrics consult	2011-05-05	Expiration dating
Micro review	2011-05-10	Approvable
Telecon	2011-05-19	Request clarification of testing sites
Amendment	2011-05-13	Clarify testing sites
Biometrics review	2011-05-13	Expiration 18 months
Chem Review #3	2011-05-20	Approvable with 18 month expiry pending Compliance plus labeling comments

## 6. SUBMISSION(S)/COMMUNICATIONS being reviewed:

<u>Document</u>	<u>DARRTS Date</u>	<u>EDR/E-mail Date</u>	<u>Comment</u>
IR Letter	2011-05-24	2011-04-19	Labeling comments from Chem Review #3.
Amendment	2011-05-27		Revised labeling
EES Report		2011-06-08	Recommend approval

## 7. NAME &amp; ADDRESS OF APPLICANT AND AGENT:

Applicant Name	Lannett Holdings
Address	9000 State Road Philadelphia, PA 19136
Representative Name	Ernest Sabo
Phone	215-333-9000 X 2277
Fax	215- 624-6126

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proposed Proprietary Name: Morphine Sulfate Oral Solution
- b) Non-Proprietary Name (USAN): Morphine Sulfate Oral Solution
- c) Chem. Type/Submission Priority
  - Chem. Type: 4
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) RLD NDA 22195, Morphine sulfate (Roxane)

10. PHARMACOL. CATEGORY: opiate

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

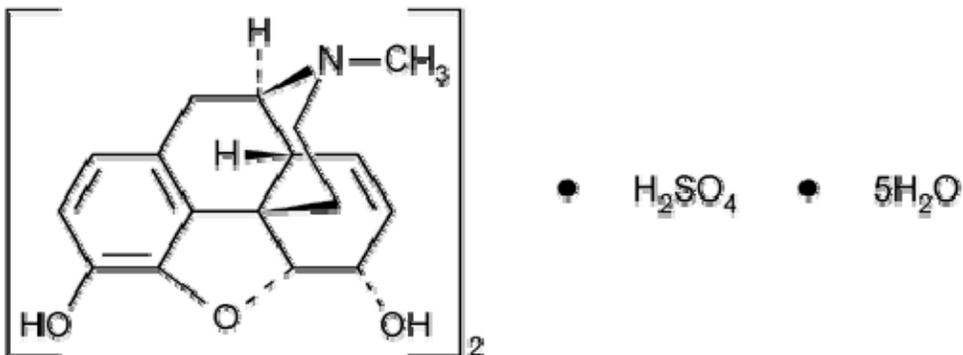
14. Rx/OTC DISPENSED:   X   Rx      OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): None

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

7,8-Didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol

sulfate salt (2:1) pentahydrate

C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>10</sub>S (anhydrous), C<sub>34</sub>H<sub>50</sub>N<sub>2</sub>O<sub>15</sub>S (pentahydrate)

Molecular weight: 668.75 (anhydrous), 758.83 (pentahydrate)

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**Reviewed: **ACCEPTABLE**

DMF	Holder	DMF Subject	Review Date
		(b) (4)	Acceptable 2011-04-01

**COMMENT:** DMFs for packaging materials were not reviewed since the applicant provided sufficient information to ensure that the materials of construction comply with applicable indirect food additive regulations. See discussion below under P.7.

**B. Other Documents:** PIND 105256

## 18. STATUS:

**CONSULTS/ CMC RELATED REVIEWS:**

Microbiology: Completed Sept 01, 2010. Recommended evaluating preservative effectiveness testing for ability to control *Burkholderi cepaci* DR sent 09/08/2010. Test method and validation in December 7 and 23, 2010 amendments found acceptable in review dated May 10, 2011.

Biometrics: Expiration date of 18 months Review dated May 13, 2011

EA waiver requested in 1.12.14. Granted **ACCEPTABLE**

Inspection: Complete. All sites acceptable (June 8, 2011).

## The Chemistry Review for NDA 201517

### I. Recommendations

#### 1. Recommendation and Conclusion on Approvability

The application may be approved with an expiration date of eighteen months.

#### 2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. None

?

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### 1. Drug Substances

The drug substance, morphine sulfate, is a USP item and its properties and synthesis have been assessed many times to support many applications. It is manufactured by (b) (4) under DMF (b) (4)

As of June 8, 2011, this site was acceptable from a CGMP point of view. Morphine sulfate is a white to off-white, fine crystalline powder and is soluble in water. A list of potential process impurities provided by the DMF holder is included in the application. The manufacturing information, specifications and stability data in the DMF were found acceptable in a review dated April 1, 2011. The applicant's specifications include all of the USP tests and additional tests for related substances and residual solvents. The applicant relies on validation information in the DMF for these additional tests and has also performed verification experiments to show that these tests are valid when performed by the applicant. All impurities, including the potentially genotoxic impurity, (b) (4) are well-controlled. A toxicology review (November 4, 2010) has found that (b) (4) is not genotoxic. The results of batch analysis (three batches) are satisfactory. The applicant relies on stability data from the drug substance manufacturer.

Since the drug product is a solution polymorphism is not an issue.

##### 2. Drug Product

The drug product is an oral liquid so there is no issue regarding dissolution. It contains three preservatives: propylparaben, methylparaben and sodium benzoate. The manufacturing process and controls performed by the contract manufacturer, Cody Laboratories, are straightforward. All of the excipients are compendial. The specifications are adequate to control the drug product, including tests for degradants. The applicant has provided data to demonstrate the preservatives retain their effectiveness when they three preservatives at levels of (b) (4) of the label claim. A statistical analysis of the stability data support an expiration date of (b) (4) months based on an acceptance criterion of NLT (b) (4) for sodium benzoate, a preservative. However a statistical analysis of the stability data support an expiration date of eighteen months based on an acceptance criterion of NMT (b) (4) for a novel degradant eluting at Relative Retention Time (RRT) (b) (4). The degradant has been identified but not qualified. In order to grant a longer expiration date, that impurity would have to be qualified.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is intended to be used for the relief of moderate to severe acute and chronic pain in opioid-tolerant patients at a dose of 10 to 20 mg every four hours, as needed. The drug product might also be used for chronic administration.

**C. Basis for Approvability or Not-Approval Recommendation**

There is adequate CMC data to show that the drug product will perform as expected when stored in its original packaging for eighteen months at Controlled Room Temperature.

**III. Administrative**

See DARRTS signatures and cc's

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ARTHUR B SHAW  
06/13/2011

PRASAD PERI  
06/14/2011  
I concur

# **Chemistry Review Cover Sheet**

**NDA 201517**

**Morphine Sulfate Oral Solution**

**Arthur B. Shaw, Ph.D.  
ONDQA/DNDQA3/DAAP**

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## Chemistry Review Data Sheet

1. NDA 201517
2. REVIEW #3
3. REVIEW DATE: May 19, 2011
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Document</u>	<u>Document Date</u>	<u>Comment</u>
Original	2010-02-26	
Filing Letter	2010-05-17	Request for stability info, safety of excipients, (b) (4) and container-closure
IR Letter (e-mail)	2010-05-20	Request for sample dosing device
Amendment	2010-06-23	Response to 17-May-2010 letter (b) (4) and c-c
Amendment	2010-07-01	Response to 17-May-2010 letter Excipients
Amendment	2010-07-09	Response to 17-May-2010 letter Photostability data
IR Letter (e-mail)	2010-07-12	Request for info regarding preservatives
IR Letter (e-mail)	2010-07-13	Request for info regarding delivery volume
Amendment	2010-07-14	Response to 12-Jul-2010 IR
Amendment	2010-07-15	Response to 13-Jul-2010 IR
Amendment	2010-07-20	Response to 17-May-2010 letter Stability data
Quality Micro Review	2010-09-01	Issues regarding testing for Burkholderia
Chem. Review #1	2010-09-20	Many issues
Discipline Review Letter	2010-09-17	See Chem Review #1
Amendment	2010-10-25	CFR citations for packaging
Amendment	2010-11-12	Response to DR letter
Amendment	2010-12-03	Response to DR letter micro issues
Amendment	2010-12-03	Updated stability
Pharm/tox review	2010-11-04	(b) (4) not genotoxic
Chem Review #2	2010-12-07	Minor issues DMF (b) (4) deficient
General info and advice letter	2010-12-08	See Chem review #2
Complete Response Letter	2010-12-10	Inspection issues and DMF issues. Other CMC from 2010-12-08 letter not included as approvability issues

## 6. SUBMISSION(S)/COMMUNICATIONS:

Document	DARRTS Date	EDR/E-mail Date	Comment
Resubmission	2010-12-23		Responds to all comments
IR Letter	2011-04-05	2011-03-30	Request revision of tables to conform to revision in text
Amendment	2011-04-07	2011-04-05	Response to 2011-04-05 IR
IR Letter	2011-04-19	2011-04-08	Request for Placebo samples
Amendment	2011-04-19	2011-04-15	Placebo samples
Amendment	2011-05-02	2011-04-29	(b) (4)
Biometrics consult	2011-05-05	2011-05-05	Expiration dating
Micro review	2011-05-10	2011-05-10	Approvable
Telecon	2011-05-19	2011-05-12	Request clarification of testing sites
Amendment	2011-05-13	2011-05-13	Clarify testing sites
Biometrics review	2011-05-13	2011-05-13	Expiration 18 months

## 7. NAME &amp; ADDRESS OF APPLICANT AND AGENT:

Applicant Name                      Lannett Holdings  
 Address                                    9000 State Road  
    Philadelphia, PA 19136  
 Representative Name                Ernest Sabo  
 Phone                                        215-333-9000 X 2277  
 Fax    215- 624-6126

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proposed Proprietary Name: Morphine Sulfate Oral Solution
- b) Non-Proprietary Name (USAN): Morphine Sulfate Oral Solution
- c) Chem. Type/Submission Priority
  - Chem. Type:                      4
  - Submission Priority:            S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) RLD NDA 22195, Morphine sulfate (Roxane)

10. PHARMACOL. CATEGORY: opiate

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

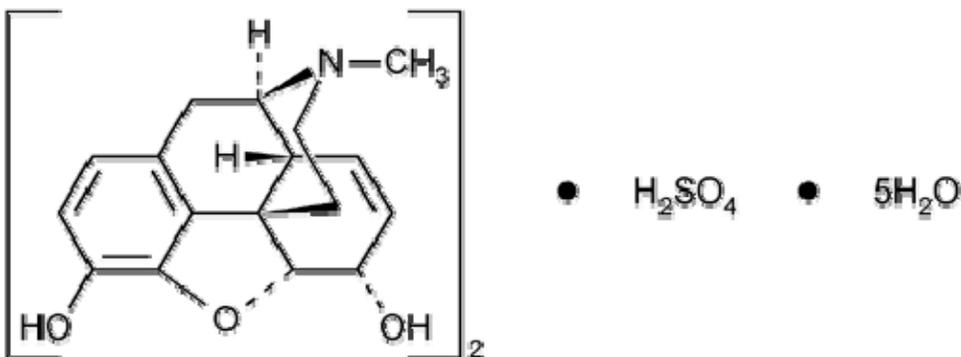
14. Rx/OTC DISPENSED:      X   Rx             OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): None

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

7,8-Didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol sulfate salt (2:1) pentahydrate

C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>10</sub>S (anhydrous), C<sub>34</sub>H<sub>50</sub>N<sub>2</sub>O<sub>15</sub>S (pentahydrate)



Molecular weight: 668.75 (anhydrous), 758.83 (pentahydrate)

#### 17. RELATED/SUPPORTING DOCUMENTS:

##### A. DMFs:

Reviewed: **ACCEPTABLE**

DMF	Holder	DMF Subject	Review Date
		(b) (4)	Acceptable 2011-04-01

**COMMENT:** DMFs for packaging materials were not reviewed since the applicant provided sufficient information to ensure that the materials of construction comply with applicable indirect food additive regulations. See discussion below under P.7.

**B. Other Documents:** PIND 105256

#### 18. STATUS:

##### CONSULTS/ CMC RELATED REVIEWS:

Microbiology: Completed Sept 01, 2010. Recommended evaluating preservative effectiveness testing for ability to control *Burkholderi cepaci* DR sent 09/08/2010. Test method and validation in December 7 and 23, 2010 amendments found acceptable in review dated May 10, 2011.

Biometrics: Expiration date of 18 months Review dated May 13, 2011

EA waiver requested in 1.12.14. Granted **ACCEPTABLE**

Inspection: Complete. All sites acceptable except for the applicant's site (November 10, 2010) for release testing of drug product. OC recommends withhold for the over-all application.

## The Chemistry Review for NDA 201517

### I. Recommendations

#### 1. Recommendation and Conclusion on Approvability

The application is approvable with an expiration date of eighteen months provided all sites receive a satisfactory inspection. At this time one site has an unacceptable inspection.

#### 2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. None

?

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### 1. Drug Substances

The drug substance, morphine sulfate, is a USP item and its properties and synthesis have been assessed many times to support many applications. It is manufactured by (b) (4) under DMF (b) (4)

As of March 10, 2010, this site was acceptable from a CGMP point of view. Morphine sulfate is a white to off-white, fine crystalline powder and is soluble in water. A list of potential process impurities provided by the DMF holder is included in the application. The manufacturing information, specifications and stability data in the DMF were found acceptable in a review dated April 1, 2011. The applicant's specifications include all of the USP tests and additional tests for related substances and residual solvents. The applicant relies on validation information in the DMF for these additional tests and has also performed verification experiments to show that these tests are valid when performed by the applicant. All impurities, including the potentially genotoxic impurity, (b) (4) are well-controlled. A toxicology review (November 4, 2010) has found that (b) (4) is not genotoxic. The results of batch analysis (three batches) are satisfactory. The applicant relies on stability data from the drug substance manufacturer.

Since the drug product is a solution polymorphism is not an issue.

##### 2. Drug Product

The drug product is an oral liquid so there is no issue regarding dissolution. It contains three preservatives: propylparaben, methylparaben and sodium benzoate. The manufacturing process and controls performed by the contract manufacturer, Cody Laboratories, are straightforward. All of the excipients are compendial. The specifications are adequate to control the drug product, including tests for degradants. The applicant has provided data to demonstrate the preservatives retain their effectiveness when they three preservatives at levels of (b) (4) of the label claim. A statistical analysis of the stability data support an expiration date of (b) (4) months based on an acceptance criterion of NLT (b) (4) for sodium benzoate, a preservative. However a statistical analysis of the stability data support an expiration date of eighteen months based on an acceptance criterion of NMT (b) (4) for a novel degradant eluting at RRT (b) (4). The degradant has been identified but not qualified.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is intended to be used for the relief of moderate to severe acute and chronic pain in opioid-tolerant patients at a dose of 10 to 20 mg every four hours, as needed. The drug product might also be used for chronic administration.

**C. Basis for Approvability or Not-Approval Recommendation**

There is adequate CMC data to show that the drug product will perform as expected when stored in its original packaging for eighteen months at Controlled Room Temperature. However one manufacturing site has not been found to be acceptable.

**III. Administrative**

See DARRTS signatures and cc's

23 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ARTHUR B SHAW  
05/19/2011

PRASAD PERI  
05/20/2011

# **Chemistry Review Cover Sheet**

**NDA 201517**

**Morphine Sulfate Oral Solution**

**Arthur B. Shaw, Ph.D.  
ONDQA/DNDQA3/DAAP**

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## Chemistry Review Data Sheet

1. NDA 201517
2. REVIEW #2
3. REVIEW DATE: December 7, 2010
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Comment</u>
Original	26-Feb-2010	
Filing Letter	17-May-2010	Request for stability info, safety of excipients, (b) (4) and container-closure
IR Letter (e-mail)	20-May-2010	Request for sample dosing device
Amendment	23-Jun-2010	Response to 17-May-2010 letter (b) (4) and c-c
Amendment	01-Jul-2010	Response to 17-May-2010 letter Excipients
Amendment	09-Jul-2010	Response to 17-May-2010 letter Photostability data
IR Letter (e-mail)	12-Jul-2010	Request for info regarding preservatives
IR Letter (e-mail)	13-Jul-2010	Request for info regarding delivery volume
Amendment	14-Jul-2010	Response to 12-Jul-2010 IR
Amendment	15-Jul-2010	Response to 13-Jul-2010 IR
Amendment	20-Jul-2010	Response to 17-May-2010 letter Stability data
Chem. Review #1		
Discipline Review Letter		

### 6. SUBMISSION(S) BEING REVIEWED:

Amendment 25-Oct-2010 CFR citations for packaging components  
 Amendment 12-Nov-2010 Response to DR Letter

### 7. NAME & ADDRESS OF APPLICANT AND AGENT:

Applicant Name	Lannett Holdings
Address	9000 State Road Philadelphia, PA 19136
Representative Name	Ernest Sabo
Phone	215-333-9000 X 2277
Fax	215- 624-6126

### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proposed Proprietary Name: Morphine Sulfate Oral Solution
- b) Non-Proprietary Name (USAN): Morphine Sulfate Oral Solution
- c) Chem. Type/Submission Priority

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) RLD NDA 22195, Morphine sulfate (Roxane)

10. PHARMACOL. CATEGORY: opiate

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

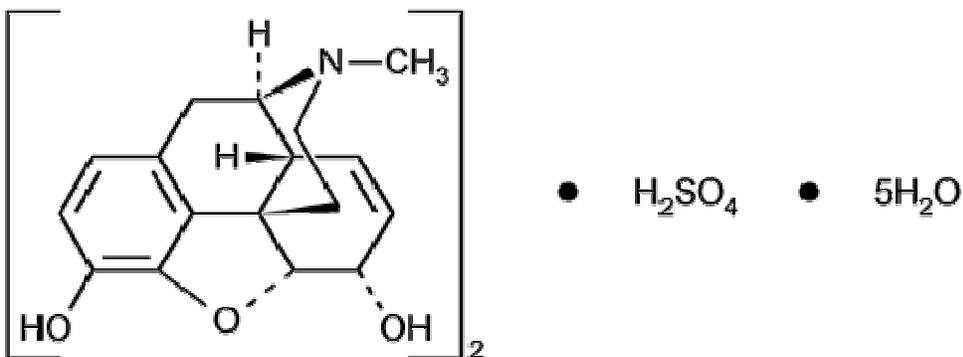
14. Rx/OTC DISPENSED:   X   Rx      OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): None

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

7,8-Didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol sulfate salt (2:1) pentahydrate

C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>10</sub>S (anhydrous), C<sub>34</sub>H<sub>50</sub>N<sub>2</sub>O<sub>15</sub>S (pentahydrate)



Molecular weight: 668.75 (anhydrous), 758.83 (pentahydrate)

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

Reviewed: **ACCEPTABLE**

DMF	Holder	DMF Subject	Review Date
		(b) (4)	IR letter: 04/30/2010 Review: 08/18/2010 IR letter: 8/30/2010. Def letter: 09/14/2010 Review: 12/01/2010 Def letter: 12/02/2010

**COMMENT:** DMF (b) (4) for morphine sulfate held by (b) (4) was found deficient and the holder notified on December 2, 2010.

DMFs for packaging materials were not reviewed since the applicant provided sufficient information to ensure that the materials of construction comply with applicable indirect food additive regulations. See discussion below under P.7.

**B. Other Documents:** PIND 105256

18. STATUS:

**CONSULTS/ CMC RELATED REVIEWS:**

Microbiology: Completed Sept 01, 2010. Recommended evaluating preservative effectiveness testing for ability to control *Burkholderi cepaci* DR sent 09/08/2010

EA waiver requested in 1.12.14. Granted **ACCEPTABLE**

Inspection: Complete. All sites acceptable except for the applicant's site (November 10, 2010) for release testing of drug product. OC recommends withhold for the over-all application.

## The Chemistry Review for NDA 201517

### I. Recommendations

#### 1. Recommendation and Conclusion on Approvability

The application is approvable with an expiration date of (b) (4) months, provided the applicant provides satisfactory response to the questions in the draft information requests and provided all sites receive a satisfactory inspection. At this time one site has an unacceptable inspection.

#### 2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. None

?

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### 1. Drug Substances

The drug substance, morphine sulfate, is a USP item and its properties and synthesis have been assessed many times to support many applications. It is manufactured by (b) (4) under DMF (b) (4)

As of March 10, 2010, this site was acceptable from a CGMP point of view. It is a white to off-white, fine crystalline powder and is soluble in water. A list of potential process impurities provided by the DMF holder is included in the application. The manufacturing information, specifications and stability data have been reviewed in the DMF and a DMF deficiency letter was filed in DARRTS on December 2, 2010. The applicant's specifications include all of the USP tests and additional tests for related substances and residual solvents. The applicant relies on validation information in the DMF for these additional tests and has also performed verification experiments to show that these tests are valid when performed by the applicant. All impurities, including the potentially genotoxic impurity, (b) (4) are well-controlled. The results of batch analysis (three batches) are satisfactory. The applicant relies on stability data from the drug substance manufacturer.

Since the drug product is a solution polymorphism is not an issue.

##### 2. Drug Product

- B. The drug product is an oral liquid so there is no issue regarding dissolution. The manufacturing process and controls performed by the contract manufacturer, Cody Laboratories, are straightforward. All of the excipients are compendial. The specifications are adequate to control the drug product, including tests for degradants. However a statistical analysis of the stability data support an expiration date of (b) (4) months based on an acceptance criterion of NLT (b) (4) for sodium benzoate, a preservative. Note that the applicant has proposed to test batches on stability for antimicrobial effective testing if the values of any preservative is between (b) (4). However this type of testing is not applicable to determining an expiration date. In addition a statistical analysis of the stability data support an expiration date of (b) (4) months based on an

acceptance criterion of NMT (b) (4) for a novel degradant eluting at RRT (b) (4)  
The degradant has been identified but not qualified.

**C. Description of How the Drug Product is Intended to be Used**

The drug product is intended to be used for the relief of moderate to severe acute and chronic pain in opioid-tolerant patients at a dose of 10 to 20 mg every four hours, as needed. The drug product may be used for chronic administration.

**D. Basis for Approvability or Not-Approval Recommendation**

If the questions in the draft IR are adequately addressed there is adequate CMC data to show that the drug product will perform as expected when stored in its original packaging for (b) (4) months at Controlled Room Temperature. However one manufacturing site has not been found to be acceptable.

**III. Administrative**

See DARRTS signatures and cc's

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/s/  
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ARTHUR B SHAW

12/07/2010

Satbility data only support (b) (4) expiration. Lannett's site unacceptable

PRASAD PERI

12/07/2010

I concur

# **Chemistry Review Cover Sheet**

**NDA 201517**

**Morphine Sulfate Oral Solution**

**Arthur B. Shaw, Ph.D.  
ONDQA/DPA3/DARP**

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## Chemistry Review Data Sheet

1. NDA 201517
2. REVIEW #1
3. REVIEW DATE: September 17, 2010
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Comment</u>
Original	26-Feb-2010	
Filing Letter	17-May-2010	Request for stability info, safety of excipients, (b) (4) and container-closure
IR Letter (e-mail)	20-May-2010	Request for sample dosing device
Amendment	23-Jun-2010	Response to 17-May-2010 letter (b) (4) and c-c
Amendment	01-Jul-2010	Response to 17-May-2010 letter Excipients
Amendment	09-Jul-2010	Response to 17-May-2010 letter Photostability data
IR Letter (e-mail)	12-Jul-2010	Request for info regarding preservatives
IR Letter (e-mail)	13-Jul-2010	Request for info regarding delivery volume
Amendment	14-Jul-2010	Response to 12-Jul-2010 IR
Amendment	15-Jul-2010	Response to 13-Jul-2010 IR
Amendment	20-Jul-2010	Response to 17-May-2010 letter Stability data

7. NAME & ADDRESS OF APPLICANT AND AGENT:

Applicant Name	Lannett Holdings
Address	9000 State Road Philadelphia, PA 19136
Representative Name	Ernest Sabo
Phone	215-333-9000 X 2277
Fax	215- 624-6126

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proposed Proprietary Name: Morphine Sulfate Oral Solution
- b) Non-Proprietary Name (USAN): Morphine Sulfate Oral Solution
- c) Chem. Type/Submission Priority
  - Chem. Type: 4
  - Submission Priority: S

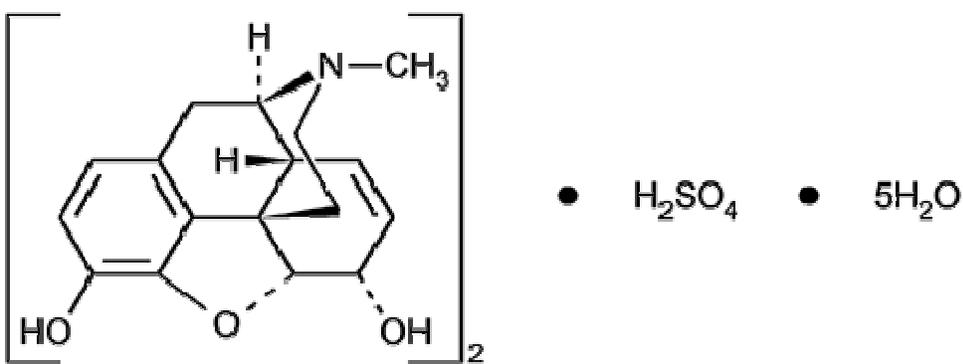
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: opiate

11. DOSAGE FORM: Solution  
 12. STRENGTH/POTENCY: 20 mg/mL  
 13. ROUTE OF ADMINISTRATION: Oral  
 14. Rx/OTC DISPENSED:   X   Rx        OTC  
 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): None  
 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

7,8-Didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol sulfate salt (2:1) pentahydrate

C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>10</sub>S (anhydrous), C<sub>34</sub>H<sub>50</sub>N<sub>2</sub>O<sub>15</sub>S (pentahydrate)



Molecular weight: 668.75 (anhydrous), 758.83 (pentahydrate)

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

Reviewed: **ACCEPTABLE**

DMF	Holder	DMF Subject	Review Date
		(b) (4)	IR letter: 04/30/2010 Review: 08/18/2010 IR letter: 8/30/2010. Def letter: 09/14/2010

DMFs for packaging materials were not reviewed since the applicant was asked to provide certification that the materials of construction comply with applicable indirect food additive regulations. See discussion below under P.7.

**B. Other Documents:** PIND 105256

18. STATUS:

**CONSULTS/ CMC RELATED REVIEWS:**

Microbiology: Completed Sept 01, 2010. Recommended evaluating preservative effectiveness testing for ability to control *Burkholderi cepaci* DR sent 09/08/2010

EA waiver requested in 1.12.14. Granted **ACCEPTABLE**

Inspection: Complete. All sites acceptable except for the applicant's site (March 10, 2010) for release testing of drug product. The EER is not final

## The Chemistry Review for NDA 201517

### I. Recommendations

#### 1. Recommendation and Conclusion on Approvability

The application is approvable with an expiration date of (b) (4) months, provided the applicant provides satisfactory response to the question in the draft information requests and provided all sites receive a satisfactory inspection. The stability data does not support the applicant's proposed expiration date of 18 months.

#### 2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. None

?

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### 1. Drug Substances

The drug substance, morphine sulfate, is a USP item and its properties and synthesis have been assessed many times to support many applications. It is manufactured by (b) (4) under DMF (b) (4)

As of March 10, 2010, this site was acceptable from a CGMP point of view. It is a white to off-white, fine crystalline powder and is soluble in water. A list of potential process impurities provided by the DMF holder is included in the application. The manufacturing information, specifications and stability data have been reviewed in the DMF and the DMF deficiency letter was filed in DARRTS on September 14, 2010. The applicant's specifications include all of the USP tests and additional tests for related substances and residual solvents. The applicant relies on validation information in the DMF for these additional tests and has also performed verification experiments to show that these tests are valid when performed by the applicant. All impurities, including the potentially genotoxic impurity, (b) (4) are well-controlled. The results of batch analysis (one batch) are satisfactory. The applicant relies on stability data from the drug substance manufacturer but has not provided a retest date. The applicant is being requested to provide testing from more batches of drug substance and data to justify their own retest date.

Since the drug product is a solution polymorphism is not an issue.

##### 2. Drug Product

The drug product is an oral liquid so there is no issue regarding dissolution. The manufacturing process and controls performed by the contract manufacturer, Cody Laboratories, are straightforward. All of the excipients are compendial. The specifications are adequate to control the drug product, including tests for degradants. However there are four issues of concern regarding the stability:

- a. Stability data for only two batches of drug product was provided in the three different package sizes.
- c. The sodium benzoate is close to its lower limit at (b) (4) months and falls below the lower limit at (b) (4) months for one batch in one packaging configuration.

d. An unqualified impurity (acceptance criterion NMT (b) (4)) increases steadily to (b) (4) at (b) (4) months for one batch and fails (b) (4) for another batch.

Therefore an expiration date of (b) (4) will be acceptable.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is intended to be used for the relief of moderate to severe acute and chronic pain in opioid-tolerant patients at a dose of 10 to 20 mg every four hours, as needed. The drug product may be used for chronic administration..

**C. Basis for Approvability or Not-Approval Recommendation**

If the questions in the draft IR are adequately addressed there is adequate CMC data to show that the drug product will perform as expected when stored in its original packaging for (b) (4) at controlled Room Temperature. However one manufacturing site has not been found to be acceptable.

**III. Administrative**

See DARRTS signatures and cc's

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/s/

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ARTHUR B SHAW

09/20/2010

Only 2 batches submitted for stability. Both failed at (b) (4) one for (b) (4) sodium benzoate failing and the other for an unknown impurity failing. (b) (4) data for sodium benzoate are near failure. Therefore only (b) (4) expiration date possible. One site not acceptable on inspection

PRASAD PERI

09/20/2010

I concur

**Initial Quality Assessment**  
**Division of Pre-Marketing Assessment I, Branch II**  
**Office of New Drug Quality Assessment**  
**Division of Anesthesia, Analgesia and Addiction Products**

OND Division:	Anesthesia, Analgesia and Addiction	
NDA:	201517	
Applicant:	Lannett Holdings, Inc.	
Stamp date:	March 1, 2010	
PDUFA Date:	January 1, 2011	
Trademark:	NA	
Established Name:	Morphine sulfate	
Dosage Form:	Oral solution, 20 mg/ml	
Route of Administration:	Oral	
Indication:	Treatment of acute and chronic moderate to severe pain	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>√</u>	_____
Comments for 74-Day Letter:	<u>√</u>	_____

## Summary, Critical Issues and Comments

### A. Summary

The application is filed as a 505(b)(2), non-priority NDA with 10-month review clock. Priority review was requested, but not granted, because of Roxane's approved product, 20 mg/ml. The referenced approved product is morphine sulfate oral solution 20 mg/5ml (NDA 22-195, Roxane). The applicant submitted a bridging relative bioavailability study versus the lower strength of the approved product, as per the Agency's request (see PIND 105,256).

Morphine sulfate concentrated solutions are used in hospice and palliative care when patients cannot ingest a large volume of solution without choking, and cannot receive IV morphine.

The solution is packaged in 30, 120 and 240 ml multi-dose bottles and dosed with a dosing (measuring) oral doser (syringe).

### B. Review, Comments and Recommendations

#### Drug Substance

#### Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

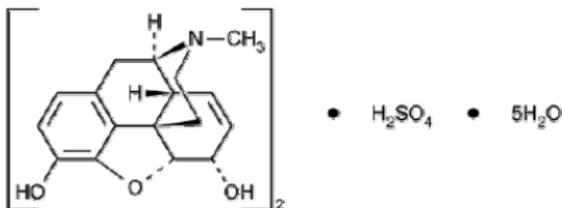
Chemical names:

- Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5,6)-, sulfate (2:1) (salt), pentahydrate
- 7,8-Didehydro-4,5 -epoxy-17-methylmorphinan-3,6 -diol sulfate (2:1) (salt), pentahydrate

CAS: 6211-15-0

MW: 758.83

Figure 1. Structure of morphine sulfate pentahydrate



The drug substance, morphine sulfate pentahydrate, is supplied by (b) (4). Description of the manufacturing processes and controls are referenced to the Drug Master File (DMF) (b) (4) submitted in May 2, 2008. Letter of Authorization (LoA) is included in the NDA. DMF (b) (4) has not been reviewed previously.

#### Characterization:

Morphine is extracted from morphine alkaloids and converted to morphine sulfate. Details of the drug substance manufacturing and characterization are referenced to DMF (b) (4). The applicant stated that morphine sulfate is produced as a (b) (4). The physical properties of morphine sulfate, e.g., solubility, morphic form, particle size distribution etc., should be assessed by the primary reviewer, for impact on manufacturability, quality and performance (e.g., solubility, bioavailability, stability) of the drug product. Since this is an oral solution, solid state properties of the API are not expected to impact drug product quality and performance.

#### Potential Impurities and degradation products:

The impurities listed in Fig. 2 are controlled by the Lannett HPLC (b) (4) which is the method in the DMF. (b) (4) is (b) (4) and a structural alert for mutagenicity and is controlled at (b) (4) according to the drug substance proposed specifications, in Table 1. The

proposed limit should be assessed in consultation with the Toxicology division, as it exceeds the limit of NMT (b) (4) total daily exposure for a structural alert.

Figure 2. Process-Related Impurities/Degradants

Structure	Chemical Name	Origin
(b) (4)		

**Drug Substance Specifications:**

Drug substance specifications are shown below, in Table 2. Methods Validation is provided for the non-compendial method for related substances. This method and its validation should be assessed as per ICH Q2B. The proposed limits for impurities/degradants should be assessed as per ICH Q3A(R2) and Q3B(R) in consultation with the Toxicology Division. Residual solvent limits (MeOH and EtOH) should be assessed for compliance with ICH Q3C.

Table 1. Drug Substance Specifications

Test	Specification	Justification of Specifications
Description	White crystalline powder	USP/NF
Identification	A) IR of sample corresponds to IR of the standard* B) Intense purple color that quickly changes to deep blue-violet color. C) A blue color is produced that changes to dark red-brown once nitric acid is added. D) Solution responds to tests for Sulfate <191>	USP/NF
Specific Rotation	Between $-107^{\circ}$ and $-109.5^{\circ}$ (Anhydrous basis)	USP/NF
Acidity	NMT 0.50 mL	USP/NF
Water	10.4% - 13.4%	USP/NF
Residue on Ignition	NMT 0.1 %	USP/NF
Chloride	No precipitate or turbidity is produced immediately.	USP/NF
Ammonium Salts	No odor of ammonium is perceptible.	USP/NF
Limit of Foreign Alkaloids	NLT 7.5 mL (1.5%)	USP/NF
Impurities (HPLC)		(b) (4)
Residual Solvents	NMT 0.3% (w/w) Methanol NMT 0.5% (w/w) Ethanol	ICH
Assay (HPLC)	98.0% – 102.0%, anhydrous basis	USP/NF

**Batch analysis:**

Batch analysis results from (b) (4) and Cody Labs (the drug product manufacturer) are included in M3, for batches B1206-070302 and B1206-080801 (used for manufacture of the NDA drug product batch). However, related substances analysis is reported only for the latter lot. (b) (4) levels are reported as (b) (4). Note that LOD/LOQ for (b) (4) have not been included in the (b) (4) method for related substances. Total impurities are reported as (b) (4) for the same batch (B1206-080801).

**Reference standard:**

No Certificates of Analysis for the working reference standards have been included; these were referenced to the DMF.

**Drug substance Stability:**

Stability data and retest date have been referenced to the DMF.

**Drug product**

The drug product formulation differs only with respect to (b) (4) in comparison to the approved product. No novel excipients are used in the formulation.

Table 2. Quantitative composition of morphine sulfate oral solution.

Ingredient	mg/mL	% (w/w)*	Functionality
Morphine Sulfate, USP	20.0	(b) (4)	Active ingredient
Propylparaben, NF		(b) (4)	
Methylparaben, NF		(b) (4)	
Sodium Benzoate, NF		(b) (4)	
Sorbitol (b) (4) USP		(b) (4)	
Glycerin, USP		(b) (4)	
Citric Acid Anhydrous, USP		(b) (4)	
Edetate Disodium Dihydrate, USP		(b) (4)	
Purified Water, USP		(b) (4)	

The applicant estimated that the excipients are within the IIG limits for orally administered products:

Table 3a. Comparison of the amounts of excipients to the IIG limit

Ingredient	% (w/w)	IIG Limit
Propylparaben, NF	(b) (4)	10.00%
Methylparaben, NF	(b) (4)	13.00%
Sodium Benzoate, NF	(b) (4)	1.08%
Sorbitol (b) (4) USP	(b) (4)	90.00%
Glycerin, USP	(b) (4)	95.00%
Citric Acid Anhydrous, USP	(b) (4)	1.50%
Edetate Disodium Dihydrate, USP	(b) (4)	0.50%
Purified Water, USP	(b) (4)	NA

Table 3b. Composition of the approved Roxane 20mg/ml oral solution (NDA 22-195)

This table was copied from the CMC review of NDA 22-195 by J. Pinto.

<u>Ingredients</u>	<u>Purpose</u>	<u>Quality Standard</u>	<u>Amount (mg/mL)</u>	<u>Amount (%)</u>
Morphine Sulfate, USP	Active Ingredient	(b) (4)	20.0	2.0%
Sorbitol (b) (4)	(b) (4)	USP	(b) (4)	(b) (4)
Glycerin, USP	(b) (4)	USP	(b) (4)	(b) (4)
Citric Acid, USP (b) (4)	(b) (4)	USP	(b) (4)	(b) (4)
Sodium Benzoate, NF (b) (4)	(b) (4)	NF	(b) (4)	(b) (4)
Disodium Edetate, USP	(b) (4)	USP	(b) (4)	(b) (4)
Water, Purified, USP	(b) (4)	USP	(b) (4)	(b) (4)

**Formulation and manufacturing process development:**

The applicant stated that chemical similarity of this product to other existing products e.g., the (b) (4) and Roxanne Labs products was the rationale for their formulation. Information on the density and viscosity of their oral solution has not been discussed. In addition the applicant claimed that the container closure attributes will be the same as the approved product; and that the containers meet the USP test <661> and USP <671> parameters for light transmission, high density polyethylene, and physico-chemical tests for plastics.

Overages: Not planned.

**Manufacturing Process:**

The manufacturing process consists of (b) (4) Batch records have been included in the NDA. (b) (4)

Cody Labs, WY is the drug product manufacturer.

**Manufacturing Process Flow Chart:**

A schematic was provided, but details with respect to manufacturing operations and process controls have not been included. These should be assessed from batch records. In-process controls are

(b) (4)

Table 4. Batch Formula

Batch Size: (b) (4)

Ingredient	mg/mL	% (w/w)*	Grams per Batch	Functionality
Morphine Sulfate, USP	20.0	(b) (4)	(b) (4)	Active ingredient
Propylparaben, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Methylparaben, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Benzoate, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sorbitol (b) (4) USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Glycerin, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Citric Acid Anhydrous, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Edetate Disodium Dihydrate, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Purified Water, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)

**NDA Registration batches:**

The applicant submitted one NDA batch, lot #08801017, filled in 30 ml, 120 ml and 240 ml bottles with 12-month stability data under normal storage and 6-month under accelerated storage.

**Batch analysis data:**

All batches met specifications; (b) (4) is reported up to levels (b) (4) and total impurities up to (b) (4) at release. Several impurities are reported by RRTs on stability, and controlled as “unidentified impurities”, below (b) (4). Note that the applicant proposed a wide specification for total impurities (b) (4) which should be assessed upon review.

The analytical methods for the drug product do not present novel elements. For the HPLC assay and impurities method, validation should be assessed, to confirm the applicant’s conclusion that the method resolves impurities of similar structure and chemical properties. Justification of specifications should be assessed as per the ICH Q3B(R) guidelines in consultation with the Toxicology Division.

**Table 5. Drug Product Specifications:**

Test	Specification	Justification of Specifications
(b) (4)		

**Container Closure:**

The applicant provided the packaging components of the HDPE bottles, caps and oral doser and references to their corresponding DMFs. Letters of Authorization to the packaging DMFs have been included in the

NDA. The applicant stated that the proposed container/closure system complies with USP<661> and <671>. In addition, they stated that “the container/closure is same with that of the approved product” but did not provide comparisons of the packaging components. The applicant did not submit any justification for leachables/extractables evaluation and compliance of the packaging components to appropriate CFR regulations for indirect food additives.

**Stability:**

Stability testing of the three fills (30 ml, 120 ml and 240 ml) of the NDA batch is performed under standard ICH conditions at 25°C/60% RH, and 40°C/75% RH. Stability protocols and post-approval stability commitment were provided in the NDA. The proposed expiration dating is 18 months. Statistical analysis evaluation has not been performed by the applicant. Photostability testing has not been reported. In addition, in-use stability data and in-use shelf life has not been provided and should be requested.

As discussed previously, several degradants are monitored by RRT on stability and controlled as “unidentified impurities” at (b)(4). The applicant submitted a report for investigation of the structure for a degradant at RRT (b)(4), which was concluded not to be a structural alert, based on LC-MS and MS-MS methods, and proposed to be controlled at (b)(4).

Proposed structures:



The applicant’s assessment of unidentified impurities and proposed limits should be evaluated upon review.

**Labeling**

Labeling information of the container labels and packaging insert should be assessed with respect to CMC related information. SPL labeling has not been included and should be requested from the applicant.

**C. Critical issues for review and recommendation**

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. The drug substance DMF (b)(4) has not been reviewed. The DMF holder should be notified that (b)(4) is a structural alert and controlled accordingly.
2. Limits of impurities and related substances in the drug substance as per ICH Q3A(R), in consultation with the Toxicology Division and limits of residual solvents for compliance with ICH Q3C.
3. The suitability of the compendial specifications of excipients for drug product manufacturability, quality and performance should be assessed.

4. Details of the manufacturing process of the drug product, (b) (4)
5. Drug product specifications, e.g., impurity/degradant limits as per ICH Q3B(R), (b) (4) limits as a structural alert, and unidentified impurity limits, in consultation with the Toxicology Division. The applicant proposed that the solution can be dosed every four hours.
6. The suitability of the HPLC method for related substances to detect (b) (4) and unidentified impurities.
7. The proposed morphine sulfate oral solution expiration dating of 18 months. The expiry date was proposed based on 12-month real time data on one batch packaged in three different size bottles.
8. No photostability testing of the drug product has been reported and should be requested. Morphine is photosensitive.
9. In-use stability data, to support in-use shelf life and conditions for the multi-dose presentations.
10. No justification for extractables/leachables has been provided. Compliance of all packaging components to appropriate CFR regulations for indirect food additives, should be requested.
11. The applicant requested a “biowaiver” for “human clinical efficacy and safety trials other than the relative bioavailability study performed” (M1.12.13). However, this is a moot point since they have performed a relative bioavailability study versus the lower strength of the approved product.
12. Labeling in Structured Product Labeling (SPL) format has not been provided and should be requested.

**D. Comments for 74-day Letter:**

1. Provide in-use stability data, to support in-use shelf life and conditions for the multi-dose presentations.
2. Provide a photostability study for the drug product, as per ICH Q1B.
3. Provide adequate justification and evaluation of leachables/extractables of the container/closure system. To support compatibility of your drug product with the proposed container/closure system, provide information on the compliance of all packaging components to appropriate CFRs for indirect food additives.

**E. Recommendation for fileability:** The NDA is fileable based on pre-NDA agreements and one NDA batch, with 12-month long term/6-month accelerated stability data for drug product packaged in the three proposed commercial presentations. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

**Recommendation for Team Review:** The NDA is not recommended for a team review.

**Consults:**

1. **Toxicology** (to be determined and initiated by the primary reviewer)
2. **Biopharmaceutics, ONDQA** (submitted 4/14/10; Angelica Dorantes was notified; However, Clinical Pharmacology will perform review of the relative bioavailability study.)

Microbiology consult was not deemed necessary. However, it may be initiated by the primary reviewer after evaluation of the firm's specifications, and supporting data.

Danae D. Christodoulou, Ph.D.  
CMC Lead

4/21/2010  
Date

Prasad Peri, Ph.D.  
Branch II Chief (Acting), ONDQA

4/25/2010  
Date

NDA Number: 201517

Supplement Number and Type:

Established/Proper Name:

Morphine sulfate oral solution

Applicant: Lannett  
Holdings Inc.

Letter Date: 02/25/2010

Stamp Date: 3/01/2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		PIND 105,256 July 1, 2009

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		<div style="background-color: gray; width: 100%; height: 20px; margin-bottom: 5px;"></div> <div style="text-align: right;">(b) (4)</div>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		Clarifications and communications with OC.
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		Clarifications and communications with OC.

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	
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\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		Relative BE study has been performed
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	NA (Solution Oral Dosage Form)

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
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(b) (4)



<b>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>			Based on pre-NDA agreements and sufficient data
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	X		Describe filing issues here or on additional sheets
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		See p. 9, above

*{See appended electronic signature page}*

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Name of

PAL: Danae Christodoulou 4/21/10  
 Division of Pre-Marketing Assessment I  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

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Name of

Branch Chief (Acting): Prasad Peri  
 Division of Pre-Marketing Assessment I  
 Office of New Drug Quality Assessment

Date

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

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

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/s/

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DANAE D CHRISTODOULOU  
04/26/2010  
Initial Quality Assessment

PRASAD PERI  
04/26/2010  
I concur