CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-195 & 22-207

CHEMISTRY REVIEW(S)

Chemistry Review Cover Sheet

NDA 22207
Morphine Sulfate Tablets
Arthur B. Shaw, Ph.D.
ONDQA/DPA1/DAARP

Table of Contents

Chemistry Review Data Sheet

1. NDA 22207
2. REVIEW #3

3. REVIEW DATE: March 13, 2008

4. REVIEWER: Arthur B. Shaw, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	Comment
Original	07-Jun-2007	None
Amendment BC	30-Aug-2007	Response to IR Letter
Amendment BC	07-Sep-2007	Response to DR letter to NDA 22195 for morphine sulfate oral solution.
Amendment	28-Jan-2008	Response to questions in 20-Dec-2008 DR Letter

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Amendment	28-Feb-2008	Response to questions in 14-Feb-2008 DR Letter
Amendment	06-Mar-2008	Update stability data
Amendment (via e-mail)	13-Mar-2008	Commitment to submit MV package for b(4)

FDA Documents	Document Date	Comment
Chemistry DR Letter to NDA 22195	05-Jul-2007	Request info about MV for DP assay common to both NDAs
Chemist's Initial Quality Assessment	10-Aug-2007	Acceptable for filing. Additional info requested
Chemistry IR Letter #1	16-Aug-2007	Request info in IQA
Chem Review #1	18-Dec-2007	Approvable some issues regarding MV and stability
DR Letter	20-Dec-2007	Questions from CR#1
Chem Review #2	12-Feb-2008	Approvable some issues regarding MV and stability
DR Letter	14-Feb-2008	Questions from CR21
Memo to File	04-Mar-2008	Comments on Drug Listing Data Elements (DLDE)

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

Note that all the documentation is submitted by "Boehringer Ingelheim Roxane Inc." (BIRI). The procedures, etc. have "BIRI" numbers.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Morphine sulfate

b) Non-Proprietary Name (USAN): Morphine sulfate
c) Code Name/# None provided
d) Chem. Type/Submission Priority
- Chem. Type: 7
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Opiate

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 15 and 30 mg

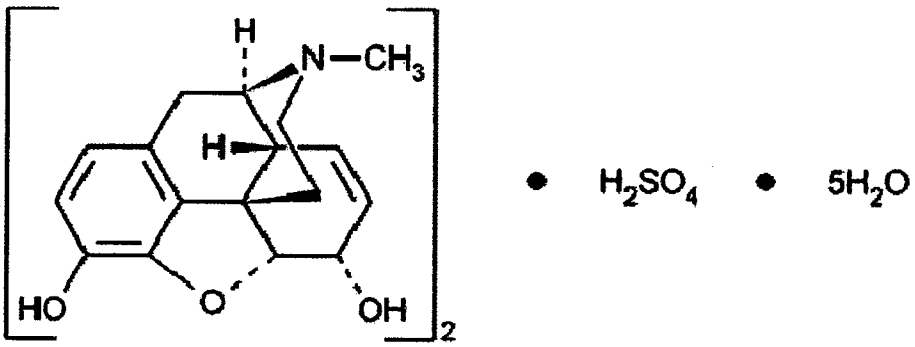
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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

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



$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$
MW = 758.33
Anhydrous MW = 668.77

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:
Reviewed: **ACCEPTABLE**

DMF	Holder	DMF Subject	LOA Date	Review Date
			27-Feb-2007	19-Nov-2007
			15-May-2007	07-Dec-2007

b(4)

Not Reviewed since there is sufficient information in the NDA See Section P Container Closure below

DMF	Holder	DMF Subject	Item Referenced

b(4)

b(4)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22195	Morphine Sulfate Oral Solution (Pending)
IND	75041	Morphine Sulfate Tablets and Oral Solution

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS: Inspections completed and all sites satisfactory (05-Mar-2008) See EER at the end of the review

EA waiver requested in 1.12.14, Granted.

The Chemistry Review for NDA 22-207

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval from a CMC point of view with an 18 month expiration date.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

The applicant will provide a methods validation report for the measurement of [redacted] in the first Annual Report. b(4)

II. Summary of Chemistry Assessments

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

1. Drug Substance

The drug substance is a USP item and its properties and synthesis have been assessed many times to support many applications. It is provided by [redacted] manufacturers, [redacted]. The DMFs [redacted], respectively, have been recently reviewed and found acceptable. The suppliers and the applicant have developed tests for impurities in the drug substance beyond the requirements in the USP. The acceptance criteria for these impurities are acceptable from a chemistry point of view. b(4)

Since the drug product is manufactured by [redacted] the applicant was asked to provide information about potential polymorphs. There are [redacted] polymorphs, [redacted] corresponding to a hydration state of the molecule. Since only the pentahydrate is used to manufacture the drug product polymorphism is not an issue. b(4)

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2. Drug Product

The drug product is provided as tablets for oral administration in 15 and 30 mg tablets, packaged in ——bottles and blister packages. The tablets are manufactured ——— using compendial excipients. Since this drug product has been sold for many years without an NDA, there is a long history of its manufacture. Therefore there is no pharmaceutical development report. The specifications include a dissolution test and are adequate for their intended use. The applicant has provided historical stability data for batches stored for up to 36 months. They have also provided primary stability data for up to eighteen months and requested an expiration date of months. The stability-limiting factor is the level of —— formed on storage. Review of the toxicology information by the pharmacology/toxicology review team supports an acceptance criterion of NMT — Using this value as the upper limit the recommended expiration date is eighteen months.

b(4)

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

The drug is intended to be used for the relief of moderate to severe acute and chronic pain, with a recommended starting dose of 15 to 30 mg every four hours.

C. Basis for Approvability or Not-Approval Recommendation

The drug may be approved because the CMC review shows that the drug can be manufactured consistently to deliver the labeled amount of drug with each dose.

III. Administrative

See DFS signatures and cc's

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6 Trade Secret / Confidential b(4)

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Arthur B. Shaw
3/13/2008 05:12:48 PM
CHEMIST

Ali Al-Hakim
3/13/2008 05:28:25 PM
CHEMIST

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 05-MAR-2008

TO: Lisa Basham, Project Manager, DAARP and N 22-195
File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Review of Drug Listing Data Elements (DLDE) Table for Morphine Sulfate Oral Solution, NDA 22-195

EVALUATION: The DLDE tables for the 20 mg/5 mL and the 10 mg/5 mL strengths were reviewed in the SPL and the following should be addressed by the applicant for both:

- *Add the appropriate entry for the "DEA Schedule" element.*
- *Change "edetate disodium."*
- *Change "FD&C Green No. 3 (fast green)."* b(4)
- *Revise "water."*
- *Revise "sorbitol."*

For the 10 mg/5 mL strength only:

- *Revise the packaging entry to specify the multilevel packaging used for the unit dose cup presentations, i.e., ten unit dose cups per shelf pack.*

ACTION ITEM: It is requested that the PM forward the above six comments (in *italics*) to the firm to direct their revision of the DLDE tables in the SPL.

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
DAARP/LBasham
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/DChristodoulou
ONDQA/DIV 1/AAl-Hakim

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/s/

Craig Bertha
3/5/2008 08:06:36 AM
CHEMIST

Ali Al-Hakim
3/5/2008 06:02:27 PM
CHEMIST

REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 4, 2008

From: Arthur B. Shaw, Ph.D., Chemist, Division of Pre-Marketing Assessment 1, Office of New Drug Quality Assessment

To: Lisa Basham, Project Manager, Division of Anesthesia, Analgesia, and Rheumatology Products

Subject: Review of Drug Listing Data elements (DLDE) for Morphine Sulfate Tablets, NDA 22207

The following tables are based on the Drug Listing Data Elements (DLDE) submitted in the Structured Product Labeling (SPL) on January 28, 2008.

Product Information				
Product Code	0054-0235			Assessment
Dosage Form	TABLET			**Acceptable**
Route Of Administration	ORAL			**Acceptable**
DEA Schedule				*Should be CII*
Ingredients				
Name (Active Moiety)	Type	Strength		
morphine sulfate (morphine)	Active	15 MILLIGRAM In 1 TABLET		**Acceptable**
colloidal silicon dioxide	Inactive			**Acceptable**
corn starch	Inactive			**Acceptable**
microcrystalline cellulose	Inactive			**Acceptable**
pregelatinized starch	Inactive			**Acceptable**
Stearic acid	Inactive			**Acceptable**
Imprint Information				
Color	WHITE			**Acceptable**
Shape	ROUND			**Acceptable**
Imprint Code	54 733			**Acceptable**
Size	1mm			*Should be 6mm*
Score	2			**Acceptable**
Symbol	FALSE			**Acceptable**
Coating	FALSE			**Acceptable**
Packaging				
#	NDC	Package Description	Multilevel Packaging	
1	0054-0235-25	100 TABLET In 1 BOTTLE	None	**Acceptable**
2	0054-0235-24	25 TABLET In 1 BLISTER PACK	None	*Should be multi-level*

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Product Information				
Product Code	0054-0236			Assessment
Dosage Form	TABLET			**Acceptable**
Route Of Administration	ORAL			**Acceptable**
DEA Schedule				*Should be CII*
Ingredients				
Name (Active Moiety)	Type	Strength		
morphine sulfate (morphine)	Active	30 MILLIGRAM In 1 TABLET		**Acceptable**
colloidal silicon dioxide	Inactive			**Acceptable**
corn starch	Inactive			**Acceptable**
microcrystalline cellulose	Inactive			**Acceptable**
pregelatinized starch	Inactive			**Acceptable**
Stearic acid	Inactive			**Acceptable**
Imprint Information				
Color	WHITE			**Acceptable**
Shape	ROUND			**Acceptable**
Imprint Code	54 262			**Acceptable**
Size	1mm			*Should be 8mm*
Score	2			**Acceptable**
Symbol	FALSE			**Acceptable**
Coating	FALSE			**Acceptable**
Packaging				
#	NDC	Package Description	Multilevel Packaging	
1	0054-0236-25	100 TABLET In 1 BOTTLE	None	**Acceptable**
2	0054-0236-24	25 TABLET In 1 BLISTER PACK	None	*Should be multi-level*

Discussion

DEA Code: This product is Schedule II.
COMMENT: Enter the Code CII for the DEA Code for both strengths.

Size: The lengths of the tablets are, according to the Specification in SectionP.5, [redacted] (15 mg tablet); [redacted] (30 mg tablet). These convert to [redacted], respectively. b(4)
COMMENT: Change the sizes [redacted] (15 mg Tablet) [redacted] (30 mg Tablet)

Packaging: The blisters are packaged as "4 cards Per Shipper." (Label submitted 28-Jan-2008, How Supplied section). Therefore this is "multilevel packaging"
COMMENT: Change the Packaging Section as follows
15 mg Tablets b(4)

Packaging

[redacted]

30 mg Tablets b(4)

[redacted]

[redacted]

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Comments to be Communicated to the Applicant

1. Enter the Code CII for the DEA Code for both strengths
2. Change the sizes (15 mg Tablet) (30 mg Tablet)
3. Change the Packaging Section as follows

b(4)

15 mg Tablets

b(4)

30 mg Tablets

b(4)

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/s/

Arthur B. Shaw
3/4/2008 03:25:27 PM
CHEMIST

Ali Al-Hakim
3/4/2008 05:34:39 PM
CHEMIST

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 26-FEB-2008

TO: N 22-195 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Minor corrections to methods used for determination of related substances in the morphine sulfate drug substance (amendment dated 22-FEB-2008)

EVALUATION: The methods used for determining the levels of related substances in the morphine sulfate form [redacted] included an error in the calculation of the relative retention time of the [redacted] impurity. This has been corrected. In addition, the response factor for the [redacted] related substance has been corrected from the originally reported value of 1.9 to 2.0. These changes are minor in nature and do not change the earlier conclusion that the related substances methods are suitably validated.

b(4)

CONCLUSION/RECOMMENDATION/ACTION ITEM: NAI

Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:
Orig. NDA 22-195
C.Bertha/ONDQA//Reviewer/2/26/08
AAl-Hakim/ONDQA/Branch Chief
DChristodoulou/ONDQA/PAL
LBasham/DAARP/Regulatory PM
AShaw/ONDQA/Reviewer

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/s/

Craig Bertha
3/3/2008 12:32:41 PM
CHEMIST

Ali Al-Hakim
3/3/2008 12:49:35 PM
CHEMIST

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11-FEB-2008

TO: N 22-195 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Review of CMC-related information for Dosing Cup requested by DAARP clinicians for inclusion in the packaging with the bottled drug product (amendments dated 29-JAN-2008, and 07-FEB-2008)

BACKGROUND: The applicant claims in the 29-JAN-2008, amendment that DAARP requested that they provide a "dosage mechanism with the packaging of [their] multi-use bottles (120 mL and 500 mL bottles." Information regarding the proposed dosing cup was included in the two amendments listed above.

EVALUATION: The dimensions, drawings, and specification of the dosing cup are provided in attachment A. As a result of the request, the applicant proposes to include a dosing cup with the two sizes of the bottled product. The dosing cup will be prepared from

b(4)

The dosing cup will have limited contact with the formulation, thus, the potential for leachables to be extracted from the dosing cup and ingested, is low. Conformance with the food contact regulations, for the used to manufacture the dosing cup, will suffice in allaying any leachable/compatibility concerns.[1]

The applicant was asked to submit statements regarding the compliance of the with the appropriate regulations and these were included in the 07-FEB-2008, amendment. b(4)
will comply with 21 CFR 177.1520(c)3.1a and that the finished is restricted to food contact under the conditions of B-H in table 2 of 21

[1] Recall that the Agency packaging guidance states that for the container closure system "for liquid-based oral drug products which the patient will continue to take for an extended period (i.e., months or years (chronic drug regimen)), a material of construction that meets the requirements for indirect food additives will be considered safe — on that basis alone — only if the patient's exposure to extractables can be expected to be no greater than the exposure through foods."

CFR 176.170(c). Furthermore, the components used to prepare the ~~~ are said to be permitted for use in food-contact packaging articles covered under 21 CFR 170-189. b(4)

The 21 CFR 176.170(c) regulation is primarily for components of paper and paperboard that contact both aqueous and fatty foods. In this case the component in question is not part of a paper or paperboard component of a package. However, the extractables tests covered under subsection (c), which considers both the composition and processing conditions for packaged food, should still be analogously applicable to provide assurance of safety, and are tests cross-referenced by 21 CFR 177.1520 for testing of polyolefins for food packaging applicability.

The ~~~ is stated to comply with the extraction limits such that it can be used with beverages containing more than 8% alcohol and with acidic aqueous products, simultaneously under various "conditions of use" pertinent to processing to reduce microbial load (i.e., boiling water sterilization, hot filled or pasteurized above 150°F, etc.). These are the types of food most appropriate for consideration based on the formulation of the drug product of N22-195. Thus, it is a reasonable to assume that a patient's exposure to leachables from use of the dosing cup would not be greater than the exposure to leachables from the types of food sanctioned for use with this same material and as processed by the various "conditions of use" described in 21 CFR 176.170(c). b(4)

The specification for the dosing cups includes testing and acceptance criteria for delivery. The clinical Division Deputy Directory, Sharon Hertz, MD, was asked about the clinical acceptability of the delivery requirements outlined in the specification for the dosing cup in an electronic mail message dated 01-FEB-2008. Dr. Hertz concluded in an electronic mail message of 05-FEB-2008, that the current acceptance criteria would be adequate for the current formulation. She did indicate that there might be other considerations that would need to be made (regarding a dosing cup) if the applicant were to seek approval for a higher concentration formulation.

CONCLUSION/RECOMMENDATION/ACTION ITEM: The dosing cup proposed is acceptable from the CMC perspective.

Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:
Orig. NDA 22-195
C.Bertha/ONDQA//Reviewer/2/11/08
AAl-Hakim/ONDQA/Branch Chief_____
DChristodoulou/ONDQA/PAL
LBasham/DAARP/Regulatory PM

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/s/

Craig Bertha
2/25/2008 06:06:20 AM
CHEMIST

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10-JAN-2008

TO: N 22-195 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Stability update provided in 20-DEC-2007, amendment to NDA 22-195

SUMMARY: The applicant has provided a stability update for the primary stability batches providing up to 12 months of data with long term storage under conditions of 25°C/60%RH. Recall from chemistry review #1 that the 36 month expiration dating periods proposed for both strengths were found to be acceptable, primarily based on historical batch data for old samples of this marketed but unapproved drug product. The provision of the 12 month long term stability data in attachment A of the 20-DEC-2007, amendment does not alter the previous determination that a 36 month expiry was acceptable. The new data do not provide evidence of any increase in observed stability trends when compared to the data already reviewed.

CONCLUSION/RECOMMENDATION/ACTION ITEM: NAI

Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:
Orig. NDA 22-195
C.Bertha/ONDQA//Reviewer/1/10/08
AAl-Hakim/ONDQA/Branch Chief_____
DChristodoulou/ONDQA/PAL
LBasham/DAARP/Regulatory PM

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/s/

Craig Bertha
1/10/2008 05:35:31 AM
CHEMIST

Ali Al-Hakim
1/11/2008 01:26:53 PM
CHEMIST

4 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

CHEMISTRY REVIEW

NDA 22-195

Morphine Sulfate Oral Solution

Roxane Laboratories, Inc.

Craig M. Bertha, Ph.D.
Division I of ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-195

2. REVIEW #:2

3. REVIEW DATE: 03-DEC-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	16-MAY-2007 (assigned 29-MAY-2007)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	07-SEP-2007 (assigned 19-SEP-2007)
Amendment	26-SEP-2007 (assigned 09-OCT-2007)
Amendment	07-NOV-2007 (assigned 03-DEC-2007)

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc.

Address: 1809 Wilson Road

Representative: Elizabeth A. Ernst, Associate Director

Telephone: 614-272-4785

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: none
b) Non-Proprietary Name (USAN): morphine sulfate

c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2); Avinza extended release capsules, Ligand Pharmaceuticals, NDA 21-260; The current application N22-195 is for a *marketed but unapproved* product.[1]

10. PHARMACOL. CATEGORY: analgesic

11. DOSAGE FORM: solution

12. STRENGTH/POTENCY: 10 and 20 mg/5 mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: ___X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____**SPOTS product – Form Completed**

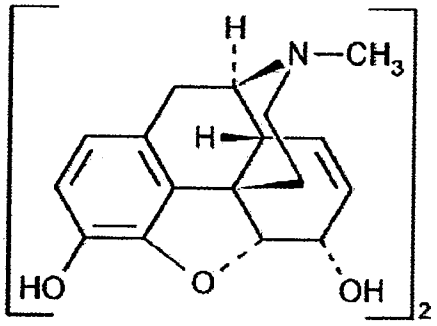
___X___Not a SPOTS product

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

Morphine Sulfate has the chemical name Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-methyl, (5α, 6α)-, sulfate (2:1) (salt) pentahydrate and the structural formula:

[1] **Roxane indicates in the cover letter to the application that they have "marketed the formulation since the 1980's** under the brand name Morphine Sulfate (Immediate Release) **Oral Solution, 10 mg/5 mL and 20 mg/5 mL."**

Chemistry Review Data Sheet



• H_2SO_4 • $5H_2O$

$(C_{17}H_{19}NO_3)_2\ H_2SO_4\ 5H_2O$ MW = 758.85 g/mole (w/o water of hydration 668.77; morphine free base MW is 285.33)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
	2			1	Adequate	05-JUN-2007	
	2			1	Adequate	05-JUN-2007	
	3			1	Adequate	07-JUN-2007 06-SEP-2007 29-NOV-2007	
	3			1	Adequate	11-JUN-2007 18-SEP-2007	
	3			3	Adequate	12-JAN-2005	
	3			4	N/A		Cap performance evaluated via stability data, no direct product contact
	3			3	Adequate	07-JAN-2004	Cap has no direct contact with formulation (see liner review, DMF
	3			1	Adequate	12-JUN-2007	

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	75,041	Roxane	IND for both tablet and oral solution dosage forms of morphine sulfate

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A see P.8.3 evaluation
EES	cGMP compliance/PAI	04-JUN-2007	Pending	
Pharm/Tox	Limit of NMT — in drug product (structural alert containing compound). Qualification of drug substance impurities.	By electronic mail to D. Mellon, Ph.D. on 06-JUN-2007	Pending	
Biopharm	N/A			N/A
DMETS/DDMAC	Labeling			DAARP PM forwarded on 16-AUG-2007.
Methods Validation				N/A, see p. 9
EA				Categorical exclusion requested, see p. 46 of CR#1.
Microbiology	Microbial limits, preservative effectiveness testing, and preservative assay acceptance criteria	05-JUN-2007	Pending	

b(4)

The Chemistry Review for NDA 22-195

The Executive Summary

The application N22-195 is filed under 505b(2) of the act and is for support of a marketed but unapproved drug product.

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

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

The drug product is morphine sulfate oral solution and is to be marketed in two strengths, 10 mg/5 mL and 20 mg/5 mL. The low strength will be packaged in — bottles with child resistant closures containing 100 and 500 mL of formulation or in 30 mL — unit dose cups containing either 5 or 10 mL of formulation. The high strength will only be packaged in the 100 and 500 mL — bottles with child resistant closures. The drug substance morphine sulfate pentahydrate, is an opioid analgesic already approved for oral usage. The crystalline form of the drug substance is of limited consequence as the drug product formulation is a solution. The applicant provides additional tests with acceptance criteria for the purity of the drug substance above the compendial monograph requirements. Most drug substance-related information is contained in — drug master files from the proposed suppliers. b(4)

The drug product formulation contains compendial excipients already in use with other oral drug products and also contains FDA certified colorant FD&C Green No. 3. The low strength formulation contains only sodium benzoate — but the high strength also includes — methylparaben and propylparaben. Both formulations include edetate disodium — b(4)

As this drug is a marketed unapproved drug, there is no noted difference between the drug product used in the biostudy and that which is to be manufactured for commercial distribution under the approved application.

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

The dosage recommended in the label is 10 to 20 mg every four hours (for acute or chronic pain). The product formulations have concentrations of 10 mg/5mL and 20 mg/5mL. Thus the 100 mL containers contain 20 doses and the 500 mL containers contain 100 doses. There are also unit dose containers of the 10 mg/5 mL strength for both a 10 and 20 mg dose. There is no additional preparation necessary prior to dose administration.

The application provides data that support a **36 month expiration dating period** for all packaging types and for both strengths.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/12/03/07
AAlHakim/ONDQA/DIV I//Branch II/Branch Chief_____

C. CC Block

LBasham/DAARP/Regulatory PM
AAlHakim/ONDQA/DIV I/Branch II/Branch Chief
SGoldie/ONDQA/DIV I/Regulatory PM

17 Page(s) Withheld

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_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Craig Bertha
12/3/2007 10:28:34 AM
CHEMIST

Blair Fraser
12/3/2007 10:35:52 AM
CHEMIST

Chemistry Review Cover Sheet

NDA 22207
Morphine Sulfate Tablets
Arthur B. Shaw, Ph.D.
ONDQA/DPA1/DAARP

Table of Contents

Chemistry Review Data Sheet

1. NDA 22207
2. REVIEW #2
3. REVIEW DATE: February 12, 2008
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date	Comment
Original	07-Jun-2007	None
Amendment BC	30-Aug-2007	Response to IR Letter
Amendment BC	07-Sep-2007	Response to DR letter to NDA 22195 for morphine sulfate oral solution.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Amendment	28-Jan-2008	Response to questions in 20-Dec-2008 DR Letter

FDA Documents	Document Date	Comment
Chemistry DR Letter to NDA 22195	05-Jul-2007	Request info about MV for DP assay common to both NDAs
Chemist's Initial Quality Assessment	10-Aug-2007	Acceptable for filing. Additional info requested
Chemistry IR Letter #1	16-Aug-2007	Request info in IQA
Chem Review #1	18-Dec-2007	Approvable some issues regarding MV and stability
DR Letter	20-Dec-2008	Questions from CR#1

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

Note that all the documentation is submitted by "Boehringer Ingelheim Roxane Inc." (BIRI). The procedures, etc. have "BIRI" numbers.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Morphine sulfate
b) Non-Proprietary Name (USAN): Morphine sulfate
c) Code Name/# None provided
d) Chem. Type/Submission Priority
   - Chem. Type: 7

- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Opiate

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 15 and 30 mg

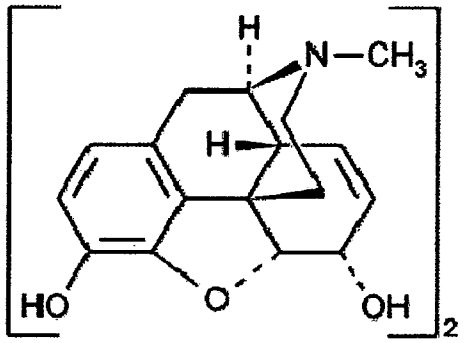
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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

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



• H_2SO_4 • $5H_2O$

$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

MW = 758.33

Anhydrous MW = 668.77

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Reviewed: **ACCEPTABLE**

DMF	Holder	DMF Subject	LOA Date	Review Date
			27-Feb-2007	19-Nov-2007
			15-May-2007	07-Dec-2007

b(4)

Not Reviewed since there is sufficient information in the NDA See Section P Container Closure below

DMF	Holder	DMF Subject	Item Referenced

b(4)

b(4)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22195	Morphine Sulfate Oral Solution (Pending)
IND	75041	Morphine Sulfate Tablets and Oral Solution

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS: Inspections completed except for the drug product manufacturing facility (submitted to District Office June 21, 2007),
EA waiver requested in 1.12.14, Granted.

The Chemistry Review for NDA 22-207

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval pending a satisfactory CGMP evaluation of the manufacturing facilities. There are some minor CMC issues outlined in the attached comments that should be conveyed to the applicant in a Discipline Review letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

There are minor CMC issues that can be dealt with in a post-approval agreement.

II. Summary of Chemistry Assessments

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

1. Drug Substance

The drug substance is a USP item and its properties and synthesis have been assessed many times to support many applications. It is provided by — manufacturers, . The DMFs , respectively, have been recently reviewed and found acceptable. The suppliers and the applicant have developed tests for impurities in the drug substance beyond the requirements in the USP. The acceptance criteria for these impurities are acceptable from a chemistry point of view. b(4)

Since the drug product is manufactured the applicant was asked to provide information about potential polymorphs. There are polymorphs, corresponding to a hydration state of the molecule. Since only the pentahydrate is used to manufacture the drug product polymorphism is not an issue. b(4)

2. Drug Product

The drug product is provided as tablets for oral administration in 15 and 30 mg tablets, packaged in — bottles and blister packages. The tablets are manufactured by a method using compendial excipients. Since this drug product has been sold for many years without an NDA, there is a long history of its manufacture. Therefore there is no pharmaceutical development report. The specifications include a dissolution test and are adequate for their intended use. However the applicant has proposed separate release and stability specifications, They are being requested to provide one set of specifications. The applicant has provided historical stability data for batches stored for up to 36 months. They have also provided primary stability data for up to twelve months. The stability-determining factor is the level of formed on storage. Review of the toxicology information by the pharmacology/toxicology review team supports an b(4)

acceptance criterion of NMT — Using this value as the upper limit the recommended expiration date is eighteen months.

b(4)

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

The drug is intended to be used for the relief of moderate to severe acute and chronic pain, with a recommended starting dose of 15 to 30 mg every four hours.

C. Basis for Approvability or Not-Approval Recommendation

The drug may be approved because the CMC review shows that the drug can be manufactured consistently to deliver the labeled amount of drug with each dose.

III. Administrative

See DFS signatures and cc's

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/s/

Arthur B. Shaw
2/12/2008 03:10:53 PM
CHEMIST
Cehm Review #2

Ali Al-Hakim
2/12/2008 03:56:42 PM
CHEMIST

Chemistry Review Cover Sheet

NDA 22207
Morphine Sulfate Tablets
Arthur B. Shaw, Ph.D.
DNDC2/DAARP

Table of Contents

Chemistry Review Data Sheet

1. NDA 22207
2. REVIEW #:1
3. REVIEW DATE: December 17, 2007
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Original	07-Jun-2007	None
Amendment BC	30-Aug-2007	Response to IR Letter
Amendment BC	07-Sep-2007	Response to DR letter to NDA 22195 for morphine sulfate oral solution.

FDA Documents	Document Date	Comment
Chemistry DR Letter to NDA 22195	05-Jul-2007	Request info about MV for DP assay common to both NDAs
Chemist's Initial Quality Assessment	10-Aug-2007	Acceptable for filing. Additional info requested
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7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

Note that all the documentation is submitted by "Boehringer Ingelheim Roxane Inc." (BIRI). The procedures, etc. have "BIRI" numbers.

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Morphine sulfate
   b) Non-Proprietary Name (USAN): Morphine sulfate
   c) Code Name/# None provided
   d) Chem. Type/Submission Priority
      - Chem. Type: 7
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: Opiate
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 15 and 30 mg

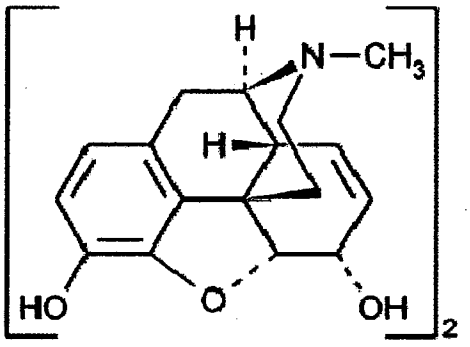
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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

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



• H_2SO_4 • $5H_2O$

$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

MW = 758.33

Anhydrous MW = 668.77

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Reviewed: **ACCEPTABLE**

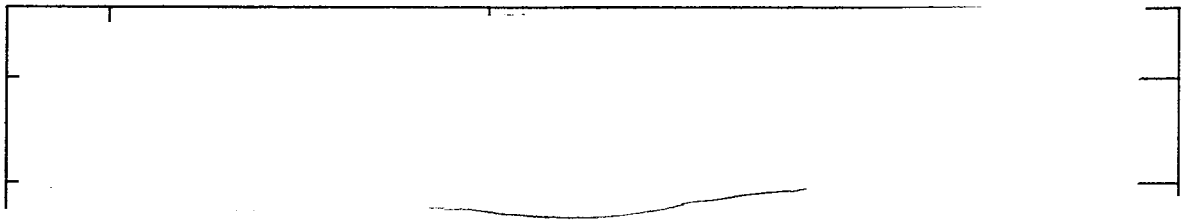
DMF	Holder	DMF Subject	LOA Date	Review Date
			27-Feb-2007	19-Nov-2007
			15-May-2007	07-Dec-2007

b(4)

Not Reviewed since there is sufficient information in the NDA See Section P Container Closure below

DMF	Holder	DMF Subject	Item Referenced

b(4)



b(4)

The DMFs for the morphine sulfate were found acceptable in recent reviews. The other DMFs do not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22195	Morphine Sulfate Oral Solution (Pending)
IND	75041	Morphine Sulfate Tablets and Oral Solution

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS: Inspections completed except for the drug product manufacturing facility (submitted to District Office June 21, 2007),
EA waiver requested in 1.12.14, Granted.

The Chemistry Review for NDA 22-207

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval pending a satisfactory CGMP evaluation of the manufacturing facilities. There are some minor CMC issues outlined in the attached comments that should be conveyed to the applicant in a Discipline Review letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

There are minor CMC issues that can be dealt with in a post-approval agreement.

II. Summary of Chemistry Assessments

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

1. Drug Substance

The drug substance is a USP item and its properties and synthesis have been assessed many times to support many applications. It is provided by manufacturers, . The DMFs respectively, have been recently reviewed and found acceptable. The suppliers and the applicant have developed tests for impurities in the drug substance beyond the requirements in the USP. The acceptance criteria for these impurities are acceptable from a chemistry point of view. The acceptability of these impurity levels from a safety pint of view is currently being reviewed by the pharmacology/toxicology review team. b(4)

Since the drug product is manufactured the applicant was asked to provide information about potential polymorphs. There are polymorphs, corresponding to a hydration state of the molecule. Since only the pentahydrate is used to manufacture the drug product polymorphism is not an issue. b(4)

2. Drug Product

The drug product is provided as tablets for oral administration in 15 and 30 mg tablets, packaged in bottles and blister packages. The tablets are manufactured method using compendial excipients. Since this drug product has been sold for many years without an NDA, there is a long history of its manufacture. Therefore there is no pharmaceutical development report. The specifications include a dissolution test and are adequate for their intended use. The applicant has provided historical stability data for batches stored for up to 36 months. They have also provided primary stability data for up to nine months. Additional data has been requested to assist in setting an expiration date. The acceptability of these impurity levels from a safety pint of view is currently being reviewed by the b(4)

pharmacology/toxicology review team.

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

The drug is intended to be used for the relief of moderate to severe acute and chronic pain, with a recommended starting dose of 15 to 30 mg every four hours.

C. Basis for Approvability or Not-Approval Recommendation

The drug may be approved because the CMC review shows that the drug can be manufactured consistently to deliver the labeled amount of drug with each dose.

III. Administrative

See DFS signatures and cc's

57 Page(s) Withheld

6 Trade Secret / Confidential b(4)

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Arthur B. Shaw
12/18/2007 10:26:33 AM
CHEMIST

Ali Al-Hakim
12/18/2007 11:08:35 AM
CHEMIST

INITIAL QUALITY ASSESSMENT
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products
NDA 22207

Applicant: Roxane, Inc.
Submission Date: 07-Jun-2007
Stamp Date: 08-Jun-2007
PDUFA Date: 08-Apr-2008
Pharmacological Category: analgesic; opioid agonist
Proposed Proprietary Name: N/A
Established Name: morphine sulfate tablet
Dosage Form and Strength: 15 and 30 mg
Route of Administration: oral
Indication(s): relief of moderate to severe acute and chronic pain

PAL: Ali Al-Hakim

REVIEWER: Arthur B. Shaw, Ph.D., Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

GRMP Time goals:

Initial Quality Assessment (IQA) in DFS:	07-Aug-2007
Chemistry filing memo in DFS: (combined with IQA):	07-Aug-2007
Filing meeting	25-Jul-2007
Filing Decision Day 45:	07-Aug-2007
Filing review issues Day 74:	20-Aug-2007
Chemistry Review and (DR) draft letter to secondary reviewer:	07-Nov-2007
Final Chemistry Review in DFS:	08-Feb-2008
PDUFA Goal Date:	08-Apr-2008

CONSULTS/ CMC RELATED REVIEWS	COMMENT
ClinPharm	Not applicable.
CDRH	Not applicable
EA	The applicant requests a categorical exclusion from the requirement to provide an EA, thus no consult is necessary.
EES	EER sent to Office of Compliance on 20-JUN-2007.
ODS/DMETS	**Labeling consult request will be sent as part of Division's request.**
Methods Validation	The reviewer will assess whether or not the methods need to be evaluated by the Agency laboratory with consideration given to the method validation request categories in the office policy document.
Microbiology	N/A
Pharm/Tox	A consult (informal suggested by DAARP) was sent for NDA 22195 (morphine sulfate oral solution) for drug substance impurities that have acceptance criteria proposed above the ICH Q3A(R) qualification thresholds. The pharm/tox team was also be asked to evaluate the drug substance and drug product impurity — that contains a structural alert moiety for

b(4)

	mutagenicity
Biometrics	To be decided after review of supplied stability data.

b(4)

SUMMARY:

Submission type: The NDA (CMC in paper) was submitted as a 505(b)(2) application and is for a marketed but unapproved drug, morphine sulfate tablet. An electronic portion of the application contains a short Quality Overall Summary and the labeling, which is stated to be in the structured product labeling (SPL) format. The active ingredient is morphine sulfate, which is not a new molecular or chemical entity. An NDA (22195) for morphine sulfate solution was submitted on 16-May-2007 and is currently under review. Many of the issues concerning the drug substance and impurities have been addressed in the review of that NDA.

Pharmacologic Category: Opioid analgesic

Clinical indication(s): The drug is to be used to treat both acute and chronic pain

Pre-submission CMC history, issues and/or agreements: A pre-IND meeting (IND 75041) was held on 12-SEP-2006. At this meeting there was some discussion of what would be required to support the stability of the drug product. The applicant indicates that the lots presented in the application were **"manufactured using the same formula, manufacturing** site, equipment and processes" **and there are no differences between the commercial/registration lots and the "historical commercial lots." The applicant has not provided any information to indicate which lots are "historical" lots. There is long-term data for some "late" time** points for some batches. There is no indication as to which lots **are the "historical" lots. However, based upon Mike Adams' review (14-Jun-2007) for the Special** Protocol Assessment (SPA) (submitted to the IND on 12-Sep-2006) it appears that these batches had been prepared over the years and had been placed on stability. However it is only recently that the applicant has begun testing these batches for related substances.
COMMENT: Provide information to indicate which stability batches are "historical" batches. Explain why there is only one data point for some batches e.g. Batch 456304A has a data point at 34 months.

The application provides stability data for two commercial/registration batches at each strength (15 and 30 mg) in bottles and unit dose packages), batches 657378 and 657615 (biobatch), with 6 months 25°C/60%RH and 3 months 40°C/75%RH data.

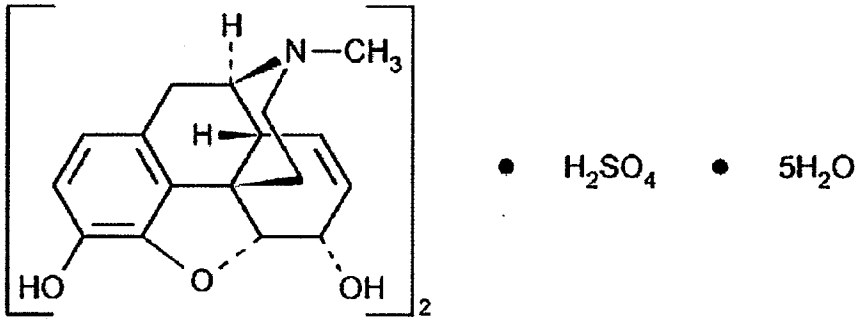
One of the commercial/registration stability drug product batches at each strength was made with morphine sulfate sourced from and the other was made with drug substance obtained from b(4)

The sponsor had originally proposed to submit only a single batch of the drug product (presumably one for each strength) in the stability studies to be presented in the application. However, at the pre-IND meeting the reviewer had requested the inclusion of stability data for three lots of each strength with one at the approximate commercial scale (the other two could be at smaller scale). Considering the fact that this is a marketed but unapproved drug product with a long history (marketed since the 1980s), the simple nature of the dosage form, and the fact that the historical and commercial/registration batches are prepared in the same manner and on the same equipment, the amount of stability data (i.e., 2 batches each strength with corresponding historical supportive data) should be sufficient for the reviewer to make a determination of the stability characteristics of the two strengths of the product. However, if there are indications of trends in the data, the limited nature of

the data will not lend itself to any statistical treatment by the biometrics team. The reviewer will need to use the historical batch data to aid in the evaluation of the proposed — expiration dating period proposed by the applicant for both strengths. The reviewer will need to rely solely on the limited commercial/registration stability data to evaluate whether or not there are any differences in drug product stability that might be due to the source of the drug substance — b(4)

Drug Substance: The chemical name for morphine sulfate is:

Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-methyl, (5α, 6α)-, sulfate (2:1) (salt) pentahydrate and the structural formula:



$(C_{17}H_{19}NO_3)_2\ H_2SO_4\ 5H_2O$ MW = 758.85 g/mole (w/o water of hydration 668.77; morphine free base MW is 285.33)

The drug substance is formulated — . Therefore polymorphism may be an issue. b(4)

COMMENT: Provide information regarding polymorphs of the drug substance and how this may affect the dissolution properties of the drug product.

The drug substance is obtained —

— The DMFs and these have been reviewed many times since their submission. The most recent reviews (06-Jun-2007) found the DMFs Adequate. There have been no submissions since then. Review of updates may be necessary if they are submitted before the final CMC review date. The application contains the necessary letters of authorization (LOA). b(4)

The applicant proposes to use the USP specifications for the morphine sulfate with the addition of tests and acceptance criteria for particle size, residual —, and related substances. One of the impurities listed for the drug substance — which contains — a structural alert moiety for mutagenicity. As part of the review of NDA 22195 (morphine sulfate oral solution), the DAARP pharmacology team was contacted by the reviewer Craig Bertha, and made aware of this impurity in the drug substance and drug product. They have been asked to evaluate the associated proposed acceptance criteria as well as the need for qualification data for the other identified impurities (electronic mail to D. Mellon, Ph.D. of 06-JUN-2007). Note that in a review — dated 20-Mar-2006, this impurity was found not to be genotoxic and to be consistently below —. Therefore the DMF holder does not test for this impurity. The applicant's acceptance criteria for morphine sulfate from — do not include — (see below). b(4)

The applicant has provided historical data on the **drug substance impurities from supplier's COAs. Of** These will be evaluated in the assessment of the proposed impurities specifications.

The applicant has two specifications for the drug substance depending on the supplier. These differ in particular in the fact that the drug substance obtained from does not have a test or acceptance criterion for residual solvents and the impurity, while the spec for drug substance from does ( ). Most other parts of the S section of the application rely on the information and data presented in the respective **supplier's DMFs.** b(4)

Test Name	Procedure	Acceptance Criteria
Specific Rotation	USP <781S>	
Acidity	USP	
Water	USP <921> Method I	
Residue on Ignition	USP <81>	
	USP <221>	Meets Requirements
	USP	Meets Requirements
Limit of Foreign Alkaloids	USP	Meets Requirements
Particle Size Greater than		
Residual Solvents		
Related Substances		
Any Unspecified Impurity		
Total Impurities		
Assay	USP	

b(4)

ND = Not Determined

Although the test methods have different code numbers they appear to be the same. Closer review may reveal differences.

Drug Product:

The formulations of the two strengths of the product are.

Ingredient	15 mg Tablet (mg/tablet)	30 mg Tablet (mg/tablet)	Function
Morphine Sulfate	15.15	30.3	.Active
Microcrystalline cellulose NF			
Pregelatinized Starch, NF			
Starch, NF			
Colloidal Silicon Dioxide, NF			
Stearic Acid, NF			
Tablet Weight	100.0	200.0	

b(4)

The manufacture of the drug product is done by Boehringer Ingelheim Roxane Incorporated (BIRI) at the Wilson Road facility in Columbus, OH. An EER was submitted to the Office of Compliance through the EES on 19-JUN-2007, for this site as well as sites involved with the manufacture of the drug substance and an additional Roxane testing site.

The manufacturing procedure is a standard into tablets. There is no pharmaceutical development report. The applicant has provided reports on the manufacture of two commercial batches showing the results of blend uniformity testing, assessment of in-process, and content uniformity in-process. These parameters are not tested routinely, according to the master batch record. There is no executed batch record.
COMMENT: Provide a sample executed batch record.

b(4)

The tablets are packaged in bottles (100 tablets/bottle, and blisters The applicant has provided no information regarding the safety or composition of these packaging materials for use with solid oral dosage forms. This requirement can be met by having the applicant provide a statement that the materials in contact with the drug product are suitable for indirect food contact. Otherwise the DMFs will have to be reviewed.
COMMENT: Provide statements that the chemical components in the packaging components that are in contact with the drug product materials are safe for use in packaging tablets for oral administration. This can be done by citing the correct sections of the Code of Federal Regulations applicable to indirect food contact. For the aluminum foil/paper peelable blister backing, this information should be provided

b(4)

For a discussion of the stability data for the drug product, see above. Stability test parameters include description, assay of morphine sulfate, determination of degradation products unspecified and total, as well as microbial testing (for the registration batches only, not routine for future annual batches). The containers are all

b(4)

Drug Master Files (DMF):

There are suppliers of the drug substance, DMFs are referenced for container/closure components: If sufficient is provided in the application, as requested in the comment above, these DMFs will not need to be reviewed. b(4)

NDA FILABLILITY CHECKLIST:

Is the CMC section of the application fileable? Yes.

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		CTD format
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		Certification that all facilities conform with cGMPs is provided.
6	Has an environmental assessment report or categorical exclusion been provided?	X		Older CFR reference cited however.
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?		X	No statistical analysis of the stability data has been performed. Not necessarily needed, however.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		See discussion of drug product stability program above.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?		X	N/A; Drug has been marketed for an extended period of time
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	Not needed

Critical Issues Identified: None

Preliminary Comments to be Communicated to Applicant

1. Provide information regarding polymorphs of the drug substance and how this may affect the dissolution properties of the drug product.

2. Provide a sample executed batch record for manufacture of the drug product..

3. **Provide information to indicate which stability batches are "historical" batches. Explain why** there is only one data point for some batches e.g. Batch 456304A has a data point at 34 months.

4. Provide statements that the chemical components in the packaging components that are in contact with the drug product materials are safe for use in packaging tablets for oral administration. This can be done by citing the correct sections of the Code of Federal Regulations applicable to indirect food contact. For the aluminum foil/paper peelable blister backing, this information should be provided b(4)

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/s/

Arthur B. Shaw
8/10/2007 01:17:51 PM
CHEMIST

Ali Al-Hakim
8/10/2007 01:47:22 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-195

Morphine Sulfate Oral Solution

Roxane Laboratories, Inc.

Craig M. Bertha, Ph.D.
ONDQA for DAARP

Table of Contents

b(4)

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Chemistry Review Data Sheet

1. NDA 22-195

2. REVIEW #:1

3. REVIEW DATE: 21-JUN-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-MAY-2007 (assigned 29-MAY-2007)

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc.

Address: 1809 Wilson Road

Representative: Elizabeth A. Ernst, Associate Director

Telephone: 614-272-4785

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: none
b) Non-Proprietary Name (USAN): morphine sulfate
c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2); Avinza extended release capsules, Ligand Pharmaceuticals, NDA 21260; The current application N22-195 is for a *marketed but unapproved* product.[1]

10. PHARMACOL. CATEGORY: analgesic

11. DOSAGE FORM: solution

12. STRENGTH/POTENCY: 10 and 20 mg/5 mL

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: ___X___Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____**SPOTS product – Form Completed**

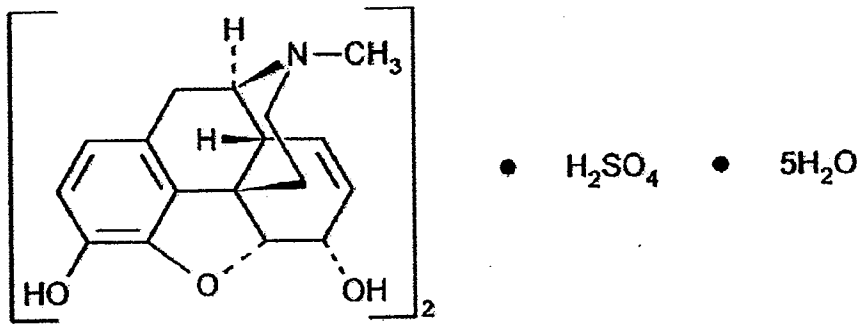
___X___Not a SPOTS product

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

Morphine Sulfate has the chemical name Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-methyl, (5α, 6α)-, sulfate (2:1) (salt) pentahydrate and the structural formula:

[1] **Roxane indicates in the cover letter to the application that they have "marketed the formulation since the 1980's** under the brand name Morphine Sulfate (Immediate Release) **Oral Solution, 10 mg/5 mL and 20 mg/5 mL."**

Chemistry Review Data Sheet



$(C_{17}H_{19}NO_3)_2\ H_2SO_4\ 5H_2O$ MW = 758.85 g/mole (w/o water of hydration 668.77; morphine free base MW is 285.33)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
	2			1	Adequate	05-JUN-2007	
	2			1	Adequate	05-JUN-2007	
	3			1	Adequate	07-JUN-2007	IR letter forwarded to holder, however.
	3			1	Inadequate	11-JUN-2007	IR letter requesting location of information/data to review.
	3			3	Adequate	12-JAN-2005	
	3			4	N/A		Cap performance evaluated via stability data, no direct product contact
	3			3	Adequate	07-JAN-2004	Cap has no direct contact with formulation (see liner review, DMF
	3			1	Adequate	12-JUN-2007	

b(4)

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	75,041	Roxane	IND for both tablet and oral solution dosage forms of morphine sulfate

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				N/A see P.8.3 evaluation
EES	cGMP compliance/PAI	04-JUN-2007	Pending	
Pharm/Tox	Limit of NMT — w/w for — in drug product (structural alert containing compound). Qualification of drug substance impurities.	By electronic mail to D. Mellon, Ph.D. on 06-JUN-2007	Pending	
Biopharm	N/A			N/A
OSE	Labeling			DAARP PM will forward to OSE.
Methods Validation				May be forwarded pending revision by applicant.
EA				Categorical exclusion requested, see p. 46.
Microbiology	Microbial limits, preservative effectiveness testing, and preservative assay acceptance criteria	05-JUN-2007	Pending	

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The Chemistry Review for NDA 22-195

The Executive Summary

The application N22-195 is filed under 505b(2) of the act and is for support of a marketed but unapproved drug product.

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval**, however there are some minor CMC issues outlined in the attached deficiency letter that should be resolved by the applicant, preferably prior to the approval, in order to assure a complete application is on file for this marketed but unapproved drug product.

The PM is requested to forward the comments in the attached draft letter to the applicant once the Agency files the application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendation at this time pending applicant's response to deficiency letter.

II. Summary of Chemistry Assessments

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

The drug product is morphine sulfate oral solution and is to be marketed in two strengths, 10 mg/5 mL and 20 mg/5 mL. The low strength will be packaged in [redacted] bottles with child resistant closures containing 100 and 500 mL of formulation or in 30 mL [redacted] unit dose cups containing either 5 or 10 mL of formulation. The high strength will only be packaged in the 100 and 500 mL [redacted] bottles with child resistant closures. The drug substance morphine sulfate pentahydrate, is an opioid analgesic already approved for oral usage. The crystalline form of the drug substance is of limited consequence as the drug product formulation is a solution. The applicant provides additional tests with acceptance criteria for the purity of the drug substance above the compendial monograph requirements. Most drug substance-related information is contained in [redacted] drug master files from the [redacted] proposed suppliers. b(4)

The drug product formulation contains compendial excipients already in use with other oral drug products and also contains FDA certified colorant FD&C Green No. 3. The low strength formulation contains only sodium benzoate [redacted] but the high strength also includes [redacted] methylparaben and b(4)

propylparaben. Both formulations include edetate disodium

b(4)

As this drug is a marketed unapproved drug, there is no noted difference between the drug product used in the biostudy and that which is to be manufactured for commercial distribution under the approved application.

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

The dosage recommended in the label is 10 to 20 mg every four hours (for acute or chronic pain). The product formulations have concentrations of 10 mg/5mL and 20 mg/5mL. Thus the 100 mL containers contain 20 doses and the 500 mL containers contain 100 doses. There are also unit dose containers of the 10 mg/5 mL strength for both a 10 and 20 mg dose. There is no unusual preparation necessary prior to dose administration.

The application provides data that support a **36 month expiration dating period** for all packaging types and for both strengths.

There are currently no recommended storage conditions listed in the label. The applicant will be asked to address this deficiency.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/6/21/07
AAlHakim/ONDQA/DIV I//Branch II/Branch Chief_____

C. CC Block

LBasham/DAARP/Regulatory PM
AAlHakim/ONDQA/DIV I/Branch II/Branch Chief
SGoldie/ONDQA/DIV I/Regulatory PM

36 Page(s) Withheld

10 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Craig Bertha
6/21/2007 08:30:27 AM
CHEMIST

Ali Al-Hakim
6/21/2007 11:18:21 AM
CHEMIST

INITIAL QUALITY ASSESSMENT
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products
NDA 22-195

Applicant: Roxane, Inc.
Stamp Date: 17-MAY-2007
PDUFA Date: 17-MAR-2008
Pharmacological Category: analgesic; opioid agonist
Proposed Proprietary Name: N/A
Established Name: morphine sulfate oral solution
Dosage Form and Strength: solution; 10 and 20 mg/5 mL
Route of Administration: oral
Indication(s): relief of moderate to severe acute and chronic pain

PAL: N/A

REVIEWER: Craig M. Bertha, Ph.D., Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

GRMP Time goals:

Initial Quality Assessment (IQA) in DFS: 12-JUN-2007
Chemistry filing memo in DFS: 12-JUN-2007 (combined with IQA)
Filing decision "Day 45": No CMC filing issues found
Filing review issues "Day 74": No CMC filing review issues.
Chemistry Review and (DR) draft letter to secondary reviewer: 03-OCT-2007
Chemistry Review (DR/IR) letter: 17-OCT-2007
Final Chemistry Review in DFS: 17-JAN-2008
PDUFA Goal Date: 17-MAR-2008

CONSULTS/ CMC RELATED REVIEWS	COMMENT
ClinPharm	Not applicable.
CDRH	Not applicable
EA	The applicant requests a categorical exclusion from the requirement to provide an EA, thus no consult is necessary.
EES	EER sent to Office of Compliance on 04-JUN-2007.
ODS/DMETS	**Labeling consult request will be sent as part of D's request.**
Methods Validation	The reviewer will assess whether or not the methods need to be evaluated by the Agency laboratory with consideration given to the method validation request categories in the office policy document.
Microbiology	Consult on preservative effectiveness testing and acceptance criteria for preservative assays sent on 05-JUN-2007.
Pharm/Tox	Consult (informal suggested by DAARP) needed for drug substance impurities that have acceptance criteria proposed above the ICH Q3A(R) qualification thresholds. The pharm/tox team will also be asked to evaluate the drug substance and drug product impurity —, that contains a structural alert moiety for mutagenicity

b(4)

Biometrics	To be decided after review of supplied stability data.

SUMMARY:

Submission type: The NDA (majority in paper form) was submitted electronically as a 505(b)(2) application and is for a marketed but unapproved drug, morphine sulfate oral solution. The electronic portion of the application contains a short Quality Overall Summary and the labeling, which is stated to be in the structured product labeling (SPL) format. The active ingredient is morphine sulfate, which is not a new molecular or chemical entity.

Clinical indication(s): The drug is to be used to treat both acute and chronic pain and is an opioid analgesic.

Pre-submission CMC history, issues and/or agreements: A pre-IND meeting was held on 12-SEP-2006. At this meeting there was some discussion of what would be required to support the stability of the drug product. The applicant presents two types of batches in the application to support product stability: commercial/registration batches (one of low strength used in biostudy) and commercial stability lots. The applicant indicates that the lots presented in the application were **"manufactured using the same formula, manufacturing site, equipment and processes" and there are no differences between the commercial/registration lots and the "historical commercial lots." The** exception is that the commercial/registration lots of the 20mg/5mL strength were prepared at ~ scale but will later be scaled up to — during future commercial production. b(4)

The application provides stability data for two commercial/registration batches of the 10mg/5mL strength (100 & 500 mL bottles and unit does packages), batches 657378 and 657615 (biobatch), with 6 months 25°C/60%RH and 3 months 40°C/75%RH data. However, the applicant also includes stability data from single final time points collected to date after 25°C/60%RH storage (on side) for 6 **historical batches (marketed but unapproved batches termed "commercial stability" batches). Here** the single time points are 6, 13, 18, 21, 24, and 24 months.

The application provides stability data for two commercial/registration batches of the 20mg/5mL strength (100 & 500 mL bottles), batches 657616 and 657376, with 6 months 25°C/60%RH and 3 months 40°C/75%RH data. However, the applicant also includes stability data from single final time points collected to date after 25°C/60%RH storage for 3 historical batches (marketed but unapproved). Here the single time points are 9, 13 and 24 months.

One of the commercial/registration stability drug product batches was made with morphine sulfate sourced from , for each of the strengths. However, the supportive historical batches, for which limited stability data are provided, were only prepared with — sourced drug substance. b(4)

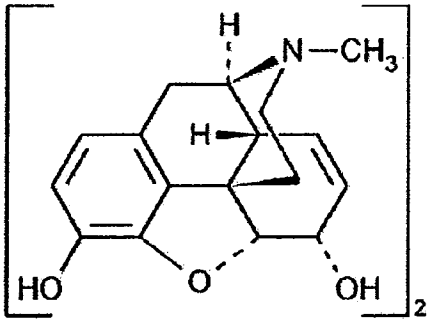
The sponsor had originally proposed to submit only a single batch of the drug product (presumably for each strength) in the stability studies to be presented in the application. However, at the pre-IND meeting the reviewer had requested the inclusion of stability data for three lots of each strength with one at the approximate commercial scale (the other two could be at smaller scale). And it was also indicated by the Agency that historical data could be accepted as supportive if the formulation and manufacturing process were the same as that proposed in the application. The Agency proposed that the applicant submit a special protocol assessment for a proposed protocol for stability that would more closely meet the Agency expectations (e.g., 3 batches of each strength with all packaging

represented and with drug substance from both sources). This special protocol was not submitted so the previous reviewer recently informed the applicant by telephone that we would need to assess the adequacy at the time of submission. Considering the fact that this is a marketed but unapproved drug product with a long history (marketed since the 1980s), the simple nature of the dosage form, and the fact that the historical and commercial/registration batches are prepared in the same manner and on the same equipment, the amount of stability data (i.e., 2 batches each strength with corresponding historical supportive data) should be sufficient for the reviewer to make a determination of the stability characteristics of the two strengths of the product. However, if there are indications of trends in the data, the limited nature of the data will not lend itself to any statistical treatment by the biometrics team. The reviewer will need to use the historical batch data to aid in the evaluation of the proposed **36 month** expiration dating period proposed by the applicant for both strengths. The reviewer will need to rely solely on the limited commercial/registration stability data to evaluate whether or not there are any differences in drug product stability that might be due to the source of the drug substance . It is suggested that the reviewer follow the principles outlined in ICH Q1E when determining the appropriate expiry period for both strengths of the drug product. b(4)

There were no other CMC issues discussed at the pre-IND meeting. There is no CMC review of IND 75,041 in the Division File System.

Drug Substance: The chemical name for morphine sulfate is:

Morphinan-3, 6-diol, 7, 8-didehydro-4, 5-epoxy-17-methyl, (5α, 6α)-, sulfate (2:1) (salt) pentahydrate and the structural formula:



• H_2SO_4 • $5H_2O$

$(C_{17}H_{19}NO_3)_2\ H_2SO_4\ 5H_2O$ MW = 758.85 g/mole (w/o water of hydration 668.77; morphine free base MW is 285.33)

The drug substance is formulated in solution so there are no issues with regard to polymorphism. The drug substance is obtained from suppliers, . suppliers have DMFs and these have been reviewed many times since their submission. Review of these DMFs will be necessary since there are updates included that are reflective of amendments to the CMC information supporting the production of the morphine sulfate by suppliers. The application contains the necessary letters of authorization (LOA). b(4)

The applicant proposes to use the USP specifications for the morphine sulfate but with the addition of tests and acceptance criteria for particle size, residual ethanol, and related substances. It is notable that one of the impurities listed for the drug substance is which contains an , a structural alert moiety for mutagenicity. The DAARP pharmacology team has been contacted and made aware of this impurity in the drug substance and drug product and have b(4)

been asked to evaluate the associated proposed acceptance criteria as well as the need for qualification data for the other identified impurities (electronic mail to D. Mellon, Ph.D. of 06-JUN-2007).

The applicant has provided historical data on the **drug substance impurities from supplier's COAs.** Of these 23 lots, The reviewer will need to consider these data when evaluating the proposed impurities specifications. It is unusual that the applicant has distinct specifications for the drug substance depending on the supplier. These only differ very slightly with respect to the impurities acceptance criteria, however, there may be implications depending on the results of the qualification of impurities made by the pharmacology/toxicology team in DAARP. Most other parts of the S section of the application rely on the information and data presented in the respective supplier's DMFs. b(4)

Drug Product:

The formulation of the two strengths of the product are reproduced from the quality overall summary section in module 2.

Morphine Sulfate Oral Solution 10 mg/5 mL

Ingredients	Purpose	Quality Standard	Amount (Amount per 5 mL)
Morphine Sulfate, USP	Active Ingredient		10 mg
Sorbitol USP		USP	
Glycerin, USP		USP	
Citric Acid, USP		USP	
Sodium Benzoate, NF		NF	
Disodium Edetate, USP		USP	
FD & C Green No. 3 Certified (Fast Green)			
Water,		USP	

b(4)

Morphine Sulfate Oral Solution 20 mg/5 mL

Ingredients	Purpose	Quality Standard	Amount (mg per 5 mL)
Morphine Sulfate, USP	Active Ingredient		20.0 mg
Sorbitol USP		USP	
Glycerin, USP		USP	
Methylparaben, NF		NF	
Propylparaben, NF		NF	
Citric Acid, USP		USP	
Sodium Benzoate, NF		NF	
Disodium Edetate, USP		USP	
FD & C Green No. 3 (Fast Green)			
Water		USP	

b(4)

An obvious difference between the two formulations is the addition of the methylparaben and the propylparaben the 20mg/5mL strength, when compared to the 10mg/5mL strength, although both strengths contain sodium benzoate . The other minor difference between the two formulations, apart from the difference in terms of the active concentration, is that the sorbitol concentration is higher in the 10mg/5mL strength but the glycerin content is lower, when compared to the 20mg/5mL formulation. The pharmaceutical development section is sparse and does not elaborate on how the formulations were developed or why there are these differences. It is notable that the application contains the results of preservative effectiveness studies. The results of these studies were forwarded in a consult request on 05-JUN-2007, for evaluation by the microbiological team.

b(4)

The manufacture of the drug product is done by Boehringer Ingelheim Roxane at the Wilson Road facility in Columbus, OH. An EER was submitted to the Office of Compliance through the EES on 04-JUN-2007, for this site as well as the two sites involved with the manufacture of the drug substance and an additional Roxane testing site.

The container closure systems for the 10mg/5mL and 20mg/5mL strengths include a bottle and a 500 mL bottle. The bottle has calibration marks at 20-120 mL in increments of 10 mL and the 500 mL bottle has calibrations at 50-475 mL in 25 mL increments. Both bottles use a child-resistant PP closure. The 10mg/5mL strength is also packaged in a 30mL unit dose aluminum container . Note that testing is performed on the two bottle configurations.

b(4)

For a description of the stability data for the drug product, see above. Stability test parameters include description, assay of morphine sulfate, assay of sodium benzoate, determination of degradation

products
unspecified and total, as well as microbial testing and preservative effective testing (for the registration batches only, not routine for future annual batches). The drug product specification does not include a test for leachables. The containers are all in nature .
And as per ICH Q6A, if the development and stability data provide evidence that the leachables from the container closure system are "consistently below levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted." These conditions may be satisfied by the compliance of the materials with the food contact regulations, particularly those that deal with packaging that is designed for use with aqueous based foods. Aside from this parameter, the specification for the oral solution drug products includes all of the other parameters that are to be expected. b(4)

Drug Master Files (DMF):

There are DMFs for the suppliers of the drug substance, . These were reviewed on 05-JUN-2007, and were found to be adequate to support the application. In addition there are DMFs that are referenced for container/closure components: . The reviewer will need to determine if these are in need of review. b(4)

NDA FILABLILITY CHECKLIST:

Is the CMC section of the application fileable? Yes.

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		CTD format
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		Certification that all facilities conform with cGMPs is provided.
6	Has an environmental assessment report or categorical exclusion been provided?	X		Older CFR reference cited however.
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?		X	No statistical analysis of the stability data has been performed. Not necessarily needed, however.

10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		See discussion of drug product stability program above.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?		X	N/A; Drug has been marketed for and extended period of time but unapproved. P2 section contains limited information.
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		Preservative effectiveness test results included.

Critical Issues Identified: None

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/s/

Craig Bertha
6/11/2007 11:25:30 AM
CHEMIST

Ali Al-Hakim
6/11/2007 03:27:14 PM
CHEMIST