

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-671**

**Chemistry Review(s)**

Addendum to the CMC Team Leader Memo

NDA 21671: DepoDur™ (Morphine sulfate extended-release liposome injection)

Ravi S. Harapanhalli, Ph.D.

Team Leader, CMC

HFD-170

(May 18, 2004)

Overall recommendation:

The NDA is recommended for "approval" from CMC perspective with the caveat that the agreements made between the Agency and the firm should be included in the action letter as reminder.

Some of the listed reminders from the Team Leader Memo dated May 17, 2004 have been modified and/or deleted as discussed below.

The following reminder commitment has been revised in the action letter to indicate that a prior-approval supplement will be submitted for the addition of a new specification by the stated date.

Reminder 1:

Develop and validate a method for the determination of  $\zeta$  content and to include the test in the post-approval stability protocol within four months from the date of this letter.

The following reminder has been deleted from the action letter since we cannot require Skye Pharma to get the data from  $\zeta$ .  $\zeta$  has already agreed to submit the data to their DMF.

Reminder 3:

Contact  $\zeta$  to obtain a copy of the final reports of the genotoxicity testing of  $\zeta$  to assess the results and to submit a copy of these reports to NDA 21-671.

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

/s/

-----  
Ravi Harapanhalli  
5/18/04 05:45:06 PM  
CHEMIST  
AP with agreement reminder

NDA 21671: DepoDur™ (Morphine sulfate extended-release liposome injection)

Team Leader Memo to File

Ravi S. Harapanhalli, Ph.D.  
Team Leader, CMC  
HFD-170  
(May 17, 2004)

Overall recommendation:

The NDA is recommended for "approval" from CMC perspective with the caveat that the agreements made between the Agency and the firm should be included in the action letter as a reminder.

Secondary review evaluation:

On May 17, 2004, Stephen Langille, Ph.D., the review microbiologist recommended "approval" of the NDA from the product quality microbiology.

In his CMC review # 2 dated May 14, 2004, Mike Theodorakis, Ph.D., the review chemist recommended "approval" action for this NDA after evaluating the written responses to the deficiencies generated by his review # 1 and the secondary review.

All DMFs have been deemed to be adequate to support the NDA. However, review of some DMF generated comments that were not directly related the approvability of the NDA. Therefore, these comments were sent to the DMF holders with a statement that their DMF was deemed adequate to support the NDA.

Several deficiencies and comments were identified by the reviewer Mike Theodorakis, Ph.D. during his primary review of this NDA. In addition, while doing the secondary review, this reviewer identified the following additional deficiencies.

Inadequate in-process controls:

There are  in the manufacture of the liposomal injection product, namely, the

The listed in-process tests included microbial quality,

The developmental report indicated that in the manufacture

[ ] However, this finding was not incorporated as routine in-process test, and the primary reviewer did not evaluate this aspect of the manufacturing process in detail. Moreover, the firm did not evaluate the effect of particle size distribution on either the in vitro or in vivo drug release. Instead, they provided a justification that the manufacturing process is very robust with respect to the particle size distributions of the liposomal particles formed from lot to lot and therefore that it was not necessary to conduct such studies. In view of these findings, the secondary reviewer determined that the firm should have an in-process specification [

] of the manufacturing process that is critical to the consistent formation of the liposomal particles. Therefore, the following question was raised with the firm during the teleconference dated May 14, 2004.

Question:

Provide in-process tests, [ ]

[

] A proposal for such studies, including appropriate timeframes for conducting the studies and reporting results would be prepared by the firm and provided to the Agency for review by June 1, 2004.

[

] [ ]

Inadequate specification for the in vitro drug release:

[

]

During the OCPB briefing by the reviewing Biopharmaceutics reviewer, David Lee, Ph.D., the issue of the use of [ ] in the test method came up for discussion... [

] Therefore, in the opinion of this reviewer, the chosen medium was an adequate selection and that the use of additional media without proper justification is unwarranted. Therefore, it was decided not to ask the sponsor to do additional in vitro studies using different media.

However, this reviewer opined that the acceptance criteria for the in vitro drug release were not adequate to ascertain the product quality batch-to-batch. The in-vitro drug release of morphine sulfate from the liposomal dispersion occurs over a 4-day period whereas the in vivo release occurred over 24-48 hours. The firm argued that the in vitro release test is being used only as a QC tool to characterize reproducibility of the process and that it has no bearing on the in vivo drug release rate. Non-demonstration of an IVIVC does not rule out the possibility of the existence of one based on the current test method. The chosen test method closely mimics the in vivo conditions to which the liposomes are exposed to and therefore may represent the in vivo drug release. The originally proposed acceptance criteria are as follows.

Day 1: NLT ( ) retained  
Day 2: ( ) retained  
Day 3: ( ) retained  
Day 4: NMT ( ) retained

These were based on the data from all the developmental and the — commercial scale batches. Upon the analysis of the data this reviewer determined that the best approach to setting the acceptance criteria would be to use the data from only the commercial scale batches that were used in the clinical and stability studies. Therefore, based on the discussion among this reviewer, Dr. Eric Duffy, and Dr. Mike Theodorakis, the following recommendations were made to the acceptance criteria on an interim basis. The firm was asked to reinvestigate the specifications upon accrual of data from — commercial batches and to submit a prior-approval supplement to finalize the specifications for the drug release test.

Day 1: NLT( ) retained  
Day 2: ( ) retained  
Day 3: ( ) retained  
Day 4: NMT( ) retained

Skye Pharma tightened the acceptance criteria to the recommended interim levels and agreed to revise the specifications following manufacturing experience of — additional batches of the drug product by the end of year 2005 and to submit a prior-approval supplement to this effect.

Inadequate specifications for the degradation products in the drug product:

There were no thresholds for the unspecified degradation products and the total degradation products in the specifications. This reviewer asked the firm to provide the following additions to the specifications.

Individual drug-related unspecified and unidentified degradation products: NMT ( )  
Total (sum of all reportable degradation products ( )):

The firm submitted a revised specification sheet containing the above additions and included a limit of NMT ( ) for the total.

**Appears This Way  
On Original**

## CMC List of agreements made between the Agency and the Firm

The following are the CMC list of agreements made between the Agency and the firm following a teleconference dated May 14, 2004 and the written responses from the sponsor dated May 14, 2004. These are based on the comments generated by the primary reviewer and by the secondary reviewer. They should be included in the "approval" action letter to remind the sponsor.

We remind you of your agreement to provide the following revisions to the NDA.

1. Develop and validate a method for the determination of [redacted] content and to include the test in the post-approval stability protocol within four months from the date of this letter.
2. Revise the drug substance specifications concurrently with the revisions made by [redacted] to include a limit on [redacted] impurity.
3. Contact [redacted] to obtain a copy of the final reports of the genotoxicity testing [redacted] to assess the results and to submit a copy of these reports to NDA 21-671.
4. Revise the in-vitro release specifications following manufacturing experience of [redacted] additional batches, which should be expected to be completed in 2005. Submit a prior approval supplement with this additional information.
5. Conduct [redacted]

[redacted] J A  
proposal for such studies, including appropriate timeframes for conducting the studies and reporting the results, will be prepared and provided to the Agency for review by June 1, 2004.

**Appears This Way  
On Original**

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

/s/

-----  
Ravi Harapanhalli  
5/17/04 04:51:54 PM  
CHEMIST  
AP with agreement reminder

**NDA 21-671**

**DepoDur  
(Morphine Sulfate Extended-Release Liposome)  
Injection**

**SkyePharma, Inc.**

**Michael C. Theodorakis, Ph.D.**

**Division of New Drug Chemistry II  
(HFD-820)**

**Division of Anesthetic, Critical Care  
and  
Addiction Drug Products  
(HFD-170)**

# Chemistry Review Data Sheet

1. NDA 21-671
2. REVIEW # 2
3. May 14, 2004
4. Michael C. Theodorakis, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
N/A Original application	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment BC	14-MAY-2004

7. NAME & ADDRESS OF APPLICANT:

Name: SkyePharma, Inc.  
Address: 10450 Science Center Drive  
San Diego, CA 92121  
Representative: Gordon L. Schooley, Ph.D.  
Chief Scientific Officer  
Telephone: 858-625-2414 ext. 3215

8. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: DepoDur
- b. Non-Proprietary Name: morphine sulfate extend-release  
liposome injection
- c. Code Name/# : SKY0401
- d. Chem. Type/Submission Priority (ONDC only):
  - Chem. Type : 3

- Submission Priority: S

**9. LEGAL BASIS FOR SUBMISSION:**

505b(2), RLD NDA 18-565 Duramorph (morphine sulfate)  
Injection

**10. PHARMACOL. CATEGORY:**

Opioid analgesic

**11. DOSAGE FORM:**

Multivesicular Liposome Injection  
DepoFoam™ drug delivery system

**12. STRENGTH/POTENCY:**

10 mg/mL, in three packaging presentations: 20 mg/2 mL, 15  
mg/1.5 mL and 10 mg/1 mL

**13. ROUTE OF ADMINISTRATION:**

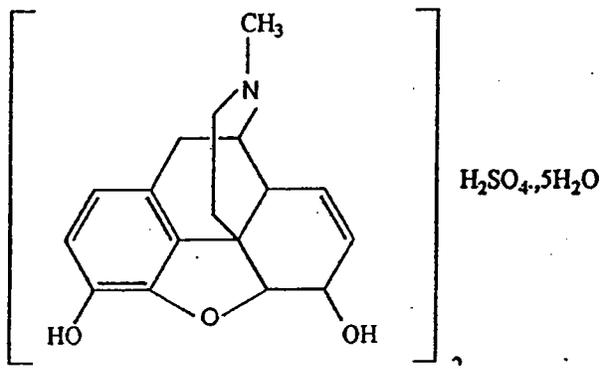
epidural

**14. Rx/OTC DISPENSED:     Rx     OTC****15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

SPOTS product - Form Completed

Not a SPOTS product

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



Molecular formula:  $(C_{17}H_{19}NO_3)_2H_2SO_4 \cdot 5H_2O$

Relative molecular mass:

Morphine sulphate (pentahydrate)	758.8
Morphine sulphate (anhydrous)	668.8
Morphine (base)	285.3

Appears This Way  
On Original

17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CO DE <sup>1</sup>	STATU S <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II		Morphine sulphate, pentahydrate USP	1	Adequate	Chemistry Review #12, dated 2/17/2004	Reviewed by Michael C. Theodorakis
	IV			3	Adequate	Chemistry Review #3 dated 5/1/98 and Review #4 dated 3/12/04	Reviewed by Paul E. Dietze and by Michael C. Theodorakis
	IV			1, 3	Adequate, comments to DMF holder	Chem.Rev. #2, dated 2/17/2004	Reviewed by Michael C. Theodorakis
	IV			1	Adequate, comments to DMF holder	Chem.Rev. #1, dated 3/16/2004	Reviewed by Michael C. Theodorakis
	IV			1 3	Adequate	Chem.Rev. # 2 dated 12-NOV-03 Chem.Rev. # 3 dated 29-FEB-04	Reviewed by Ravindra K. Kasliwal and by Michael C. Theodorakis

	IV		3	Adequate	Chemistry Review #2 dated 7/2/97 and Chem.Rev. #3, dated 3/16/2004	Reviewed by Paul E. Dietze  and by Michael C. Theodorakis
	IV		1	Adequate, comments to DMF holder	Chem.Rev. # 1 dated 29-FEB-04	Reviewed by Michael C. Theodorakis
	IV		3	Adequate	Chemistry Review #2 dated 4/30/97	Reviewed by Paul E. Dietze
	III		1, 3	Adequate	Chem.Rev. #4 dated 17-FEB-04	Reviewed by Michael C. Theodorakis
	III		3	Adequate	Chem.Rev. #11 dated 10-JUL-03	Reviewed by Dr. Lewis

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	52,113	
NDA	18-565; approved	SKY0401
NDA	[ ] not approved	Duramorph (morphine sulfate injection)
NDA	21-041; approved	[ ] DepoCyt (cytarabine) liposome injection (intrathecal)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Does not support — months	5/4/04	Joan Buenconsejo
EES	All facilities are acceptable	5/6/04	Janine D'Ambrogio
Pharm/Tox	[ ] issue see Dan Mellon		
Biopharm			
LNC			
Methods Validation	In-process		
DMETS/ODS	Review Completed		
EA	Categorical exclusion		
Microbiology	Microbial quality/sterility 2 <sup>nd</sup> review is pending		

Chemistry Review for NDA 21-671The Executive Summary:

See Chemistry Review #1. The Applicant provided satisfactory responses to the issues raised in Chemistry Review #1. It is recommended that approval be granted to this NDA.

III. AdministrativeA. Reviewer's SignatureB. Endorsement Block

Review Chemist/MCTheodorakis/  
Team Leader/RSharahanalli/  
CSO/KCompton/

C. CC Block

Appears This Way  
On Original

7 Page(s) Withheld



       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

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

/s/

-----  
Michael Theodorakis  
5/14/04 06:07:03 PM  
CHEMIST

Ravi Harapanhalli  
5/14/04 06:09:44 PM  
CHEMIST  
AP with agreements

**NDA 21-671**

**DepoDur  
(Morphine Sulfate Extended-Release Liposome)  
Injection**

**SkyePharma, Inc.**

**Michael C. Theodorakis, Ph.D.**

**Division of New Drug Chemistry II  
(HFD-820)**

**Division of Anesthetic, Critical Care  
and  
Addiction Drug Products  
(HFD-170)**

# Chemistry Review Data Sheet

1. NDA 21-671
2. REVIEW # **1**
3. April 16, 2004
4. Michael C. Theodorakis, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
N/A Original application	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	
Amendment BC	18-JUL-2003
Amendment BC	25-AUG-2003
Amendment BC	03-SEP-2003
Amendment BC	10-SEP-2003
Amendment BC	17-SEP-2003
Amendment BC	17-NOV-2003
Amendment BC	15-DEC-2003
Amendment BC	02-FEB-2004
Amendment BC	18-FEB-2004
Amendment BC	20-FEB-2004
Amendment BC	18-MAR-2004
Amendment BC	26-MAR-2004
Amendment BC	09-APR-2004
Amendment BC	21-APR-2004
Amendment BC	21-APR-2004 (A)
Amendment BC	07-MAY-2004

**7. NAME & ADDRESS OF APPLICANT:**

Name: SkyePharma, Inc.  
Address: 10450 Science Center Drive  
San Diego, CA 92121  
Representative: Gordon L. Schooley, Ph.D.  
Chief Scientific Officer  
Telephone: 858-625-2414 ext. 3215

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

- a. Proprietary Name: DepoDur  
b. Non-Proprietary Name: morphine sulfate extend-release  
liposome injection  
c. Code Name/# : SKY0401  
d. Chem. Type/Submission Priority (ONDC only):  
• Chem. Type : 3  
• Submission Priority: S

**9. LEGAL BASIS FOR SUBMISSION:**

505b(2), RLD NDA 18-565 Duramorph (morphine sulfate)  
Injection

**10. PHARMACOL. CATEGORY:**

Opioid analgesic

**11. DOSAGE FORM:**

Multivesicular Liposome Injection  
DepoFoam™ drug delivery system

**12. STRENGTH/POTENCY:**

10 mg/mL, in three packaging presentations: 20 mg/2 mL, 15  
mg/1.5 mL and 10 mg/1 mL

**13. ROUTE OF ADMINISTRATION:**

epidural

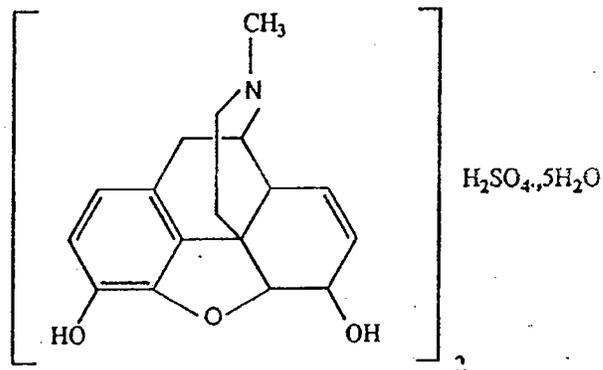
14. Rx/OTC DISPENSED:      X   Rx       OTC

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

      X       SPOTS product - Form Completed

                   Not a SPOTS product

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



Molecular formula:     $(\text{C}_{17}\text{H}_{19}\text{NO}_3)_2\text{H}_2\text{SO}_4 \cdot 5\text{H}_2\text{O}$

Relative molecular mass:

Morphine sulphate (pentahydrate)	758.8
Morphine sulphate (anhydrous)	668.8
Morphine (base)	285.3

17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CO DE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II		Morphine sulphate, pentahydrate USP	1	Adequate	Chemistry Review #12, dated 2/17/2004	Reviewed by Michael C. Theodorakis
	IV			3	Adequate	Chemistry Review #3 dated 5/1/98 and Review #4 dated 3/12/04	Reviewed by Paul E. Dietze and by Michael C. Theodorakis
	IV			1, 3	Adequate, comments to DMF holder	Chem.Rev. #2, dated 2/17/2004	Reviewed by Michael C. Theodorakis
	IV			1	Adequate, comments to DMF holder	Chem.Rev. #1, dated 3/16/2004	Reviewed by Michael C. Theodorakis
	IV			1 3	Adequate	Chem.Rev. # 2 dated 12-NOV-03  Chem.Rev. # 3 dated 29-FEB-04	Reviewed by Ravindra K. Kasliwal  and by Michael C. Theodorakis

	IV		3	Adequate	Chemistry Review #2 dated 7/2/97 and Chem.Rev. #3, dated 3/16/2004	Reviewed by Paul E. Dietze and by Michael C. Theodorakis
	IV		1	Adequate, comments to DMF holder	Chem.Rev. # 1 dated 29-FEB-04	Reviewed by Michael C. Theodorakis
	IV		3	Adequate	Chemistry Review #2 dated 4/30/97	Reviewed by Paul E. Dietze
	III		1, 3	Adequate	Chem.Rev. #4 dated 17-FEB-04	Reviewed by Michael C. Theodorakis
	III		3	Adequate	Chem.Rev. #11 dated 10-JUL-03	Reviewed by Dr. Lewis

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	52,113	SKY0401
NDA	18-565; approved	Duramorph (morphine sulfate injection)
NDA	[ ] not approved	[ ] <span style="float: right;">J</span>
NDA	21-041; approved	DepoCyt (cytarabine) liposome injection (intrathecal)

*Appears This Way  
On Original*

**18. STATUS:**

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Does not support ~ months	5/4/04	Joan Buenconsejo
EES	All facilities are acceptable	5/6/04	Janine D'Ambrogio
Pharm/Tox	[ ] issue see Dan Mellon		
Biopharm			
LNC			
Methods Validation	In-process		
DMETS/ODS	Review Completed		
EA	Categorical exclusion		
Microbiology	Microbial quality/sterility 2 <sup>nd</sup> review is pending		

Appears This Way  
On Original

The Chemistry Review for NDA 21-671The Executive Summary:I. RecommendationsA. Recommendation and Conclusion on Approvability:

This Application is approvable from the chemistry standpoint. The deficiencies listed in the draft letter must be conveyed to the Applicant. None of these deficiencies are critical to the safety of this drug product.

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

No Phase IV commitments were made. The Applicant will establish a [ ] test as an in-process test, provide a limit for [ ] and develop a test, assess the [ ] study reports and respond, tighten the in-vitro release specifications, provide [ ] for [ ] for the drug product.

II. Summary of Chemistry AssessmentsA. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, morphine sulfate pentahydrate is same active ingredient as that used in NDA 18-565, Duramorph (morphine sulfate) Injection; the reference drug product. Any information concerning the manufacturing and testing of morphine sulfate pentahydrate was incorporated into this NDA by reference to DMF ( ) DMF ( ) was found to be adequate for this drug product. An inquire was addressed to [ ] regarding the impurity, [ ]

Morphine sulfate extended-release liposome injection is a sterile, non-pyrogenic, white to off-white aqueous suspension of multivesicular liposomes (MVL) containing morphine sulfate, intended for local extended release following epidural administration. Morphine is expressed as morphine sulfate pentahydrate equivalent, and is present at a nominal concentration of 10.0 mg/mL. It is packaged in 2 mL [ ] amber glass vials and in

three different fills: 1 mL (10 mg/vial), 1.5 (15 mg/vial) and 2 mL (20 mg/vial).

Morphine sulfate is in solution within the compartments (vesicles) of the MVL. A small amount of free (non-encapsulated) morphine sulfate is present in the aqueous phase in which the MVLs are suspended. At the end of the shelf life of the drug product free morphine does not exceed [ ] of the labeled amount.

The liposome bilayer membrane is composed of dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylglycerol (DPPG), cholesterol, triolein, and tricaprylin. The combination of these lipids that form the walls of the MVL liposomes and the honeycomb structure of the MVL confer the extended release characteristics to the formulation. The size of these liposomes is  $\mu\text{m}$  expressed as volume weighted median diameter. The electrical charge of the liposomes was found to be [ ]

DOPC is a zwitterionic phospholipid and the major component of lipid bilayer membranes. DPPG is a negatively charged phospholipid which prevents the MVLs aggregation. Cholesterol provides mechanical stabilization of lipid bilayer. The triolein and tricaprylin stabilize the multivesicular liposomal structure.

The critical parameters in the manufacturing process are the molar ratios of the lipids that form the bilayer membrane that controls the release of morphine. Specifically, the molar ratio of — of triolein to tricaprylin gave an optimum in-vitro release profile. In addition, the presence of DPPG is essential because it confers a negative charge to the liposomes. Other critical parameters are the viscosity, duration and rate of mixing of the 1<sup>st</sup> emulsion, removal of chloroform phase from the 2<sup>nd</sup> emulsion and the subsequent microfiltration and diafiltration steps of the liposome dispersion.

This product cannot be [ ] The entire process takes place aseptically in a closed sterile system. The ingredients are sterilized initially by filtration and thereafter the entire manufacturing process proceeds aseptically until the

liposomes are formed and aseptically filled into sterile amber glass vials and sealed. Consequently, strict adherence to related cGMP procedures, above and beyond of what is normally required, is very critical at all stages of manufacture for this drug product in order to assure its safety.

The liposome dispersion is sensitive to light.

A formulation [

] but

it was not pursued further.

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

The formulation is administered epidurally. The liposome injection was compatible with saline dilution and lactated Ringers solution and with catheters used for epidural administration. The injection was not compatible with lidocaine with epinephrine injections.

The maximum daily dose (MDD) is 20 mg of morphine sulfate.

The levels of impurities and degradation products were well below the qualification threshold per ICH Guidance on Impurities in New Drug Substances (Q3A), February 2003. Similarly, the bacterial endotoxin levels were below the limit for products for intrathecal administration.

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

All CMC aspects have been adequately addressed and supported by data. The Applicant provided a narrative description and flow diagrams describing the manufacturing process. Also it included executed batch records for solution preparation and filling of one of the full scale batches used in the primary stability program for the drug, and blank master batch records that detail the commercial process up through filling of the product.

The container is composed of [ ] amber glass vial (2 mL), [ ] closure (13 mm in diameter) and an overseal. The [ ] closure is especially

designed to prevent any components leaching from the [ ] closure into the injection. The surface of the [ ] closure [ ] that is in contact with the formulation is covered with [ ] [ ]

components from the [ ] closure. .

The Applicant provided [ ] stability data on three commercial lots stored at  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$  inverted and for — months at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  inverted. In addition, stability data on pilot scale lots for up to 24 months as well as results of temperature cycle and photo stability testing were included in this submission.

The [ ] data at  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$  inverted, showed that the product was stable and all values were well within specifications. The [ ] data for samples stored at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  inverted showed that the morphine sulfate content remained unchanged. However, the free morphine was [ ] specifications. Some [ ] were observed, as well as slight reduction in the liposome size and reduction of the pH.

The 24 month data from a pilot scale batch stored at  $8^{\circ}\text{C} \pm 2^{\circ}\text{C}$  were also well within specifications.

The Agency's statistical analysis of the [ ] data of the three commercial lots showed that the drug product was able to meet the 24 months expiration dating period for the following parameters: morphine content, free morphine, [ ] [ ]

pH, particle size distribution and the Day-3 and Day-4 in-vitro release test. The statistical analysis showed that the drug product could not meet the in-vitro release for the Day-1 and Day-2 day. Closer examination revealed that only one lot failed because [ ] [ ]

] The Agency's statistical review also indicated that if [ ] did not exist then the drug product would have met the 24 months for the Day-1 and Day-2 in-vitro release. Since the rest of the parameters met the expiration dating period of 24 months, it was concluded that the Applicant's request for a shelf-life of 24 months when stored between  $2^{\circ}\text{C}$  and  $8^{\circ}\text{C}$  should be granted. The only restriction being

of avoiding freezing the drug product. The Applicant will be requested to further investigate [ ] and report to the Agency.

The Applicant requested a categorical exclusion pursuant to 21 CFR 25.31(b). This was based on the Applicant's certification that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb), calculated according to FDA's Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, July 1998. It is recommended that the Applicant's request be granted.

As of May 5, 2004, Compliance has determined that all six facilities related to manufacturing, quality control and packaging of this drug product were acceptable.

Cholesterol is the only component in this drug product [ ] It is manufactured from [ ]

This NDA made reference to ten DMFs. All DMFs were found to be adequate for supporting this NDA. This reviewer wrote reviews for seven of these DMFs. Comments and deficiencies have been conveyed to the DMF holders. These comments and deficiencies did not impact the safety of the drug product.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Review Chemist/MCTheodorakis/  
Team Leader/RSHarapanhalli/  
CSO/KCompton/

#### C. CC Block

114 Page(s) Withheld



§ 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

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

/s/

-----  
Michael Theodorakis  
5/14/04 04:33:17 PM  
CHEMIST

Ravi Harapanhalli  
5/14/04 05:25:36 PM  
CHEMIST  
AP with comments/agreements