

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-897

CHEMISTRY REVIEW(S)

2nd Cycle

CHEMISTRY REVIEW

NDA 21-897

**VivitrolTM (naltrexone for extended-release
injectable suspension)**

Alkermes, Inc.

Jila H. Boal, Ph. D.

**Division of Pre-marketing Assessment III and
Manufacturing Science, ONDQA**

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Chemistry Review Data Sheet

1. NDA # 21-897
2. REVIEW #: 2
3. REVIEW DATE: April 7, 2006
4. REVIEWER: Jila H. Boal, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

Type C Industry Meeting Minutes	July 11, 2002
Pre-NDA CMC Meeting Minutes	February 2, 2005
Type C Industry Meeting Minutes	July 11, 2002
IND 61,138, Serial No. 069	December 10, 2004
Pre-NDA CMC Meeting Minutes	February 2, 2005
IND 61,138, Serial No. 078	February 22, 2005
IND 61,138, Serial No. 079	February 25, 2005
N-0000 (Original Application)	31-March-2005
N-000BM (Amendment 0001)	11-May-2005
N-0000 (Amendment 0002)	31-March-2005
N-000-SU (Amendment 0013)	29-July-2005
N-000-BC (Amendment 0017)	16-August-2005
N-000-BC(Amendment 0029)	04-October-2005
N-000-BC(Amendment 0032)	14-October-2005
N-000-BC(Amendment 0033)	27-October-2005
N-000-BC(Amendment 0034)	November 3, 2005
N-000-BC(Amendment 0035)	November 4, 2005
N-000-BC(Amendment 0036)	November 14, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

N-000-BC(Amendment 0043)

February 13, 2006

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: *Alkermes, Inc.,*
Address: 88 Sidney Street
Cambridge, MA 02319
Representative: Priya Jambhekar, Global Vice President,
Regulatory and Government Affairs
Telephone: (617) 583-6547

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Vivitrol
- b) Non-Proprietary Name (USAN): Naltrexone
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3 (new dosage form)
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2). Reference listed drug (RLD) is Revia (Naltrexone HCl) Tablets, 50-mg (NDA 18-932).

10. PHARMACOL. CATEGORY: Treatment of alcohol dependence

11. DOSAGE FORM: Injectable Suspension

12. STRENGTH/POTENCY: 380 mg

13. ROUTE OF ADMINISTRATION: Intramuscular (IM)

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
Ruminant-derived materials from bovine spongiform encephalopathy (BSE)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not used or manipulated in the manufacturing facility as noted in the BSE statements for _____, naltrexone base anhydrous, 75:25 _____ polymer, _____, carboxymethylcellulose and WFI.

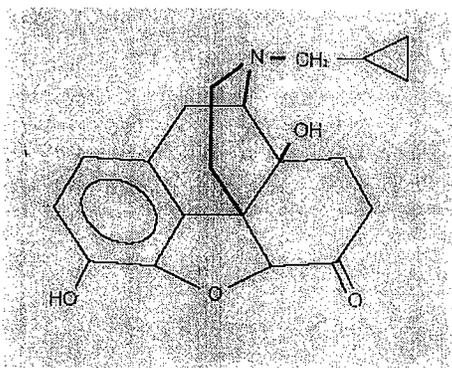
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Morphinan-6-one,17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-,(5 α).

CAS REGISTRY NUMBER: 16590-41-3

MW: 341.41 Daltons

Molecular Formula: C₂₀H₂₃NO₄



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

CHEMISTRY REVIEW

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS	DATE REVIEW COMPLETED	COMMENTS
8481	II	Alkermes	Medisorb 7525 polymer	1	Adequate	November 2, 2005	Reviewed by Chien-Hua Niu, Ph.D.
	II		Naltrexone Base Anhydrous	1	Adequate	September 23, 2005	Reviewed by Jila H. Boal Ph.D.
	II			1	Adequate	September 23, 2005	Reviewed by Jila H. Boal Ph.D.
14028	II	Alkermes, Inc.	Microsphere Diluent	1	Adequate	August 7, 2005	Reviewed by Jila H. Boal Ph.D.
	III			1	Adequate	October 7, 2005	Reviewed by Jila H. Boal Ph.D.
	III			3	Adequate	September 3, 2004	Reviewed by Jila H. Boal Ph.D.
	III			1	Adequate	October 7, 2005, Review # 4	Reviewed by Jila H. Boal Ph.D.
	III			1	Adequate	October 9, 2005, Review # 1	Reviewed by Jila H. Boal Ph.D.
	III			3	Adequate	December 12, 2001 and September 9, 2005	Gurpreet Gill-Sangha, Ph.D. and Donald Klein, Ph.D.
	III			4	Adequate	N/A	Sufficient information is provided in the NDA

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

6 – DMF not available

7 – Other (explain under "Comments")

² 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	61, 138	Original IND
NDA	18-932	Revia, Naltrexone Hydrochloride Tablet, 50 mg
—	—	Syringe, —
—	—	Syringe, —
—	—	Needle. Hypodermic —
		— Safety Needle

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Consulted		
EES	Acceptable	August 26, 2005	Mark E Parmon
Pharm/Tox	<ul style="list-style-type: none"> Acceptable with respect to qualification of the drug substance and the drug product acceptance criteria for the level of impurities. Acceptable with respect to toxicology qualification of the excipient in the drug product. 	April 7, 2006	Mamata De, Ph.D.
ClinicalPharm	<p>A mutual agreement was reached between the CMC and clinical Pharmacology discipline for the following phase 4 commitment:</p> <ol style="list-style-type: none"> The drug release specifications should be revised with addition of Day 14 and Day 28 drug release information. 	April 7, 2006	Srikanth C. Nallani, Ph.D.

CHEMISTRY REVIEW

Chemistry Review Data Sheet

	2. The acceptance criteria for drug release will be revisited after production of five commercial batches of the product or at the end of the first year from the date of the approval letter, whichever comes earlier.		
LNC	LNC recommended the following established name for Vivitrol: “Vivitrol (naltrexone for extended-release injectable suspension)”. The detail of the LNC recommendation for the established name is captured in the review of the Container and Carton Labels in DFS.	October 27, 2005	Dr. Guirag Poochikian, the LNC chair
Methods Validation	Validation of dissolution, assay and impurities test methods will be initiated by this reviewer after test methods are finalized based on the post-marketing commitment listed above.		Jila H. Boal, Ph.D.
DMETS and DDMAC	The first recommended name “Vivitrex” was not acceptable. The proprietary name “Vivitrol” was accepted by DMETS. With respect to package labels and drug product package inserts, while most of the DMETS recommendations were accepted by the chemistry discipline, a few comments were not considered in the interest of maintaining the clarity and prominence of the labels. For example, the contents of the diluents don’t need to be listed in the _____; instead they could be moved to the side panel. See DMETS review in DFS.	July 31, 2005	Michelle Safarik, PA-C, Regulatory Review Officer Iris Masucci, PharmD, Labeling Reviewer
EA	Acceptable, categorical exclusion granted as per information <i>Alkermes</i>	As per this review	Jila H. Boal, Ph.D.
Microbiology	Recommended for approval	October 24, 2005	Stephen E. Langille, Ph.D.

The Chemistry Review for NDA 21-897

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the standpoint of Product quality CMC, NDA 21-897 is recommended for approval. An expiration period of 18 months may be granted based on the assessment of the stability data.

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

All of the outstanding approvability issues have been resolved for the "approval" recommendation for this NDA. The phase four commitments listed below should be conveyed to the applicant.

1. Provide a commitment that the specification for the in vitro drug release testing will be revised to include day-14 and day-28 time points. This commitment starts from the production of first drug product batch.
2. The acceptance criteria for in vitro drug release should be revised after production of five commercial batches of the drug product or after one year from the date of the approval letter, which ever comes first.
3. Based on the above batch experience, need to establish a specification to control the percent crystallinity in Vivitrol will be assessed.
4. Submit the results of the above studies in a CBE-30 supplement.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Jila Boal, Ph.D., CMC Reviewer, ONDQA/ April 7, 2006
Ravi S. Harapanhalli, Ph.D., CMC Branch Chief, DPAMS, ONDQA/ April 7, 2006
Lisa Basham-Cruz, Project Manager, DAARP

C. CC Block

2 Page(s) Withheld

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/s/

Jila Boal
4/7/2006 04:32:08 PM
CHEMIST

Ravi Harapanhalli
4/7/2006 04:57:50 PM
CHEMIST

NDA 21-897

**VivitrolTM (naltrexone for extended-release
injectable suspension)**

Alkermes, Inc.

Jila H. Boal, Ph. D.

**Division of Pre-marketing Assessment III and
Manufacturing Science, ONDQA**



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Chemistry Review Data Sheet

1. NDA # 21-897
2. REVIEW #: 1
3. REVIEW DATE: October 20, 2005
Revised November 23, 2005
4. REVIEWER: Jila H. Boal, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Type C Industry Meeting Minutes
Pre-NDA CMC Meeting Minutes

Document Date

July 11, 2002
February 2, 2005

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IND 61,138, Serial No. 079
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N-0000 (Amendment 0002)
N-000-SU (Amendment 0013)
N-000-BC (Amendment 0017)
N-000-BC(Amendment 0029)
N-000-BC(Amendment 0032)
N-000-BC(Amendment 0033)
N-000-BC(Amendment 0034)
N-000-BC(Amendment 0035)
N-000-BC(Amendment 0036)

Document Date

July 11, 2002
December 10, 2004
February 2, 2005
February 22, 2005
February 25, 2005
31-March-2005
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14-October-2005
27-October-2005
November 3, 2005
November 4, 2005
November 14, 2005



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: *Alkermes, Inc.,*
Address: 88 Sidney Street
Cambridge, MA 02319
Representative: Priya Jambhekar, Global Vice President,
Regulatory and Government Affairs
Telephone: (617) 583-6547

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Vivitrol
- b) Non-Proprietary Name (USAN): Naltrexone
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3 (new dosage form)
 - Submission Priority: P

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12. STRENGTH/POTENCY: 380 mg

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14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
Ruminant-derived materials from bovine spongiform encephalopathy (BSE)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not used or manipulated in the manufacturing facility as noted in the BSE statements for _____, _____, naltrexone base anhydrous, 75:25 _____ polymer, _____, carboxymethylcellulose and WFI.

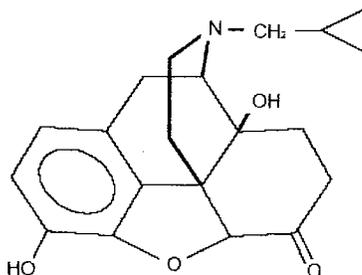
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Morphinan-6-one,17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-,(5 α).

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MW: 341.41 Daltons

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A. DMFs:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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	III			4	Adequate	N/A	Sufficient information is provided in the NDA

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1 – DMF Reviewed.

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

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Chemistry Review Data Sheet

6 – DMF not available
 7 – Other (explain under "Comments")

² 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	61, 138	Original IND
NDA	18-932	Revia, Naltrexone Hydrochloride Tablet, 50 mg
		Syringe, /
		Syringe, /
		Needle. Hypodermic, /
		Needle Safety

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Consulted		
EES	Acceptable	August 26, 2005	Mark E Parmon
Pharm/Tox	Pending		Mamata De, Ph.D.
ClinicalPharm	Acceptable provided that a mutually satisfactory agreement can be reached between the Agency and Alkermes regarding the a) The drug release specifications should be revised with addition of Day 14 and Day 28 drug release information. b) Conduct in vitro CYP inhibition studies using conventional substrates as the submitted data used florescent substrate(s) which tends to introduce nonspecificity in detection. c) Conduct in vitro studies in human hepatocytes to evaluate potential of naltrexone to induce CYP3A4 and CYP1A2.	11/21/2005	Srikanth C. Nallani, Ph.D.
LNC	LNC recommended the following established name for Vivitrol:	10/27/2005	Dr. Guirag Poochikian, the



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	<p>“Vivitrol (naltrexone for extended-release injectable suspension)”.</p> <p>The detail of the LNC recommendation for the established name is captured in the review of the Container and Carton Labels in DFS.</p>		LNC chair
Methods Validation	<p>Pending</p> <p>Validation of dissolution, assay and impurities test methods will be initiated by this reviewer after test methods are finalized.</p>		Jila H. Boal, Ph.D.
DMETS and DDMAC	<p>The first recommended name “Vivitrol” was not acceptable. The proprietary name “Vivitrol” was accepted by DMETS. With respect to package labels and drug product package inserts, while most of the DMETS recommendations were accepted by the chemistry discipline, a few comments were not considered in the interest of maintaining the clarity and prominence of the labels. For example, the contents of the diluents don’t need to be listed in the _____ instead they could be moved to the side panel.</p> <p>See DMETS review in DFS.</p>	July 31, 2005	Michelle Safarik, PA-C, Regulatory Review Officer Iris Masucci, PharmD, Labeling Reviewer
EA	<p>Acceptable, categorical exclusion granted as per information <i>Alkermes</i></p>	As per this review	Jila H. Boal, Ph.D.
Microbiology	<p>Recommended for approval</p>	October 24, 2005	Stephen E. Langille, Ph.D.



The Chemistry Review for NDA 21-897

The Executive Summary

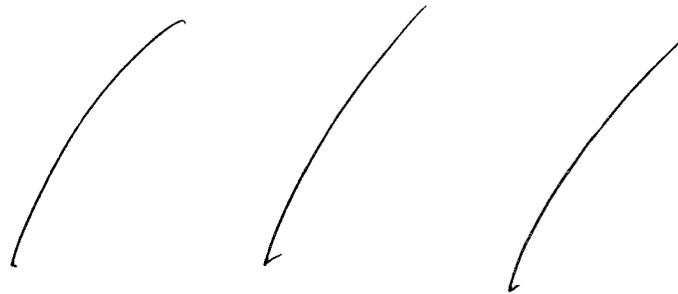
I. Recommendations

A. Recommendation and Conclusion on Approvability

From the standpoint of Product quality CMC, NDA 21-897 is recommended for approval. An expiration period of 18 months may be granted based on the assessment of the stability data.

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

The data provided in the NDA clearly indicate the correlation between in vitro drug release at Day 7 and _____ s.



Therefore, provide an agreement that percent crystallinity and the in vitro drug release will be assessed for the first five commercial batches of Vivitrol and the ranges for the in vitro drug release will be tightened and a specification to limit percent crystallinity of naltrexone in the microspheres _____

Provide this information in a "changes-being-effected in 30 days" supplement following the approval of the NDA.

The commercial batches could be released if the drug release acceptance criteria of Δ Day 7–Day 14 = _____ is achieved with the provision that in-vitro drug release test should be carried up to day 30. If the batch fails the test at that time, then the batch will be recalled.

II. Summary of Chemistry Assessments

Introduction:

Chemistry Assessment Section

The NDA was reviewed under priority review time clock. The entire submission is electronic and is provided in eCTDQ format. Several CMC issues were resolved during the course of this review; therefore this review is comprehensive and includes the assessment of CMC information from the original submission as well as from several subsequent submissions. Several comments pertaining to the carton and container labels were generated by the CMC and DMETS disciplines and were conveyed to the applicant and were resolved. The proposed tradename Vivitrol was accepted by the medical division and DMET (see DMET's consult reviews in DFS). The established name was revised from "naltrexone long acting injection" to "naltrexone for extended-release injectable suspension" in consultation with the Labeling and Nomenclature Committee.

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

Drug Product:

Vivitrol (Naltrexone for Extended-release Injectable Suspension) are parenteral microspheres. The drug product is composed of naltrexone incorporated into a biodegradable polymer matrix, polylactide-co-glycolide (PLG). The manufacturing process is the proprietary Medisorb technology developed by *Alkermes*. The Medisorb drug delivery technology is designed to enable injectable extended-release formulations lasting days to months to be made for products normally given orally or by frequent injections.

Drug Substance:

Naltrexone is an opioid antagonist and is widely used for opioid detoxification. It is available as naltrexone hydrochloride salt as well as the anhydrous base. The crystalline naltrexone base is anhydrous.

The anhydrous base is the most suitable form for formulation of naltrexone extended release microspheres, because it is low in water content and is stable.

Distinctive properties of naltrexone base anhydrous are as follows:

- **Appearance:** Off-white to light tan powder.
- **Melting point:** 168-170°C.
- **Specific Gravity:** ca. 1.3
- **Ionization Constant:** $pK_{a1} = 8.13$
- **Partition Coefficient:** $\log P_{oct} = 1.92$





Chemistry Assessment Section

Manufacture, characterization, control, reference standards, container-closure system, and stability of naltrexone base anhydrous drug substance, are provided via reference to DMF. The DMF was deemed adequate to support the NDA following review and resolution of critical CMC issues.

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

At the time of administration, Vivitrol microspheres are suspended in microsphere diluent to form Vivitrol suspension. The procedure for the preparation of the suspension is included in the "Directions for Use" section of the package insert. A copy of the direction is provided at the end of this review.

Vivitrol suspension is stable for at least 2 hours at controlled room temperature (25 ±2°C/60% ± 5% RH). Data from this study are summarized in section 3.2.P.8.1 of the NDA submission and the submitted stability data are evaluated in the drug product stability section of this review. Note that regardless of the 2 hour stability data, "Directions for Use" in the package insert directs health practitioners to administer Vivitrol suspension immediately upon preparation.

Proposed marketed product presentation:

Vivitrol will be marketed as a kit containing:

- One 5 mL vial containing a 380 mg dose of Vivitrol microspheres packaged as a dry, free-flowing powder.
- One 5 mL vial containing 4 mL of sterile, aqueous diluent to prepare a suspension for injection.
- One 5 ml syringe
- One ½ " 20 gauge needle
- Two 1½ " 20 gauge needles with safety device

The kit contains also a Patient Package Insert, Physician Package Insert and a "Directions for Use" leaflet.

C. Basis for Approvability or Not-Approval Recommendation

The main issue with the CMC assessment was the evaluation of the scale up of the manufacturing process from to . All pivotal clinical batches and primary stability batches were manufactured at scale and was proposed for commercialization. During the EOP2 and Pre-NDA meetings, the Agency commented on this scale up process and provided critical set of criteria to demonstrate the equivalence of the two processes for the NDA.



Chemistry Assessment Section



Evaluation of the sterility and sterility test method and validation was consulted to the microbiology discipline. Adequacy of the microbial quality of the drug product was assessed by the microbiology reviewer Stephen E. Langille, Ph.D., who deemed it to be adequate for NDA approval (review in DFS).

The comparability of the commercial process with the pilot scale process was demonstrated and established based upon the assessment of the following data:

- Same product components and composition
- Same manufacturing process (except for scale-related changes)
- Comparable in-process tests for _____
- Demonstration of comparable product quality attributes
- Comparable dissolution curves as assessed using f2 methodology (tiered approach for a multi-phase release product)
- Comparable percent yield for microsphere formation and isolation in the _____ vs _____ scale _____ percent yield for the _____ process vs _____ yield for the _____ scale)
- Comparable drug _____ vs _____ scale (i.e. _____)



Chemistry Assessment Section

- Comparable microsphere particle size distribution for the _____ vs _____ batches

The drug product specifications for release and stability monitoring have been adequate to ensure the product quality for its intended use. They include _____

As discussed during the Pre-NDA meeting, data was provided showing uniform release of the drug and its degradation products from the microspheres to support a maximum daily dose of approximately 26 mg of naltrexone. This resulted in a qualification threshold of _____ for the impurities and degradation products in the drug product.

Three impurities, namely: _____

_____ were identified in the drug substance and the drug product and they did not exceed the qualification threshold. An _____

_____ was identified in naltrexone and is currently controlled with an interim limit of not more than _____ until March of 2007 when its limits would be tightened to not more than _____ according to the agreement with the DMF holder.

Drug release from the microspheres is through: _____

_____ This occurs in a controlled fashion in three phases, initial drug washout phase, hydration phase, and sustained release phase. The UV based spectrophotometric method for the drug release was cross-validated with stability-indicating HPLC method and was deemed acceptable for regulatory testing. Using a release medium of phosphate buffer at pH 7.4 and at 37°C, the acceptance criteria for drug release were accepted on interim basis to include the following.

<u>Real Time In-Vitro Release</u>	<u>Proposed Release Criteria</u>	<u>Proposed Shelf life Criteria</u>
Day 1	_____	_____
Day 7	_____	_____
Δ Day 7–Day 14	_____	_____

The data indicated variability in the drug release on day 7 for the batches used in the clinical studies. The data also showed the rate and amount of drug release both increased with increasing temperatures (e.g. $\geq 40^\circ\text{C}$). Thus, there is the potential for rapid drug release and increased exposure in patients with elevated temperatures, e.g. during a fever. The data also showed that, on average, about 30% of naltrexone is released



Chemistry Assessment Section

during the first 7-10 days. This corresponds to release of approximately 114 mg of naltrexone in the initial 1-2 weeks. The Applicant proposes an upper limit drug release specification of about μ . This means that there is the potential for release of approximately μ mg of naltrexone in the first 2 weeks. In consultation with the medical reviewer, Dr. Kashoki it was determined that this was acceptable from safety considerations since patients have previously been dosed with similar doses of oral naltrexone, without significant adverse effects. However, since higher doses of naltrexone have previously been associated with adverse events, the drug release specifications should remain as 'tight' as can be reasonably achieved. Therefore, applicant is being asked to revise the specifications following accrual of additional manufacturing experience from five consecutive commercial batches.

As discussed during the Pre-NDA meeting of February 2, 2005, the applicant provided the in-vitro drug release data over 30-day period as well as projected cumulative drug release over 30-day period based on calculations from day-14 release data. Linear regression analysis of cumulative release vs. time over this interval for the μ and the μ batches yielded slopes ranging from μ per day with model fit (R^2) values of 0.912 to 0.999. Accordingly, the portion of the curve from Day 7 to Day 14 is considered indicative of the entire drug release phase from day 14 to the end i.e., day 30. The amount of drug released between Day 7 and Day 14 from the μ GMP lots and the μ development/comparability batches ranged from μ to μ with a mean of $18.0\% \pm 2.4\%$ SD.

Based on the above arguments, it will be conceivably safe to allow release of the commercial batches if the drug release acceptance criteria of Δ Day 7–Day 14 = μ is achieved with the provision that in-vitro drug release testing be continued up to day 30.

The CMC of Medisorb 75:25 μ polymer is supported by the DMF # 8481, which was deemed adequate following the review of DMF amendment. The CMC information for the diluent is supported by DMF 14028, which is adequate to support the NDA. Adequate data is provided on container closure integrity to support the proposed container closure systems. The primary packaging components are supported through several DMFs and these DMFs were found adequate (see the section on the drug product container closure, in this review).

Commercial drug product vials consists of 5 mL, USP Type 1, colorless glass vial, 20 mm μ gray μ rubber stopper, 20 mm aluminum μ seal with flip off cap. In support of the proposed expiration dating period, applicant provided 12 months stability data for three batches of 380 mg strength at μ scale, 18 months stability data for three batches of 190 mg strength at μ scale, and 3 months of stability data for three batches of 380 mg strength at proposed μ commercial scale. Applicant's proposed expiration dating period of μ is not supported by these data. However, 18 months may be granted for the product stored as dry microspheres in the commercial vials at refrigeration ($2-8^\circ\text{C}$). The

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Memo to File: NDA 21897 (Container and Carton Labels)
Vivitrol (naltrexone for extended-release injectable suspension)
Jila Boal, Ph.D. and Ravi S. Harapanhalli, Ph.D.
Division of Premarketing Assessment III and Manufacturing Science, ONDQA
October 31, 2005

VIVITROL is supplied as a microsphere formulation of naltrexone for suspension, to be administered by intramuscular injection. It is a combination of extended release microspheres for injection and a diluent for parenteral, intramuscular use. Vivitrol microspheres consist of a sterile, off-white to light-tan powder that is available in dosage strength of 380 mg naltrexone per vial. Naltrexone is micro-encapsulated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 337 mg of naltrexone per gram of microspheres. The diluent for parenteral use is a clear, colorless viscous solution. The composition of the diluent includes carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection. The microspheres are suspended in the diluent prior to injection.

HOW SUPPLIED:

VIVITROL is supplied in single use kits. Each kit contains one 380 mg vial of VIVITROL microspheres, one vial containing 4.0 mL (to deliver 3.4 mL) Diluent for the suspension of VIVITROL, one 5 mL syringe, one ½" 20 gauge needle, and two 1½" 20 gauge needles with safety device: NDC 65757-402-05.

Vivitrex Commerical Kit – Primary Packaging Components

Kit component	Description	Quantity	Label text	510K Premarket Notifications
Vivitrex Microsphere vial	5 mL, USP Type I, colorless glass vial	1	Draft vial label text	NA
Diluent vial	5 mL, USP Type 1, colorless glass vial	1	Draft diluent vial label text	NA
Plastic syringe	5 mL plastic syringe	1	Syringe label	
Injection needle	20-gauge 1 ½ inch safety needle	2	Injection needle label	
Suspension needle	20-gauge ½ inch needle	1	Suspension needle label	
Package Insert (PI)	Package Insert	1	Draft PI	NA
Patient Package Insert (PPI)	Patient Package Insert	1	Draft PPI	NA

DFU	Directions for Use	1	Draft DFU	NA
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NA = not applicable

Vivitrol Kit – Secondary Packaging Components

KIT Component	Description	Label Text	Drawing
Tray with lid	Tray with lid	Draft tray lid text	Tray, Lid
Cardboard carton	Cardboard carton	Draft carton text	Carton

Evaluation:

It is not clear why two administration needles are provided in the kit in addition to the withdrawal needle. Presence of two administration needles should not imply multiple use for this single use vial. There should not be any issues with blocking of the needle because the suspension would have already passed through the withdrawal needle before it is replaced with the application needle. The applicant should provide a justification for the inclusion of two administration needles.

The diluent contains carboxymethylcellulose and although it is true that the specification for viscosity is included for the diluent, a limit for the molecular weight range of carboxymethylcellulose should be provided to better control the physical properties of CMC that may directly impact syringeability of the drug product suspension.

Comments to the applicant:

Provide a justification for the inclusion of two administration needles in the kit that is labeled for single use.

Provide a specification to control the molecular weight range for carboxymethylcellulose, a component of the diluent.

The following comments on the container and carton labels were generated based on the following assessments.

1. CMC review of the carton and container labels (Ravi Harapanhalli and Jila Boal)
2. The review by Division of Medication Errors and Technical Support (DMETS), ODS.
3. Labeling and Nomenclature Committee review of the established name

CMC discipline assessed the adequacy of the container and carton labels and also reviewed the recommendations of the DMETS. While most of the DMETS recommendations were accepted, a few comments were not considered in the interest of maintaining the clarity and prominence of the labels. For example, the contents of the diluents don't need to be listed in the _____ instead they could be moved to the side panel.

The originally proposed proprietary and established names were the following:

“Vivitrex (naltrexone long-acting injection)”

The DMETS disagreed with the proprietary name and asked the firm to propose an alternative. Finally, “Vivitol” was accepted by the DMETS as the proprietary name. In the mean time, the CMC discipline consulted Dr. Guirag Poochikian, the LNC chair, for the appropriateness of the proposed established name. In doing so, the CMC discipline proposed the following established name.

“Naltrexone for Injectable Suspension Extended-release”

During the LNC meeting the discussion centered around whether the modifier “extended-release” is appropriate for the established name. The CDER Data Standards Manual recognizes “Injectable Suspension Extended-release” as a distinct category of four types of injectable suspension parenterals with the following definitions.

INJECTION, SUSPENSION	A liquid preparation, suitable for injection, which consists of solid particles dispersed throughout a liquid phase in which the particles are not soluble. It can also consist of an oil phase dispersed throughout an aqueous phase, or vice-versa.	INJ SUSP	704
INJECTION, SUSPENSION, SONICATED	A liquid preparation, suitable for injection, which consists of solid particles dispersed throughout a liquid phase in which the particles are not soluble. In addition, the product is sonicated while a gas is bubbled through the suspension, and this results in the formation of microspheres by the solid particles.	INJ SUSP SON	840
INJECTION, SUSPENSION, LIPOSOMAL	A liquid preparation, suitable for injection, which consists of an oil phase dispersed throughout an aqueous phase in such a manner that liposomes (a lipid bilayer vesicle usually composed of phospholipids which is used to encapsulate an active drug substance, either within a lipid	INJ SUSP LIPOS	714

	bilayer or in an aqueous space) are formed.		
INJECTION, SUSPENSION, EXTENDED RELEASE	A sterile preparation intended for parenteral use which has been formulated in a manner to allow at least a reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g., as a solution or a prompt drug-releasing, conventional solid dosage form).	INJ SUSP ER	711

The issue was whether the term "Suspension" implies the extended-release nature of the formulation or not. Not all injectable suspensions are meant to extend the duration of dose delivery. For example, the ultrasound contrast agents consist of microspheres of fluorocarbon gases and these are classified as suspensions and are not meant to extend the dose delivery rate. Another question was whether this product is meant to reduce the dosing frequency and whether the strength is expressed as naltrexone concentration. The answer is yes. The product is meant for once-a-month injection over which period, naltrexone is released systemically. There is an approved naltrexone injection that is not meant to reduce the dosing frequency. The strength is expressed as naltrexone concentration.

The other related terms "implant" and "depot" were considered inappropriate for this product. The CDER manual lists "implant" as a dosage form but not "depot."

IMPLANT	A material containing drug intended to be inserted securely of deeply in a living site for growth, slow release, or formation of an organic union.	IMP	715
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VIVITROL is an intramuscular injection, not an implant because once injected, it may not be possible to remove the product.

Based on the above discussion, two names were proposed by LNC in consultation with CMC review discipline.

(drug extended-release for injectable suspension)

(drug for extended-release injectable suspension)

Member of the LNC, Yana Mille discussed this issue with the USP and informed us that the second option is the preferred one for all. Therefore, the following established name would be recommended for Vivitrol:

"Vivitrol (naltrexone for extended-release injectable suspension)"

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