CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022462Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-462

Baclofen Injection (Intrathecal)

CNS Therapeutics, Inc.

Akm Khairuzzaman, Ph.D.
ONDQA Pre-Marketing Assessment
Division I/Branch I

Reviewed for the Division of Neurology Products, HFD-120

Chemistry Review Data Sheet

1. NDA 22-462

2. REVIEW #: 2

3. REVIEW DATE: 03-December-2009
   Revised: 18-December-2009
   Revised March 15, 2010

4. REVIEWER: Akm Khairuzzaman, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Chemistry Review of NDA-22-462	12/22/2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Information Ammendment 0013	28-Jan-2010

7. NAME & ADDRESS OF APPLICANT:

Name	CNS Therapeutics, Inc.
Address	332 Minnesota Street, Suite W1750 St. Paul, MN 55101 USA
Representative	John J. Foster, Chief Executive Office
Telephone	(651) 207-6959
FAX Number	(651) 340-2102

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	N/A
Non-Proprietary Name (USAN)	Baclofen Injection (Intrathecal)
Code Names	N/A
Chemistry Type	5
Submission Priority	S

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

10. PHARMACOL. CATEGORY: Muscle relaxer and an antispastic agent

11. DOSAGE FORM: Intrathecal injection

12. STRENGTH/POTENCY: 0.05 mg/ml, 0.5 mg/ml, 2.0 mg/ml (b)(4)

13. ROUTE OF ADMINISTRATION: Intrathecal

14. Rx/OTC DISPENSED: __**X**__Rx _____OTC

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

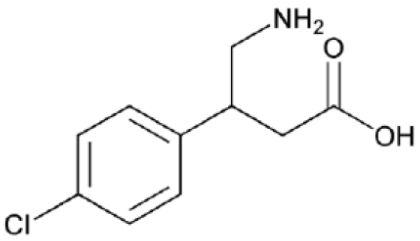
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical Names: Butanoic acid,
4-amino-3-(4-chlorophenyl)-.;
β -(Aminomethyl)-p-chlorohydrocinnamic acid

US Adopted Name (USAN): Baclofen
Laboratory Codes: N/A



Chemical Formula: $C_{10}H_{12}ClNO_2$
Molecular Weight: 213.66
CAS Number: 1134-47-0

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)	II N°		(b) (4)	3	Adequate	24-July-2008 (Wilson, Wendy)
	III			3	Adequate	15-Feb-2000 (Joseph Sieczkowski)
	III			4	Adequate	11-Dec-2009 (Akm Khairuzzaman)
	III			3	Adequate	27-Jan-2006 (Rodriguez, Libaniel)
	III			3	Adequate	29-Aug-2005 (Elsbeth Chikhale) 18-June-2009 (Zedong Dong)
	III			3	Adequate	10-Oct-2007
	III			4	Adequate	13-Oct-2009 (Klein, Donald)

[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 is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	31-August-2009	M. Stock
LNC	N/A	----	----
Methods Validation	Not Necessary	----	----
OSE-DMEPA		----	----
EA	Categorical Exclusion: Acceptable	See Review Date Above	A. Khairuzzaman
Microbiology	Acceptable	12/02/2009	Denise Miller

The Chemistry Review for NDA 22-462

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The original review (# 1, dated 12/22/2009) was concluded as "not approvable" from CMC point of view due to deficiency of some CMC information. Based on the information provided by the sponsor on January 28th, 2010, this new drug application (22-462) **can be recommended for approval from the perspective of chemistry, manufacturing, and controls**.

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this review).

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

None.

II. Summary of Information Amendment

Baclofen is a product that has been in the US market for a long period of time for the treatment of spasticity. It's intrathecal injection dosage form originally owned by Medtronic, Inc. under the trade name, Lioresal® was approved on June 17, 1992 under the NDA # 02-0075. But they are available in concentrations of 0.05 mg/mL, 0.5 mg/mL, and 2 mg/mL. This sponsor (CNS) has developed intrathecal Baclofen as a sterile, pyrogen-free, isotonic solution (b) (4) concentrations: 0.05 mg/mL, 0.5 mg/mL, 2 mg/mL (b) (4). A full CMC review (#1) was conducted and can be found in FDA's database, however, that first review (dated 12/22/2009) was concluded as "not approvable" due to deficiency of the following CMC information:

(a) Data on drug products physical stability in pump and pump components simulating its actual use
(b) The susceptibility of precipitation once the drug product is in contact with any other drug product (e.g. morphine).
(c) Additional data on the RLD (reference listed drug product)-Medronic pump compatibility study.

This review (#2) captured only the information provided in amendments on January 28th, 2010. The information that the sponsor provided in response to our CMC questions are summarized as follows:

(a) **Data on drug products (2 mg/ml [redacted]) physical stability in pump and pump components simulating its actual use**: The sponsor conducted a physical stability study of the drug product [redacted] inside and at the tips of the catheter under the flow condition at 1.5 mL/hr through the catheter into Elliotts B solution. After collecting the first drop of the drug product through the catheter tip, the pump was then reset to 1.5 ml/day. The study was conducted for 24 hours at 37 °C. INDURA closed-tip intrathecal catheter model # 8711 was used in the study. [redacted] liquid laser particle counter was used to determine any particle/precipitation formation. The sponsor claimed no precipitation from three lots of the drug product lots. **Acceptable**.

(b) **The susceptibility of precipitation once the drug product is in contact with any other drug product (e.g. morphine)**: The sponsor conducted a short term precipitation study of the Baclofen drug product, (2 mg/ml [redacted] with [redacted] (25 mg/ml morphine) [redacted]. Three lots of each products were examined. Analytical data showed no precipitation, not a single particle observed [redacted]. The [redacted]. **Acceptable.**

(c) **Additional data on the RLD (reference listed drug product)-Medronic pump compatibility study**: New stability data on 2 additional lots of the reference listed drug product (1 month data) and 2 lots of CNS drug products (1 and 3 months data) along with statistical analysis has been provided in this amendment. No substantial differences in this additional data has been observed compared to the previously submitted for the reference product as well as for the CNS product. **Acceptable.**

In addition to the above data, the sponsor provided the following key sets of data in support of product's stability and they can be found in review # 1:

- A six months stability data of the drug product (packed under commercial package): Evaluation: **Satisfactory.**
- A six months compatibility data between the drug product and the drug device. Evaluation: **Satisfactory.**
- Six months leachable study was done on the drug product as well as from the pump environment. Evaluation: **Satisfactory.**
- Drug product – catheter (approved catheter currently in the market) compatibility was done for 117 hours. Evaluation: **Satisfactory.**
- A physical stability of the drug product inside the pump when operated under clinically simulated operating condition. Evaluation: **Satisfactory.**
- Precipitation study when the drug product is coming out of the catheter and placed into artificially simulated ceribro-spinal fluid (CSF). Evaluation: **Satisfactory.**

These information were found to be sufficient to support the stability of the CNS's drug product (all strengths). (b) (4) All strengths of the product were found to be stable for a period of 6 months into the pump to be used in actual clinical condition. Since each refill of the drug product would not last more than 3 months, the reviewer found that the duration of the drug product's stability study into the pump was sufficient. However, the pump is approved for an implant life of 7 years or more. As a result, the same quality drug product that is periodically going into the pump might encounter a continually changed pump's inner environment and therefore the stability data derived from a six month period of time (from the drug-pump compatibility study) may not be truly reflective of what could happen after several years once the pump has been implanted. But this would be considered as a pump related issue.

There is some controversy on Baclofen's aqueous solubility (precipitation occurs above 2 mg/ml concentration) that is reported in some literature, particularly a white paper published by Novartis/Medtronic. (b) (4)

Therefore, based on the **Chemistry, Manufacturing and Control**, this new drug application (22-462) can be **recommended for APPROVAL** for all the strengths: 0.05 mg/ml, 0.5 mg/ml, 2 mg/ml (b) (4).

III. Administrative

A. Reviewer's Signature

/s/ A. Khairuzzaman, Ph.D.

B. Endorsement Block

Chemistry Reviewer:	Akm Khairuzzaman, Ph.D.
Pharmaceutical Assessment Lead:	Martha Heiman, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.
Project Manager:	Don Henry

C. CC Block

Orig. NDA 22-462
HFD-120/Division File

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	ORIG-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

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

/s/

AKM KHAIRUZZAMAN
03/30/2010
APPROVED from CMC Point of View

MARTHA R HEIMANN
03/30/2010
Signed for Ramesh Sood

NDA 22-462

Baclofen Injection (Intrathecal)

CNS Therapeutics, Inc.

Akm Khairuzzaman, Ph.D.
ONDQA Pre-Marketing Assessment
Division I/Branch I

Reviewed for the Division of Neurology Products, HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-462

2. REVIEW #: 1

3. REVIEW DATE: 03-December-2009
   Revised: 18-December-2009

4. REVIEWER: Akm Khairuzzaman, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	27-Mar-2009

7. NAME & ADDRESS OF APPLICANT:

Name	CNS Therapeutics, Inc.
Address	332 Minnesota Street, Suite W1750 St. Paul, MN 55101 USA
Representative	John J. Foster, Chief Executive Office
Telephone	(651) 207-6959
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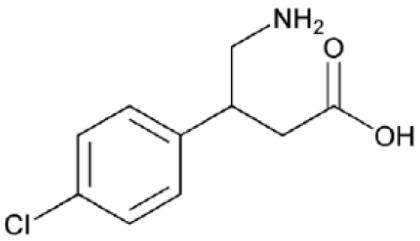
Laboratory Codes: N/A



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Methods Validation	Not Necessary	----	----
OSE-DMEPA		----	----
EA	Categorical Exclusion: Acceptable	See Review Date Above	A. Khairuzzaman
Microbiology			Denise Miller

The Chemistry Review for NDA 22-462

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (22-462) cannot be recommended for approval from the perspective of chemistry, manufacturing, and controls. Applicant agreed to send more CMC data on December 30th, 2009. Upon reviewing the data, a final CMC recommendation will be made.

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this review).

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

None.

II. Summary of Chemistry Assessments

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

Baclofen is approved in the United States for the treatment of spasticity. It is available as 10 mg and 20 mg tablets for oral administration, and as a sterile solution for intrathecal administration in concentrations of 0.05 mg/mL, 0.5 mg/mL, and 2 mg/mL. The only approved application for Baclofen Injection is NDA 20-075, which is owned by Medtronic, Inc. Medtronic distributes Baclofen Injection under the trade name, Lioresal®. Medtronic also manufactures and distributes the SynchroMed® II delivery systems that are used for chronic delivery of the drug into the intrathecal space.

Under this NDA, CNS Therapeutics (CNS) has developed intrathecal baclofen as a sterile, pyrogen-free, isotonic solution in four concentrations: 0.05 mg/mL, 0.5 mg/mL, 2 mg/mL [redacted] (b) (4) the applicant has submitted the current NDA as a 505(b)(2) application that relies on the Agency's prior findings of safety and efficacy for the reference listed drug, Lioresal®.

Drug Substance

Baclofen is a chemically-synthesized small molecule with molecular formula $C_{10}H_{12}ClNO_2$ and molecular weight 213.66. The chemical name is 4-amino-3-(4-chlorophenyl)butanoic acid (b) (4) The bulk drug substance is a white to off white crystalline solid (b) (4) It is slightly soluble in water, very slightly soluble in methanol (b) (4) The detailed CMC info in presented in the DMF (b) (4). The most recent review on this DMF was done on 24th July, 2008 and found to be adequate.

Drug Product

The drug product is a sterile, pyrogen-free, isotonic solution of baclofen (0.05 mg/mL, 0.5 mg/ml, 2 mg/ml (b) (4)). Each milliliter of Baclofen Injection contains Baclofen USP 0.05 mg, 0.5 mg, 2 mg, (b) (4) and Sodium Chloride USP 9 mg in Water for Injection. The formulated product is sterile and the excipient used is compendial. The (b) (4) strengths are quantitatively identical to the currently marketed product, Lioresal® Injection (NDA 20-075) (b) (4).

The pH range is 5.5 - 7.0. The 0.05 mg/mL strength is intended as a test dose used to screen patients for response to intrathecal baclofen. It will be marketed as a single use syringe containing 0.05 mg baclofen in 1 mL saline. The 0.5 mg/mL, 2 mg/mL (b) (4) strengths are intended for chronic use and should be administered intrathecally only via an implanted pump approved for use with baclofen. These strengths will be marketed as single use vials containing 20 mL per 20 mL vial (b) (4).

The NDA stability package includes one year long term stability data and six months accelerated stability data on 0.5 mg/ml (b) (4) products and nine (9) months long term stability data and six months accelerated stability data on 0.05 mg/ml product. A bracketing strategy was applied that included (b) (4) 3 batches of the 0.5 mg/mL (all 20 mL fills in vials), and three batches of the 0.05 mg/mL (all 1 mL fills in syringes) concentrations (a total of 9 stability batches). (b) (4) since the statistical analysis conducted on the lowest strength, 0.05 mg/ml was based on 9 months long term data, only 18 months of shelf life can be granted at this time.

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

Baclofen Injection (Intrathecal) is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, only in implantable pumps approved by the FDA specifically for the administration of Baclofen Injection (Intrathecal) into the intrathecal space. The lower strength, 0.05 mg/ml is for screening the patients and all other strengths, 0.5 mg/ml, 2 mg/ml (b) (4) are for chronic administration via the pump equipped with an injection port that allows direct access to the intrathecal catheter. The pump is placed by surgical procedure.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (22-462) is **PENDING** for approval from the perspective of chemistry, manufacturing, and controls. The sponsor is yet to submit data prior to PDUFA date on the followings:

(a) Data on drug products physical stability in pump and pump components simulating its actual use
(b) The susceptibility of precipitation once the drug product is in contact with any other drug product (e.g. morphine).
(c) Additional data on the RLD (reference listed drug product)-Medronic pump compatibility study.

Upon receiving data a final recommendation will be made at that time.

III. Administrative

A. Reviewer's Signature

/s/ A. Khairuzzaman, Ph.D.

B. Endorsement Block

Chemistry Reviewer:	Akm Khairuzzaman, Ph.D.
Pharmaceutical Assessment Lead:	Martha Heiman, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.
Project Manager:	Don Henry

C. CC Block

Orig. NDA 22-462
HFD-120/Division File

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22462	ORIG-1	CNS THERAPEUTICS INC	BACLOFEN INTRATHECAL INJ 0.05 MG/ML/0.5

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

/s/

AKM KHAIRUZZAMAN
12/22/2009
CMC approval is pending. Applicant is committed to submit more CMC data prior to PDUFA date.

RAMESH K SOOD
12/22/2009

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	22-462
Applicant:	CNS Therapeutics
Stamp Date:	30-Mar-2009
PDUFA Date:	30-Jan-2010
Trademark:	None proposed
Established Name:	Baclofen
Dosage Form:	Injection
Route of Administration:	Intrathecal
Indication:	Management of severe spasticity

PAL:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

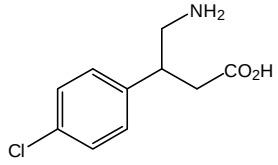
Summary

Baclofen is approved in the United States for the treatment of spasticity. It is available as 10 mg and 20 mg tablets for oral administration, and as a sterile solution for intrathecal administration in concentrations of 0.05 mg/mL, 0.5 mg/mL, and 2 mg/mL. There are a number of approved applications for Baclofen Tablets. The only approved application for Baclofen Injection is NDA 20-075, which is owned by Medtronic, Inc. Medtronic distributes Baclofen Injection under the trade name, Lioresal®. Medtronic also manufactures and distributes the SynchroMed® II delivery systems that are used for chronic delivery of the drug into the intrathecal space. A second intrathecal pump, the Codman Series 3000, is marketed by Johnson & Johnson and approved for use with baclofen.

CNS Therapeutics (CNS) has developed intrathecal baclofen (b) (4) concentrations, 0.05 mg/mL, 0.5 mg/mL, 2 mg/mL (b) (4) The (b) (4) strengths are quantitatively identical to the corresponding products marketed by Medtronic and would be eligible for submission under a generic ANDA. By prior agreement with the Agency, they are included in this NDA.

Drug Substance

The active ingredient, baclofen, is a small molecule with molecular formula $C_{10}H_{12}ClNO_2$ and molecular weight 213.66. The chemical name is 4-amino-3-(4-chlorophenyl)butanoic acid. (b) (4). The structural formula of baclofen is:



The bulk drug substance is a white to off white crystalline solid (b) (4) It is slightly soluble in water, very slightly soluble in methanol (b) (4)

Baclofen, USP is manufactured by (b) (4). DMF (b) (4) is referenced for information regarding the manufacture, characterization and control of the drug substance. The DMF was most recently reviewed in August 2006 (R. Iser, Adequate) and July 2008 (W. Wilson, Adequate to support IND studies).

Information in the NDA itself is limited to the manufacturing facility, summary of the drug substance specification, and certificates of analysis for drug substance batches used to manufacture drug product registration batches. Analytical methods and validation are referenced to current USP methods.

The (b) (4) and applicant's drug substance specifications are reproduced on the following pages. The current USP is referenced for the applicants test procedures. Refer to DMF (b) (4) for the manufacturer's analytical procedures. The primary difference between the manufacturer's specification and the applicant's specification is the (b) (4), which is not required by the Baclofen, USP monograph. The supplier' specification limits the primary process impurity/degradant, (b) (4) by HPLC. In contrast, the USP monograph allows NMT 1% of this compound (by TLC analysis). Both the supplier and the applicant use (b) (4).

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- (b) (4) The applicant was additionally advised to evaluate the accuracy of delivery of the undiluted formulation from currently used intrathecal pumps. The sponsor has submitted supporting data for the SynchroMed® II pump (b) (4) . The reviewer should verify that the product is labeled only for use in systems for which compatibility of the drug formulation with the delivery system has been demonstrated.

Additional issues

Administrative: A claim for categorical exclusion is included in Module 1 of the application.

Consults: Microbiology and Biopharmaceutics consults are needed.

Establishment Evaluation: An updated list of manufacturing sites and contract testing facilities was provided on 15-Apr-2009. [Refer to Attachment 1.] All sites have been entered into EES, and were submitted for facility evaluation on 15-Apr-2009.

Labeling/Established Name: The active ingredient, baclofen, is the free amino acid. Thus, the name "baclofen injection" is consistent with labeled potency.

Comments for 74-Day Letter

- No photostability testing appears to have been performed on the drug product. You will need to either provide adequate justification for not performing photostability testing or perform this test.

(b) (4)

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is a not new molecular entity and the dosage form is a simple parenteral. Assignment of the NDA to a single reviewer who is familiar with parenteral products is recommended. The ONDQA Biopharmaceutics team should be consulted on the biowaiver request. A microbiology consult is needed.

Martha R. Heimann, Ph.D.	20-Apr-2009
Pharmaceutical Assessment Lead, DPA 1, ONDQA	Date
Ramesh Sood, Ph.D.	20-Apr-2009
Branch Chief, DPA 1, ONDQA	Date

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Numbers: 22-462 **Applicant: CNS Therapeutics, Inc.** **Stamp Date: 30-Mar-2009**

Drug Name: baclofen injection **NDA Type: Standard**

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

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		A claim for categorical exclusion was submitted.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		LoA to cross-reference DMF (b) (4) is provided in the NDA.
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	NA		No clinical or bioequivalence studies were performed.
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	X		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Martha R. Heimann, Ph.D. 20-Apr-2009
Pharmaceutical Assessment Lead, DPA 1, ONDQA Date

Ramesh Sood, Ph.D. 20-Apr-2009
Branch Chief, DPA 1, ONDQA Date

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/s/

Martha Heimann
4/20/2009 01:08:59 PM
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Ramesh Sood
4/20/2009 03:33:49 PM
CHEMIST