

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201922Orig1s000**

**CHEMISTRY REVIEW(S)**

**Memorandum**

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

**Date: July 3, 2012**

**From: Yichun Sun, Ph.D.**  
Review Chemist, ONDQA  
Division of New Drug Quality Assessment II  
ONDQA

**Through: Moo-Jhong Rhee, Ph.D.**  
Chief, Branch IV  
Division of New Drug Quality Assessment II  
ONDQA

**To: Memorandum to CMC Review #1 of NDA 201-922**

**Subject: Recommendation of Approval**

The NDA was recommended for approval when the Memorandum to CMC review #1 was written. However, the dosage form presentation was changed from "Extended Release Capsules" to "Extended-Release Capsules" in the package insert and the carton/container labels in the amendment dated June 29, 2012.

The change of the dosage form presentation is shown in the carton/container labels of 45 mg minocycline hydrochloride Extended-Release Capsules, which are one of the five strengths (45 mg, 67.5 mg, 90 mg, 112.5 and 135 mg) of the Extended-Release Capsules (see the attached labels). The change made to the presentation of the dosage form in the package insert and the carton/container labels is acceptable since it is in line with the convention of USP monograph titles. Therefore, from the CMC perspective, the previous recommendation of approval for this NDA still stands.

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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YICHUN SUN  
07/03/2012

MOO JHONG RHEE  
07/03/2012  
Chief, Branch IV

**Memorandum**

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

**Date:** June 19, 2012

**From:** Yichun Sun, Ph.D.  
Review Chemist, ONDQA  
Division of New Drug Quality Assessment II  
ONDQA

**Through:** Moo-Jhong Rhee, Ph.D.  
Chief, Branch IV  
Division of New Drug Quality Assessment II  
ONDQA

**To:** Memorandum to Review #1 of NDA 201-922

**Subject:** Recommendation of Approval

At the time when the Memorandum (dated January 31, 2012) to review #1 of NDA 201-922 was written, the NDA was recommended for approval from the perspective of CMC.

(b) (4), (b) (5)

Therefore, from the CMC perspective, the previous recommendation of approval for this NDA still stands.

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/s/  
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YICHUN SUN  
06/19/2012

MOO JHONG RHEE  
06/19/2012  
Chief, Branch IV

**Memorandum**

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

**Date: January 31, 2012**

**From: Yichun Sun, Ph.D.**  
**Review Chemist, ONDQA**  
**Premarketing Assessment Division II**  
**ONDQA**

**Through: Moo-Jhong Rhee, Ph.D.**  
**Chief, Branch IV**  
**Premarketing Assessment Division II**  
**ONDQA**

**To: CMC Review #1 of NDA 201-922**

**Subject: Recommendation of Approval**

At the time when the CMC review #1 was written, there were three pending issues listed as follows:

- Insufficient CMC information to assure the identity, strength, purity, and stability of the drug product as required by 21 CFR 314.25 (b)(1).
- The overall acceptable recommendation of Establishment Evaluation was still pending.
- There were issues on the label/labeling that need to be resolved.

On September 28, 2011, Dr. Moo-Jhong Rhee, Branch Chief, DNDQA II/ONDQA, concluded that the CMC information as submitted is sufficient enough to meet the statutory requirements for the identity, strength, purity and stability of the drug product after re-examining the information and data submitted by the NDA applicant. Subsequently, Dr. Terrance Ocheltree, Director, DNDQA, concurred Dr. Rhee's recommendation on September 30, 2011. Therefore, only the issues of Establishment Evaluation and label/labeling had been pending.

On December 9, 2011, the Office of Compliance gave an overall "Acceptable" recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product (see the EER Summary Report in **Attachment I**).

On January 18, 2012, the NDA applicant submitted an amendment providing the finalized mock up container and carton labels. All the labels have the required

information. Additionally, the applicant also agreed to all the CMC changes made to the package insert (see the finalized labeling and labels in **Attachment II**).

**Therefore, from the CMC perspective, this NDA is now recommended for approval.**

# Attachement I:

## FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

<b>Application:</b>	NDA 201922/000	<b>Sponsor:</b>	RANBAXY LABS
<b>Org. Code:</b>	540		600 COLLEGE RD EAST
<b>Priority:</b>	3		PRINCETON, NJ 08540
<b>Stamp Date:</b>	10-MAY-2010	<b>Brand Name:</b>	MINOCYCLINE ER CAPSULES 135 mg
<b>PDUFA Date:</b>	04-MAR-2012	<b>Estab. Name:</b>	MINOCYCLINE ER CAPSULES 135 mg
<b>Action Goal:</b>		<b>Generic Name:</b>	
<b>District Goal:</b>	05-OCT-2011	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; CAPSULE, EXTENDED RELEASE; MINOCYCLINE HYDROCHLORIDE; 135MG
<b>FDA Contacts:</b>	J. DAVID	Project Manager	301-796-4247
	Y. SUN	Review Chemist	301-796-1388
	S. DING	Team Leader	301-796-1349

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**Overall Recommendation:** ACCEPTABLE on 09-DEC-2011 by D. SMITH ( )

---

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA: N 091110  
I 107472

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER

**Profile:** NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

**Last Milestone:** QC RECOMMENDATION

**Milestone Date:** 14-FEB-2011

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: OHM LABORATORIES INC  
14 TERMINAL RD  
NEW BRUNSWICK, NJ 089013616 FEI: 3004132058

**DMF No:** AADA: I 107472  
N 091118

**Responsibilities:** FINISHED DOSAGE OTHER TESTER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER

**Profile:** CAPSULES EXTENDED RELEASE OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 16-MAR-2011

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

**Profile:** CONTROL TESTING LABORATORY OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 11-MAR-2011

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

**Establishment:** CFN: 2248121 OHM LABORATORIES INC.  
1385 LIVINGSTON AVE  
NORTH BRUNSWICK, NJ 089013616 FEI: 1000222352

**DMF No:** AADA: N 091118  
I 107472

**Responsibilities:** FINISHED DOSAGE OTHER TESTER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER

**Profile:** CAPSULES EXTENDED RELEASE OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 14-FEB-2011

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

**Profile:** CONTROL TESTING LABORATORY OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 14-FEB-2011

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: FEI: 3003663288  
RANBAXY LABORATORIES LTD (DRUG PRODUCT MANUFACTURING)  
UNIT III, A41, PHASE VIII A  
MOHALI, PUNJAB, INDIA 160 071

**DMF No:** AADA: N 091118  
I 107472

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Profile:** CAPSULES EXTENDED RELEASE OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 09-DEC-2011

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** CFN: FEI: (b) (4)  
(b) (4)

**DMF No:** AADA: N 091118  
I 107472

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER

**Profile:** CONTROL TESTING LABORATORY OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 14-FEB-2011

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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## Attachement II:

### Finalized Labeling and Labels

#### 1) Package Insert

##### (a) “Highlights” Section

These highlights do not include all the information needed to use Ximino safely and effectively. See full prescribing information for Ximino.

Ximino™ (minocycline hydrochloride) extended release capsules, for oral use  
Initial U.S. Approval: 1971

##### -----DOSAGE FORMS AND STRENGTHS-----

Extended release capsules: 45 mg, 67.5 mg, 90 mg, 112.5 mg, and 135 mg (3)

##### (b) “Full Prescribing Information” Section

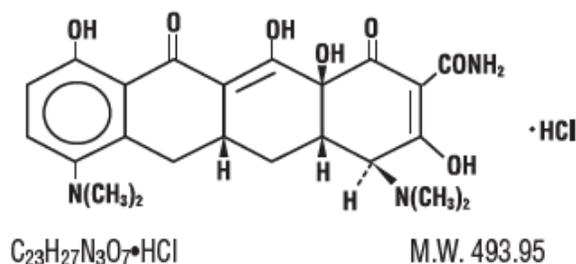
#### #3. Dosage Form and Strength

- **45 mg extended release capsules:** Opaque bluish green cap and opaque yellow body hard gelatin capsule with ‘**RI18**’ imprinted on both cap and body in black ink containing one yellow to grayish yellow colored film-coated, round tablet plain on both sides.
- **67.5 mg extended-release capsules:** Opaque bluish green cap and white body hard gelatin capsule imprinted with ‘**RI92**’ on both cap and body in black ink containing one yellow to grayish yellow colored film-coated, round tablet plain on both sides.
- **90 mg extended-release capsules:** Opaque light blue cap and body hard gelatin capsule with ‘**RI19**’ imprinted on both cap and body in black ink containing two yellow to grayish yellow colored film-coated, round tablets plain on both sides.
- **112.5 mg extended-release capsules:** Opaque light blue cap and white body hard gelatin capsule imprinted with ‘**RI93**’ on both cap and body in black ink containing two yellow to grayish yellow colored film-coated, round tablets debossed with ‘X’ on one side and plain on the other side.
- **135 mg extended-release capsules:** Opaque bluish green cap and opaque light blue body hard gelatin capsule with ‘**RI20**’ imprinted on both cap and body in black ink containing three yellow to grayish yellow colored film-coated, round tablets plain on both sides.

#### #11. Description

The active ingredient in Ximino extended release capsules is minocycline

hydrochloride, a semi synthetic derivative of tetracycline. Ximino is a tetracycline-class drug. Ximino is known chemically as [4S-(4 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ,12 $\alpha$ )]-4,7-Bis(dimethylamino)-1,4,4 $\alpha$ ,5,5 $\alpha$ ,6,11,12 $\alpha$ -octahydro-3,10,12,12 $\alpha$ -tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide mono hydrochloride. The structural formula is represented below:



Minocycline hydrochloride, USP is a yellow crystalline powder, sparingly soluble in water, soluble in solutions of alkali hydroxides and carbonates, slightly soluble in alcohol, practically insoluble in chloroform and in ether.

Ximino (minocycline hydrochloride) extended release capsules for oral administration contain minocycline hydrochloride, USP equivalent to 45 mg, 67.5 mg, 90 mg, 112.5 mg, or 135 mg of minocycline. The extended release capsules contain the following inactive ingredients: colloidal silicon dioxide, D&C Yellow #10 (in 45 mg strength), FD&C Blue #1, FD&C Yellow #6 (in 45 mg, 67.5 mg, and 135 mg strength), gelatin, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and titanium dioxide.

The 45 mg, 67.5 mg, 90 mg, 112.5 mg, and 135 mg capsules also contain Opadry Clear which contains hypromellose, polyethylene glycol 400, polyethylene glycol 6000, and talc.

Ximino extended release capsules also contain black ink which contains black iron oxide, potassium hydroxide, propylene glycol, and shellac.

#### #16. How Supplied/Storage and Handling

##### **How Supplied:**

Ximino (minocycline hydrochloride) extended release capsules are hard-gelatin capsules containing minocycline hydrochloride, USP equivalent to 45 mg, 67.5 mg, 90 mg, 112.5 mg or 135 mg minocycline. The extended release capsules are supplied as follows:

##### **Ximino (minocycline hydrochloride) extended release capsules 45 mg:**

Opaque bluish green cap and opaque yellow body hard gelatin capsule with 'RI18' imprinted on both cap and body in black ink containing one yellow to grayish yellow colored film-coated, round tablet plain on both sides and are supplied as follows:

NDC 10631-330-30 Bottle of 30  
NDC 10631-330-05 Bottle of 500  
NDC 10631-330-69 Blister pack of 10

**Ximino (minocycline hydrochloride) extended release capsules 67.5 mg:**

Opaque bluish green cap and white body hard gelatin capsule imprinted with ‘RI92’ on both cap and body in black ink containing one yellow to grayish yellow colored film-coated, round tablet plain on both sides and are supplied as follows:

NDC 10631-230-30 Bottle of 30  
NDC 10631-230-05 Bottle of 500  
NDC 10631-230-69 Blister pack of 10

**Ximino (minocycline hydrochloride) extended release capsules 90 mg:**

Opaque light blue cap and body hard gelatin capsule with ‘RI19’ imprinted on both cap and body in black ink containing two yellow to grayish yellow colored film-coated, round tablets plain on both sides and are supplied as follows:

NDC 10631-331-30 Bottle of 30  
NDC 10631-331-05 Bottle of 500  
NDC 10631-331-69 Blister pack of 10

**Ximino (minocycline hydrochloride) extended release capsules 112.5 mg:**

Opaque light blue cap and white body hard gelatin capsule imprinted with ‘RI93’ on both cap and body in black ink containing two yellow to grayish yellow colored film-coated, round tablets debossed with ‘X’ on one side and plain on the other side and are supplied as follows:

NDC 10631-231-30 Bottle of 30  
NDC 10631-231-05 Bottle of 500  
NDC 10631-231-69 Blister pack of 10

**Ximino (minocycline hydrochloride) extended release capsules 135 mg:**

Opaque bluish green cap and opaque light blue body hard gelatin capsule with ‘RI20’ imprinted on both cap and body in black ink containing three yellow to grayish yellow colored film-coated, round tablets plain on both sides and are supplied as follows:

NDC 10631-332-30 Bottle of 30  
NDC 10631-332-05 Bottle of 500  
NDC 10631-332-69 Blister pack of 10

**Storage:**

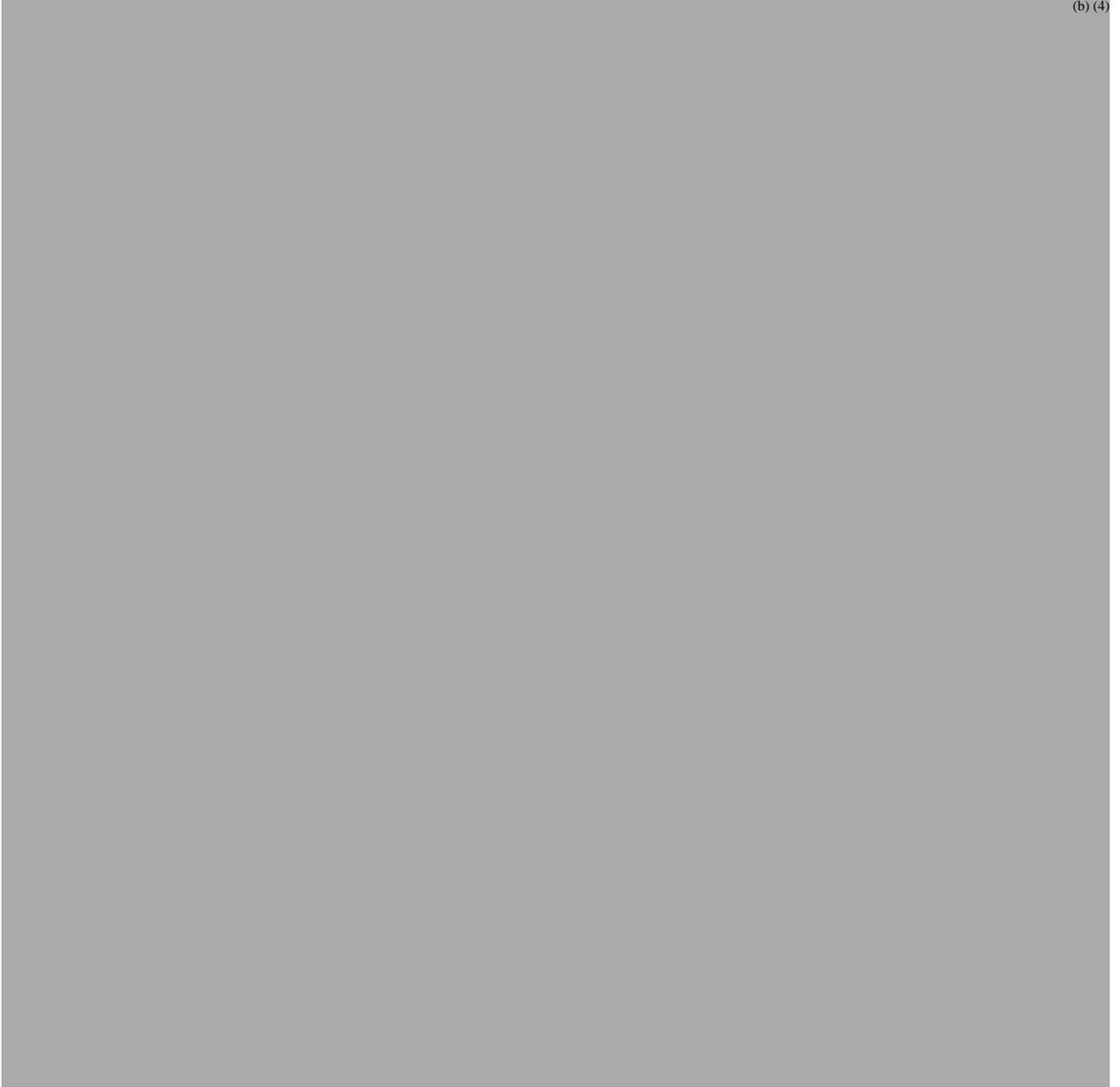
Store at 20°C - 25°C (68°F - 77°F); excursions are permitted to 15°C - 30°C (59°F - 86°F) [See USP Controlled Room Temperature].

**Handling:**

Protect from light, moisture, and excessive heat.

Dispense in tight, light-resistant container with child-resistant closure.

2) Container/Carton Labels



(b) (4)

14 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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YICHUN SUN  
01/31/2012

MOO JHONG RHEE  
01/31/2012  
Chief, Branch IV

**Memorandum**

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

**Date: January 20, 2012**

**From: Yichun Sun, Ph.D.**  
**Review Chemist, ONDQA**  
**Premarketing Assessment Division II**  
**ONDQA**

**Through: Moo-Jhong Rhee, Ph.D.**  
**Chief, Branch IV**  
**Premarketing Assessment Division II**  
**ONDQA**

**To: CMC Review #1 of NDA 201-922**

**Subject: Evaluation of the Involvement of AIP Facilities in Providing Data  
Submitted in NDA 201-922**

**I. Background:**

Concerns of potential invocation of Application Integrity Policy (AIP) on the NDA submission were raised because two of the applicant's facilities (Dewas and Paonta Sahib located in India) are on the AIP list. On December 14, 2011, an IR letter with the following information requests was sent to ask the applicant to clarify if the AIP sites were involved in providing data for the NDA submission:

1. Provide a tabulated list of the manufacture and test sites of the drug substance, drug product, and reference standards used in or as the development, pivotal, and registration batches of the drug product with inclusion of pertinent batch numbers and manufacture or test dates.
2. If any material was manufactured or provided from or tested by Ranbaxy Laboratories Limited's Paonta Sahib or Dewas facilities located in India describe how that material was used in sufficient detail to understand the connection to NDA 201922. For example, "This standard was used to analyze drug substance Batch ABC which was used to produce drug product Batch XYZ. Drug product Batch XYZ was used for dissolution method development."

The amendment responding to the IR letter was received on December 27, 2011. The information provided in the amendment has been reviewed and the findings of the involvement of the AIP sites in the NDA submission are summarized as follows:

- [Redacted] (b) (4)
- █ [Redacted]
- █ [Redacted]
- █ [Redacted]
- █ [Redacted]

**II. Conclusion:**

The impact of the involvement of the AIP sites on the pilot BE studies will be evaluated by the ClinPharm Reviewer of the NDA, Dr. Chinmay Shukla.

Based on the CMC information provided and to my best knowledge, the CMC data submitted in the NDA were not generated in the AIP sites (Dewas and Paonta Sahib located in India). Therefore, it is concluded that from the perspective of CMC, the Application Integrity Policy would not apply to this NDA.

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/s/  
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YICHUN SUN  
01/20/2012

MOO JHONG RHEE  
01/20/2012  
Chief, Branch IV

## MEMORANDUM

**Date:** September 30, 2011

**To:** NDA 201-922

**From:** Terrance Ocheltree, Ph.D., R. Ph.  
Director  
Division of New Drug Quality Assessment II  
ONDQA

**Subject:** ONDQA Final recommendation for NDA 201-922, Ximino™ (minocycline) extended release capsule.

I have reviewed Dr. Moo-Jhong Rhee's conclusion regarding suitability and method validation of the HPLC methods for NDA 201922 (see Memo in DARRTS dated September 28, 2011) and discussed this topic with both Dr. Rhee and Dr. Yichun Sun. While the methods and method validations for Identity, Assay, and Purity (impurities) are not ideal, as identified and discussed by Dr. Sun, the risk that these will negatively impact the overall quality of the product or patient safety is minimal. I further concur with Dr. Rhee's recommendation to submit the methods to DPA via the ONDQA Method Validation Program for further evaluation.

Therefore, I concur that the ONDQA recommendation for this application is a Complete Response based on the following two pending issues:

- Lack of an "Acceptable" recommendation from the Office of Compliance
- Unresolved label/labeling issues.

related post marketing commitments.

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/s/  
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TERRANCE W OCHELTRIE  
09/30/2011

# **NDA 201-922**

**Minocycline Hydrochloride Extended Release Capsules**

**Ranbaxy Laboratories Limited**

**Yichun Sun, Ph.D.**

**Branch IV**

**Division of New Drug Quality Assessment II**

**Office of New Drug Quality Assessment**

**CMC REVIEW OF NDA 201-922**

**For the Division of Dermatology and Dental Products  
(HFD-540)**

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(b) (4)	37
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Total (Core Tablet)	42
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# Chemistry Review Data Sheet

1. NDA: 201-922
2. REVIEW #: 1
3. REVIEW DATE: 28-September-2011
4. REVIEWER: Yichun Sun, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 107,472	14-December-2009
NDA 201-922	10-May-2010
Refusal to File	14-July-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Re-submission	04-February-2011
Amendment	05-July-2011
Amendment	13-July-2011
Amendment	10-August-2011
Amendment	30-August-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Ranbaxy Laboratories Limited  
Address: Sector 18, Udyog Vihar Industrial Area  
Gurgaon, 122001, India  
Representative: Scott D. Tomsky  
Telephone: 609-720-5609

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ximino

- b) Non-Proprietary Name (USAN): Minocycline hydrochloride  
c) Code Name/# (ONDQA only): N/A  
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
  - Submission Priority: Standard Review

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

10. PHARMACOL. CATEGORY: Anti-infective/Tetracycline

11. DOSAGE FORM: Extended Release Capsules

12. STRENGTH/POTENCY: Equivalent to 45 mg, 67.5 mg, 90 mg, 112.5 mg, or 135 mg minocycline per capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

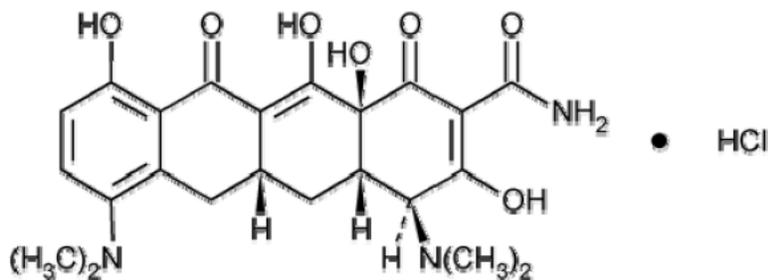
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

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

4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenicarboxamide monohydrochloride



**Structural Formula of Minocycline Hydrochloride**

Empirical formula:  $C_{23}H_{27}N_3O_7 \cdot HCl$

Molecular weight: 493.95

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	9/28/2011	NA
	III		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	
	IV		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	
	IV		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	

<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: NA**

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A	----	----
EES	Pending	----	----
Pharm/Tox	N/A	----	----
Biopharm	Acceptable	08/31/2011	J. Duan
LNC	N/A	----	----
Methods Validation	N/A	----	----
DMEPA	N/A	----	----
EA	Claim for Categorical Exclusion is granted. See review p.213	09/28/2011	Y. Sun
Microbiology	N/A	----	----

# The Chemistry Review for NDA 22-181

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has NOT provided sufficient CMC information to assure the identity, strength, purity, and stability of the drug product as required by 21 CFR 314.25 (b)(1).

The overall acceptable recommendation of Establishment Evaluation is still pending.

There are issues on the label/labeling that need to be resolved.

Therefore, from a CMC perspective, this NDA is not recommended for "Approval" in its present form until all the CMC issues have been adequately addressed, and the Office of Compliance issues an overall "Acceptable" recommendation for all the manufacturing and test facilities, and all the issues on label/labeling are resolved.

#### 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)

##### Drug Substance

The drug substance, minocycline hydrochloride, is a second-generation semi-synthetic derivative of tetracycline with a wide spectrum of antibacterial activity against gram-positive and gram-negative organisms. It exerts its action against susceptible organisms by inhibiting protein synthesis. It is known as 4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride.

Minocycline hydrochloride drug substance is a yellow crystalline powder. It is sparingly soluble in water, soluble in solutions of alkali hydroxides and carbonates; slightly soluble in alcohol; practically insoluble in chloroform and ether. The pKas of the drug are 2.5, 5.0, 7.8 and 9.5, respectively. The partition coefficient (octanol/water) of the drug is 1.48. It melts at 217°C. No polymorphism is observed on the drug substance. It is considered to be slightly hygroscopic. The specifications for the drug substance are in line with the USP monograph for the API and include all the critical attributes that may affect the manufacturing and quality of the drug product. The particle size of the drug substance is (b) (4) (NLT (b) (4) particles (b) (4) NMT (b) (4) particles are retained on (b) (4)).

The detailed CMC information regarding minocycline hydrochloride USP is referred to DMF# (b) (4), which is held by (b) (4)

(b) (4) The DMF has been reviewed and found adequate to support the use of minocycline hydrochloride in this NDA.

#### Drug Product

The drug product, Ximino (minocycline hydrochloride) extended release capsules, is proposed to be used to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris. The drug product is available in the following strengths: 45 mg, 67.5 mg, 90 mg, 112.5 mg, and 135 mg. The 45 mg capsule (size 0) has an opaque bluish green cap and opaque yellow body with 'RI18' imprinted on both cap and body in black ink. The 67.5 mg capsule (size 0) has an opaque bluish green cap and white body imprinted with 'RI92' on both cap and body in black ink. The 90 mg capsule (size 0) has an opaque light blue cap and body with 'RI19' imprinted on both cap and body in black ink. The 112.5 mg capsule (size 0) has an opaque light blue cap and white body imprinted with 'RI93' on both cap and body in black ink. The 135 mg capsule (size 0) has an opaque bluish green cap and opaque light blue body with 'RI20' imprinted on both cap and body in black ink.

The capsules are prepared

(b) (4)

The in-process controls during the manufacture of the extended release capsules are:

(b) (4)

The minocycline hydrochloride extended release capsule are packaged into high density polyethylene (HDPE) bottles (30 capsules and 500 capsules) with 1 g silica gel sachet and (b) (4) blister pack (10 capsules/blister card). Only the shelf life specification proposed by the applicant is used to ensure the identity, purity, strength and quality of the drug product. The proposed expiration dating period of 24 months is **NOT** supported by the long-term and accelerated stability data provided because the regulatory analytical methods are **NOT** valid to be used to assess the identity, purity and strength of the stability samples. The drug product would qualify for categorical exclusion from the preparation of an environmental assessment according to 21 CFR 25.31(b).

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

The minocycline hydrochloride extended release capsules are indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. The recommended dosage of minocycline hydrochloride extended-release

capsules is approximately 1 mg (minocycline)/kg once daily for 12 weeks. The capsule should be taken whole without chewing.

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

1. The identity, strength and purity of the drug product can NOT be assured by the drug product specification due to invalid regulatory analytical methods for identity, assay, and impurities.
2. Because of above deficiency, it is not possible to establish an expiration dating period.
3. The Office of Compliance has not yet issued an overall “Acceptable” recommendation for all the facilities involved in manufacturing and testing the drug substance and drug product.
4. Additionally, the issues on label/labeling still need to be resolved.

**III. Administrative**

**A. Reviewer’s Signature**

/s/ Y. Sun, Ph.D.

**B. Endorsement Block**

Yichun Sun, Ph.D. Reviewer	_____
	Date

Shulin Ding, Ph.D. Pharmaceutical Assessment lead	_____
	Date

Moo-Jhong Rhee, Ph.D. Branch Chief	_____
	Date

Jeannie David, M.S. Project Manager	_____
	Date

**C. CC Block**

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/s/  
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YICHUN SUN  
09/28/2011

MOO JHONG RHEE  
09/28/2011

I respectively disagree with his evaluation on the identity, strength, and purity of the drug product.  
See my Memorandum dated Sep-28-2011.  
Chief, Branch IV

## Memorandum

Date: September 28, 2011  
From: Moo-Jhong Rhee, Ph.D.  
Branch Chief, DNDQA II/ONDQA  
To: NDA 201-922  
Subject: Final Recommendation for NDA 201-922

### Background:

Ranbaxy Laboratories, LTD has proposed a new dosage form in this 505(b)(2) application for extended release capsules, containing 45, 67.5, 90, 112.5, and 135 mg of minocycline hydrochloride with reference to the RLD product, Solodyn extended release tablets.

The antibiotic drug products containing minocycline hydrochloride have been on the market for more than two decades with various dosage forms, ranging from oral capsules to injection. This is the first application for an extended release capsules.

### Issues:

The primary CMC reviewer, Yichun Sun, Ph.D., completed his review of application NDA 201-922, on October 2, 2011 with a final recommendation of "Not Approval". The recommendation is based on the following reasons:

1. The application has not provided adequate information to assure the identity, strength, and purity of the drug product.

This conclusion was based on the evaluation of the analytical methods described in the application for the *identity*, "assay" for the *strength*, and "assay" for the *purity* with regard to the related substances.

2. The Office of Compliance has not issued an overall recommendation of "Acceptable" for the facilities involved in manufacturing and testing the drug products described in this application.
3. Label/labeling issues have not been satisfactorily resolved.

### Purpose:

This memorandum is to re-evaluate the analytical methods as to whether the deficiencies noted by the primary reviewer are significant enough to enforce the statutory requirements, FD&C Act 505(d)(3), which states,

"..the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are **inadequate to preserve its identity, strength, quality, and purity**;... he shall issue an order **refusing to approve** the application.

### Analytical methods:

1. HPLC method for the *identity* test

In his review on p.117, Dr. Sun indicated that, “*The identity of the drug substance can NOT be reasonably assured by the HPLC method because the retention time of the major peak in the HPLC chromatogram is not specific to minocycline hydrochloride.*”

According to the submitted data on August 10, 2011, the amount of these two impurities is controlled within (b) (4) respectively.

Related substances	Previous specification	Revised specification
(b) (4)		

\*New impurities

Ideally, the impurity peaks should be sufficiently separated from the drug substance peak as discussed by Dr. Sun; however, in my opinion, the contribution of these two impurities to the drug substance peak is negligible and do not compromise the ability to identify the drug substance in the drug product when compared to the reference standard.

A second identity test utilizing an UV spectroscopic method is used to further assure the identity of the drug substance. Therefore, it is deemed extremely unlikely that the drug substance in the drug product is not properly identified and that the *identity* is compromised.

Complementary assurance of the “*identity*” comes from the fact that, during the whole manufacturing process, the drug substance is checked for the *identity* as one of the routine incoming raw material controls before it is added to the formulation.

Therefore, from a risk based approach, the *identity* of the drug substance in the drug product is deemed adequately assured.

## 2. HPLC method of the assay for the *strength* test

In his review on p. 123, Dr. Sun also indicated that because of the co-elution of the two impurities with the drug substance as mentioned above, that “*..strength of the drug product can not be adequately assured by the drug product specification due to the co-elution issue of the HPLC method.*”

From the strict regulatory point of view, when the drug product is assayed by a chromatographic method, the chromatographic peak of the drug substance should be free from any interference from the impurities so that the amount determined by the peak truly represents the amount of the drug substance in the drug product. From that perspective, I agree with Dr. Sun’s assessment that the validity of the analytical method is questionable.

However, from the practical perspective where the strength of a dosage form is allowed for varying +/- 10% of the label claim, it is questionable if the error in the assay arising from the two co-eluting impurities (maximum of (b) (4) together) could potentially compromise the strength of the drug product. The risk of this impacting the overall product quality is deemed minimal and, therefore, I am reasonably comfortable in stating that the *strength* of the drug product is adequately assured using the proposed method.

3. HPLC method of related substances for the *purity* test

After careful assessment of the analytical method for the impurities in the drug product, Dr. Sun concluded in his review on p. 121 that,

*“The chromatograms of the revised HPLC method used for quantitation of impurities in the stability samples are dramatically different from those provided in the HPLC method validation report. The chromatograms shown in the method validation report do not resemble the actual chromatograms of stability samples in terms of baseline. The baseline was fairly flat in the chromatograms shown in the validation report, but the baseline of the actual stability samples has large bumps. The accuracy and precision of the revised HPLC method for impurities are questionable due to baseline changes. Therefore, the accuracy of the data obtained using the revised HPLC method for impurities can not be ascertained. Thus, the purity of the drug product can not be adequately assured by the drug product specification.”*

Dr. Sun’s conclusion raises the regulatory challenge of how to balance regulatory decisions between idealistic approach and practical perspective.

In general, it is expected that when an analytical HPLC method is developed the resulting chromatographs should exhibit chemical constituents in the sample with a clean baseline so that the accurate quantitation of each impurity peak is achievable without interference from an unstable baseline. From that perspective, I agree with Dr. Sun’s assessment that the HPLC method for determining the impurities is not up to par.

However, when I examined the chromatograms, as is shown below, the baseline shows two broad humps which appear to be smooth enough to quantitate the impurities without introducing significant errors in the calculation.



The nature of the humps observed in the chromatographs for the stability samples is not clear at this time. However, as long as the impurities can be quantitated in a reasonably accurate manner by the computer associated with the HPLC system, the risk to the

quality of the drug product are negligible as long as the calculated levels are within the approved acceptance criteria. Therefore, it is reasonable to expect that the observed hump would not compromise the *purity* of the drug product. However, to assure that the method is appropriate as described, I recommend that a Method Validation Consult Form be completed and this method be evaluated by the Office of Testing and Research, Division of Pharmaceutical Analysis (DPA)

**Conclusion and Recommendation:**

Dr. Sun conducted a thorough review of the CMC section of this NDA 201-922 and made a recommendation of “Not Approval” based on his critical evaluation of the information submitted.

In my re-examination of the information and data, I respectively disagree with his conclusion on the inadequacy of the *identity*, *strength*, and *purity* of the drug product. My disagreement is not based on the quality of his analysis of the information, but rather it is based on an evaluation of how much risk is involved in the deviation from the typical approaches to evaluating the analytical methods and common practices within Branch IV.

It is my conclusion that although the information submitted in the application may not be as ideal as the primary reviewer, Dr. Sun, had expected, the information as submitted is sufficient enough to meet the statutory requirements for the *identity*, *strength*, and *purity* of the drug product.

Therefore, my recommendation for this application is a Complete Response based on the following two pending issues:

1. Lack of an “Acceptable” recommendation from the Office of Compliance
2. Unresolved label/labeling issues.

Furthermore, I recommend that the analytical method for impurities be submitted to DPA for evaluation (this process will be done via ONDQA).

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/s/  
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MOO JHONG RHEE  
09/28/2011  
Chief, Branch IV

Initial Quality Assessment  
Branch IV  
Division of New Drug Quality Assessment II

**OND Division:** Division of Dermatology and Dental Products  
**NDA:** 201-922  
**Applicant:** Ranbaxy Laboratories, Ltd.  
**Stamp Date:** Feb. 4, 2010  
**PDUFA Date:** Dec. 4, 2011  
**Trademark:** Not proposed  
**Established Name:** Minocycline hydrochloride  
**Dosage Form:** Extended release capsule  
**Route of Administration:** Oral  
**Indication:** Acne vulgaris

**PAL:** Shulin Ding

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

**Summary and Critical Issues:**

A. Summary

This is the initial quality assessment for the resubmission of NDA 201-922 after the refusal-to-file action on July 16, 2010. The decision of refusal-to-file was made based on clinical and administrative issues; CMC did not have filing issues.

The resubmitted NDA remains as a 505(b) (2) submission referring to Solodyn (minocycline hydrochloride) extended release tablet EQ 135 mg base (NDA 50808 approved on May 8, 2006) as the listed drug. The proposed dosage form and indication remain to be extended release capsules for the treatment of acne vulgaris. The proposed strength has, however, changed from 135 mg in the refused submission to the following five strengths in the resubmission: 135 mg, 112.5 mg, 90 mg, 67.5 mg, and 45 mg. Namely, four new strengths have been added in this resubmission.

Most of CMC information supporting the NDA remains the same as before, including drug substance supplier (DMF (b) (4)), packaging configurations (30 counts/60 cc bottle, 500 counts/850 cc bottle, and blister pack), minitab<sup>l</sup>et's formulation composition and manufacturing process, and controls. The resubmission contains one new drug product facility, one new container DMF, and some new information in manufacturing and formulation due to the new strengths. The new information is further described below:

- Drug product facility: (b) (4) is proposed as a testing site for excipients in the resubmission. (b) (4) was not included in the previous submission.

- DMF: DMF (b) (4) held by (b) (4) is proposed as an alternative supplier of HDPE bottles in the resubmission. DMF (b) (4) was not included in the previous submission.
- Manufacturing/Formulation: The proposed product is minitab-let-filled hard gelatin capsules. Three kinds of minitab-lets are proposed in the resubmission: 45 mg, 56.25 mg and 67.5 mg (whereas the refused-to-file submission had only one, the 45 mg minitab-let). The three kinds of (b) (4) Through different combinations of the three kinds of minitab-let, the five strengths of the proposed drug product are produced. The table below describes the minitab-let combination for each proposed capsule strength with capsule color:

Minocycline Hydrochloride Extended Release Capsules

Capsule Strength	Capsule Cap	Capsule Body	Minitab-let	Capsule size
45 mg	Opaque bluish green cap with RI18 printed	Opaque Yellow body with RI18 printed	One 45 mg minitab-let plain on both side	0
67.5 mg	Opaque bluish green cap with RI92 printed	White body with RI92 printed	One 67.5 mg minitab-let plain on both side	0
90 mg	Opaque light blue cap with RI19 printed	Opaque light blue body with RI19 printed	Two 45 mg minitab-lets plain on both side	0
112.5 mg	Opaque light blue cap with RI93 printed	White body with RI93 printed	Two 56.25 mg minitab-lets with "X" on one side and plain on the other side	0
135 mg	Opaque bluish green cap with RI20 printed	Opaque light blue body with RI20 printed	Three 45 mg minitab-lets plain on both side	0

The resubmission contains manufacturing/formulation information for each minitab-let and each capsule strength. Executed batch records are also provided.

- More registration stability data (6-12 months) are provided in the resubmission for each capsule strength and each packaging configuration. The proposed expiration dating period remains to be 24 months at the storage temperature of 20°-25°C.

### B. Critical issues for review

Critical issues identified in the previous filing review remain to be issues in the resubmission with the exception of the following two which have been rectified: one regarding the inappropriate letters of authorization for some DMFs, and the other regarding inadequate stability data supporting specification-setting and shelf-life-projection.

Three new critical review issues have been identified for the resubmitted NDA, and are described below:

#### Alternative Bottle Supplier

The applicant adds a new bottle supplier (DMF (b) (4)) to the CMC section of the resubmission. It appears that all registration stability data on the bottle configurations have been generated from batches made using the bottles supplied by (b) (4)

(b) (4) (DMF (b) (4) The exchangeability of (b) (4) bottles with (b) (4) bottles needs to be critically reviewed.

#### Hold Times for Drug Product Intermediates

The applicant conducted stability studies to support the hold time of the following (b) (4) intermediates: (b) (4) The applicant concluded that these (b) (4) drug product intermediates could be maintained stable for (b) (4) at USP room temperature. CMC reviewer should review Master Batch Record to determine whether a proposed hold time has been specified for each intermediate, and whether the proposed hold time for individual intermediate and total hold time for the final product are acceptable.

#### New Biopharm Issue

In addition to those biopharm issues identified in the previous IQA, this resubmission contains a new biopharm issue which is described as follow: The applicant performed only a bioequivalence study on the 135 mg strength capsule versus Solodyn 135 mg ER tablets. For the other proposed strengths, bioequivalence to Solodyn tablets have not been demonstrated in vivo. Whether biowaiver can be granted for the other strengths will require a critical review.

#### C. Comments for 74-Day Letter:

- Clarify whether the 500 count bottle is for pharmacy dispensing.
- Clarify whether the blister pack configuration is child resistant.
- You claim categorical exclusion from the preparation of an Environmental Assessment on the basis of 21 CFR 25.31(e). The basis is for INDs and not appropriate for an NDA. Resubmit the claim with an appropriate basis and supporting information. Be reminded that any claim of categorical exclusion based on 21 CFR 25.31(b) will need to be supported by an EIC calculation and five years of production forecast.

#### D. Comments/Recommendation:

The application is fileable from CMC perspective. The major CMC review issue with this NDA is drug substance DMF and testing plan, drug product specification, dissolution, in-process controls, hold times of drug product and its intermediates, and alternative bottle supplier.

The drug substance manufacturing site is located in (b) (4) The drug product manufacturing site is located in India. GMP inspection requests have been requested.

The CMC review of this NDA is recommended to be a team-review. Yichun Sun is the primary CMC reviewer, and John Duan is the BioPharm reviewer.

Shulin Ding, Ph.D.  
CMC Lead

Moo-Jhong Rhee, Ph.D.  
Chief, Branch IV

NDA Number: 201922 Supplement Number and Type: Established/Proper Name:  
Minocycline HCl USP

Applicant: Ranbaxy Letter Date: 2/4/11 Stamp Date: 2/4/11  
Laboratories Ltd.

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

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

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

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

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

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

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

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

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

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

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	12/5/2008	
	III			6/16/09	
	III			7/1/10	
	III			5/4/06	
	III			6/18/10	
	III			6/7/2007	
	III			4/19/10	
	III			11/5/08	
	III			11/8/01	
	III			5/27/06	

(b) (4)	III	(b) (4)	(b) (4)	12/18/08	
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I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			n/a
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	x		See pages 2 and 3 of IQA.

*{See appended electronic signature page}*

Shulin Ding, Ph.D.  
 CMC Lead  
 Division of New Drug Quality Assessment II  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
 Branch Chief  
 Division of New Drug Quality Assessment II  
 Office of New Drug Quality Assessment

Date

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/s/  
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SHULIN DING  
03/29/2011

MOO JHONG RHEE  
03/29/2011  
Chief, Branch IV

Initial Quality Assessment  
Branch IV  
Division of New Drug Quality Assessment II

**OND Division:** Division of Dermatology and Dental Products  
**NDA:** 201922  
**Applicant:** Ranbaxy Laboratories, Ltd.  
**Stamp Date:** May 20, 2010  
**PDUFA Date:** March 20, 2011  
**Trademark:** Not proposed  
**Established Name:** Minocycline hydrochloride  
**Dosage Form:** Extended release capsule  
**Route of Administration:** Oral  
**Indication:** Acne vulgaris

**PAL:** Shulin Ding

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

**Summary and Critical Issues:**

A. Summary

Ranbaxy Laboratories is submitting a 505(b) (2) New Drug Application (NDA) for the prescription use of minocycline hydrochloride extended release capsule (b)(4) (equivalent to 135 mg of minocycline base) in treatment of acne vulgaris. The NDA refers to Solodyn (minocycline hydrochloride) extended release tablet EQ 135 mg base (NDA 50808 approved on May 8, 2006) as the listed drug.

The applicant references to DMF (b)(4) held by (b)(4) for the CMC information of the drug substance, minocycline hydrochloride USP. DMF (b)(4) was most recently reviewed in (b)(4), and was deemed inadequate to support the ANDA.

The proposed drug product is a size 0 hard gelatin capsule containing three extended-release, film-coated minitables. The minitables are spheric in shape, yellow to grayish yellow in color, and plain on both sides. Each tablet contains (b)(4) mg of minocycline HCl. The gelatin capsule is (b)(4). In addition to minocycline HCl, the product contains the following excipients: hypromellose, USP; lactose monohydrate, NF; magnesium stearate, NF; colloidal silicon dioxide, NF; Opadry (b)(4) (clear); (b)(4), USP (b)(4), USP; and hard gelatin capsule. The proposed product involves no novel excipient.

The proposed to-be-marketed formulation is slightly different from the formulation that was used in the manufacture of pivotal BE clinical study supplies and the registration stability batches. The difference is in the color of the capsule shell. The clinical supplies and registration batches

are (b) (4) the body whereas the to-be-marketed formulation will be (b) (4) in the body. (b) (4)

The proposed commercial presentations are (b) (4)

The manufacture of the proposed product is divided into the following units of operation: (b) (4)

Process development studies were conducted to support the proposed manufacturing process, process parameters, and in-process controls.

Registration stability data provided in the initial submission to support an expiration dating period of 24 months at the storage temperature of 20-25°C include 6 months at 25°C/60% RH and 40°C/75% from three full scale (b) (4) stability batches for each proposed packaging configuration. Stability studies were also conducted to support the hold time of the bulk storage of mini-tablets and gel capsules.

## B. Critical issues for review

### Letter of Authorization

- The letters of authorization for the following DMFs are inappropriate due to the reference of Ohm Laboratories as the NDA applicant instead of Ranbaxy Laboratories, Limited: DMFs (b) (4). A request needs to be made to the applicant to resubmit letters of authorization for the aforementioned DMFs with the correct name and address of the NDA applicant.

### Drug Substance

- DMF (b) (4) was most recently reviewed (b) (4), and was deemed inadequate to support the ANDA.
- The applicant proposes a reduced testing plan for the drug substance. The adequacy of the reduced plan needs to be critically reviewed.

### Drug Product

- The dosage form of the proposed product should be “capsule” per an Appellate court decision (202 F3d 326 Warner-Lambert Company v. Donna E. Shalala, Secretary of Health and Human Services, et al., Argued Sep. 17, 1999. Decided Feb. 11, 2000.).
- The initial submission contains too few stability data to grant a viable expiration dating period. A stability update is necessary.

- The 500 count bottle is not equipped with a child resistant closure. Clarification needs to be sought to see whether this configuration is for pharmacy dispensing. .
- The sponsor does not state in the NDA whether the blister pack configuration is child resistant. A clarification should be sought.
- The proposed limits for any unknown (NMT (b) (4)) and (b) (4) (NMT (b) (4)) appear too high.
- The adequacy of in-process controls ( (b) (4) ) needs to be carefully reviewed. The proposed in-process checks for filling operation are (b) (4) . The details (b) (4) are not provided in the NDA.

#### BioPharm Issues

- The dissolution characteristics and specification of the proposed product require attention from Biopharm reviewer. Additionally, the NDA includes a study report on alcohol induced dose dumping study and a report on dissolution profile comparison with the referenced listed drug, Solodyn.

#### Environmental Assessment

- The applicant claims categorical exclusion on the basis of 21 CFR 25.31(e), which is not appropriate because 21 CFR 25.31(e) is regarding Action on an IND. A request of a proper basis should be made.

#### C. Comments for 74-Day Letter:

- The letters of authorization for the following DMFs are inappropriate due to the reference of Ohm Laboratories as the NDA applicant instead of Ranbaxy Laboratories, Limited: DMFs (b) (4) Re-submit appropriate letters of authorization for the aforementioned DMFs with correct name/address of the NDA applicant.
- Clarify whether the 500 count bottle is for pharmacy dispensing.
- Clarify whether the blister pack configuration is child resistant.
- Update drug product stability data as soon as possible. The amount of data provided in the initial submission is too little to grant a viable expiration dating period.
- You claim categorical exclusion from the preparation of an Environmental Assessment on the basis of 21 CFR 25.31(e). The basis is for INDs and not appropriate for an NDA. Resubmit the claim with an appropriate basis and supporting information. Be reminded that any claim of categorical exclusion based on 21 CFR 25.31(b) will need to be supported by an EIC calculation and five years of production forecast.

#### D. Comments/Recommendation:

The application is fileable from CMC perspective. The major CMC review issue with this NDA is drug substance DMF and testing plan, drug product specification, dissolution, and stability.

The drug substance manufacturing site is located in (b) (4). The drug product manufacturing site is located in India. GMP inspection requests have been requested.

The CMC review of this NDA is recommended to be a team-review. Ray Frankewich is the primary CMC reviewer, and Houda Mahayni is the BioPharm reviewer.

Shulin Ding, Ph.D.  
CMC Lead

Moo-Jhong Rhee, Ph.D.  
Chief, Branch IV

NDA Number: 201922 Supplement Number and Type: Established/Proper Name:  
Minocycline HCl USP

Applicant: Ranbaxy Letter Date: 5/7/10 Stamp Date: 5/20/10  
Laboratories Ltd.

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

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

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

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

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

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

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

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

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

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

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	12/5/2008	
	III			12/23/09	Wrong NDA applicant
	III			10/16/09	Wrong NDA applicant
	III			10/2/09	Wrong NDA applicant
	III			10/2/09	Wrong NDA applicant
	III			4/9/10	
	III			11/5/08	
	III			11/8/01	
	III			5/27/06	
	III			5/21/09	Wrong NDA applicant

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

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			n/a
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	x		See pages 2 and 3 of IQA.

*{See appended electronic signature page}*

Shulin Ding, Ph.D.  
 CMC Lead  
 Division of New Drug Quality Assessment II  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
 Branch Chief  
 Division of New Drug Quality Assessment II  
 Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201922	ORIG-1	RANBAXY LABORATORIES LTD	MINOCYCLINE ER CAPSULES 135 mg

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

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/s/

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SHULIN DING  
07/08/2010

MOO JHONG RHEE  
07/08/2010  
Chief, Branch IV