CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209269Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation:

This 505(b)(2) NDA is ***not*** deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

NDA 209269
Review # 1

Drug Name/Dosage Form	MINOLIRA (minocycline HCl) Extended Release Tablets
Strength	105 mg and 135 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddys Laboratories Limited
US agent, if applicable	Hari Nagaradona, Ph.D. 107 College Road East Princeton, NJ

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	07-08-2016	All
Amendment	07-20-2016	Drug substance
Amendment	10-05-2016	Drug product, drug product manufacturing process and quality microbiology
Amendment	11-23-2016	Drug product manufacturing process
Amendment	12-21-2016	Drug product and Biopharmaceutics
Amendment	02-09-2017	Drug product
Amendment	02-27-2017	Drug product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Benjamin Stevens	Branch II/Division of New Drug API
Drug Product	Hong Cai	Branch V/Division of New Drug Products II
Process	Peter Guerrieri	Branch I/Division of Process Assessment I
Microbiology	Peter Guerrieri	Branch I/Division of Process Assessment I
Facility	Donald Lech	Branch III/Division of Inspection Assessment
Biopharmaceutics	Hansong Chen	Branch II/Division of Biopharmaceutics
Regulatory Business Process Manager	Grafton Adams	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	1	December 6, 2016	Adequate
	Type II			1	December 6, 2016	Adequate
	Type IV			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A
	Type III			4	N/A	N/A

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")

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PIND Written Response	120026	Discussions of the development plan for the IND.
Pre-NDA Meeting Minutes	120026	Discussions of the content and format of the proposed NDA submission.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	----	N/A	----	----
Pharmacology/Toxicology	----	N/A	----	----
CDRH	----	N/A	----	----
Clinical	----	N/A	----	----
Other	----	N/A	----	----

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility (OPF) has issued an "Approval" recommendation for the facilities involved in this application.

However, the issues on labels/labeling are ***not*** completely resolved at this time.

Therefore, from the OPQ perspective, this NDA is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the aforementioned issues are satisfactorily resolved (See the **List of Deficiencies** on pp. 16-18).

II. Summary of Quality Assessments

A. Product Overview

Two strengths (105 mg and 135 mg) of minocycline hydrochloride extended-release tablets, which have been developed by Dr. Reddy's Laboratories (DRL), are included in this 505b(2) NDA. The currently approved drug product, SOLODYN (minocycline HCl) Extended-Release Tablets, is the reference listed drug.

The indication and recommended daily dose of the drug product are summarized in the following Table.

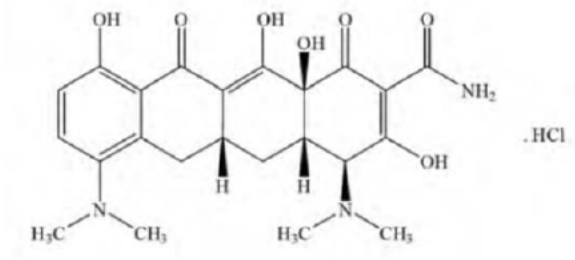
Proposed Indication(s) including Intended Patient Population	MINOLIRA is a tetracycline-class drug indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.
Duration of Treatment	12 weeks
Maximum Daily Dose	The recommended dosage of MINOLIRA is approximately 1 mg/kg once daily.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

The active pharmaceutical ingredient (API) used in the drug product, MINOLIRA (minocycline hydrochloride) extended release tablets, is minocycline hydrochloride. Minocycline hydrochloride is a second-generation, semi-synthetic tetracycline antibiotic. The chemical name of the API is [4S- (4α,4aα,5aα,12aα)]-

4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide mono hydrochloride. Its structural formula is:



The molecular formula of the API is $C_{23}H_{27}N_3O_7 \cdot HCl$, and its molecular weight is 493.94. Minocycline hydrochloride is (b) (4) Detailed CMC information on minocycline hydrochloride is referred to DMFs # (b) (4) and # (b) (4). DMFs # (b) (4) and # (b) (4) have been reviewed and found **adequate** for the approval of this NDA. The review on the CMC information of the drug substance has been conducted by Dr. Benjamin D. Stevens (See **CHAPTER I: Review of Drug Substance**).

Drug Product

Two strengths (105 mg and 135 mg) of minocycline hydrochloride extended-release tablets have been developed by Dr. Reddy's Laboratories (DRL) and are included in this 505b(2) NDA.

The drug product, MINOLIRA tablets, is manufactured (b) (4) each tablet contains 25% of minocycline in the immediate-release pellets and 75% of minocycline in the extended-release pellets. The drug product contains the following inactive excipients: microcrystalline cellulose, Opadry clear (b) (4), polyethylene glycol 400, ethyl cellulose (b) (4), hypromellose (b) (4), triethyl citrate, silicified microcrystalline cellulose, sodium stearyl fumarate, and talc. Isopropyl alcohol and purified water (b) (4) The tablets are functionally scored, rectangular shaped, white to off-white color with brown or golden colored speckles. MINOLIRA tablets contain a single score line on both surfaces. The 105 mg tablets are debossed with 'M1' on one surface, where 'M' and '1' are on either side of the score line. The 135 mg tablets are debossed with 'M3'on one surface, where 'M' and '3' are on either side of the score line.

The tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant closures (CRC). The bottles containing 30 tablets are used for marketing and the 10 tablets packaging configuration is used for physician samples. Each

HDPE bottle also contains 1 g of silica gel canister and a (b) (4) coiler.

Specification for MINOLIRA tablets is adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period. Stability data from the stability samples packaged in the proposed commercial container closure systems support an expiration dating period of **24 months** when stored at the 20 to 25°C (68 to 77°F), excursions permitted between 15°C and 30°C (59 - 86°F). The drug product should be protected from light and moisture. The results of stability studies on three pilot scale batches of each strength of the drug product were within the drug product specification over a period of 18 months under the long term storage conditions (25°C/60% RH), and 6 months under the accelerated test conditions (40°C/75% RH). Additionally, the split tablets were stable for 90 days under 25°C/60% RH test conditions as well. A claim for categorical exclusion from the environmental assessment has been submitted by the NDA applicant and the request is granted.

The drug product is recommended for **approval** from the drug product perspective. The review on the CMC information of the drug product has been conducted by Dr. Hong Cai (See **CHAPTER II: Review of Drug Product**).

Labeling and Labels

The Sections of the Package Insert related to CMC, and container labels of the drug product of the NDA have been reviewed by Dr. Hong Cai. Labeling and label issues have ***not*** been resolved satisfactorily as of this review (See **CHAPTER III: Review of Labeling and Labels**).

Drug Product Manufacturing Process

MINOLIRA tablets are manufactured (b) (4) each tablet contains 25% of minocycline in the immediate release pellets and 75% of minocycline in the extended release pellets. The manufacturing process of the immediate release (IR) pellets includes the following steps:

(b) (4)

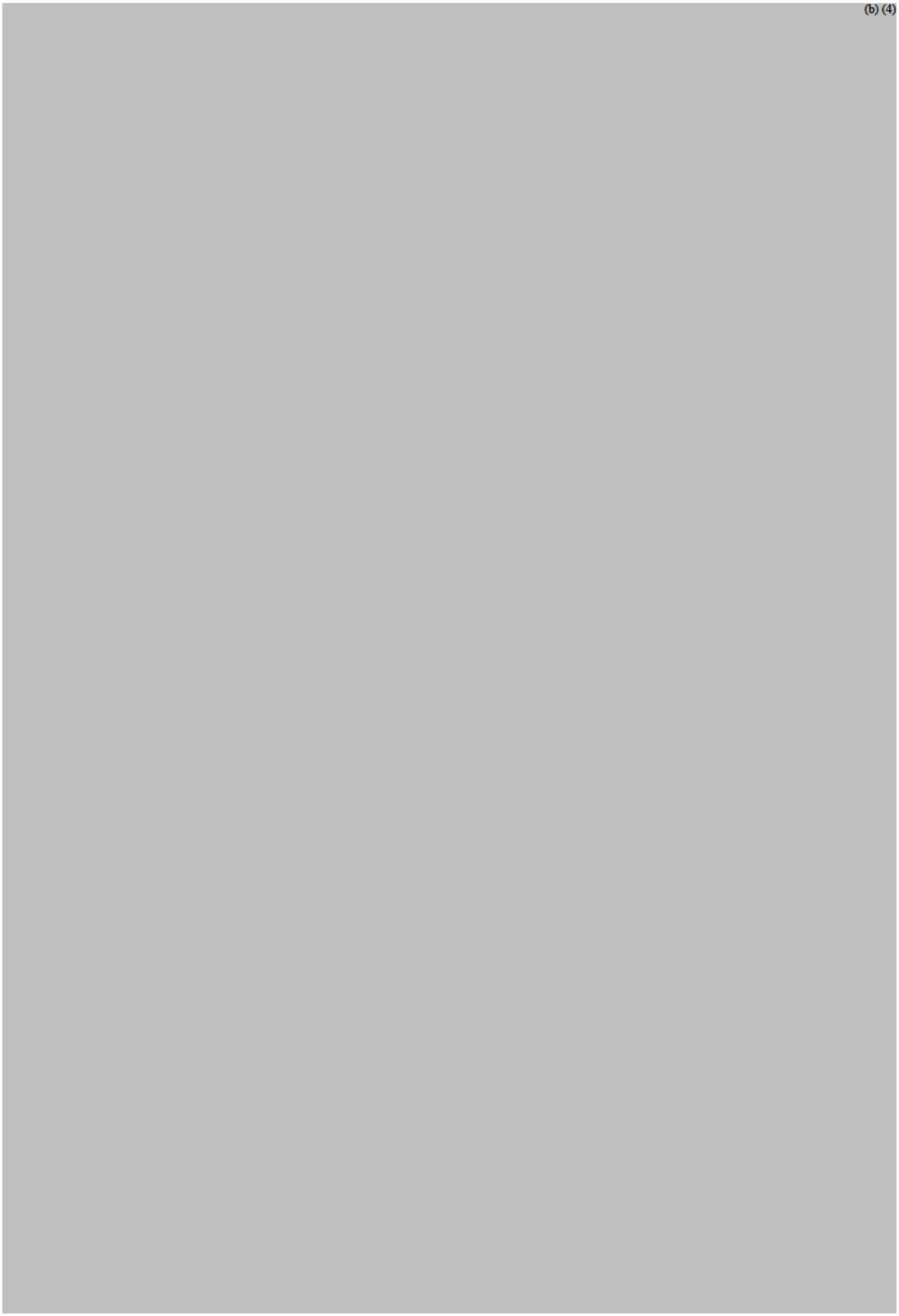
(b) (4)

(b) (4) The child resistant caps along with 1 gm silica gel canister and a (b) (4) coil in each bottle.

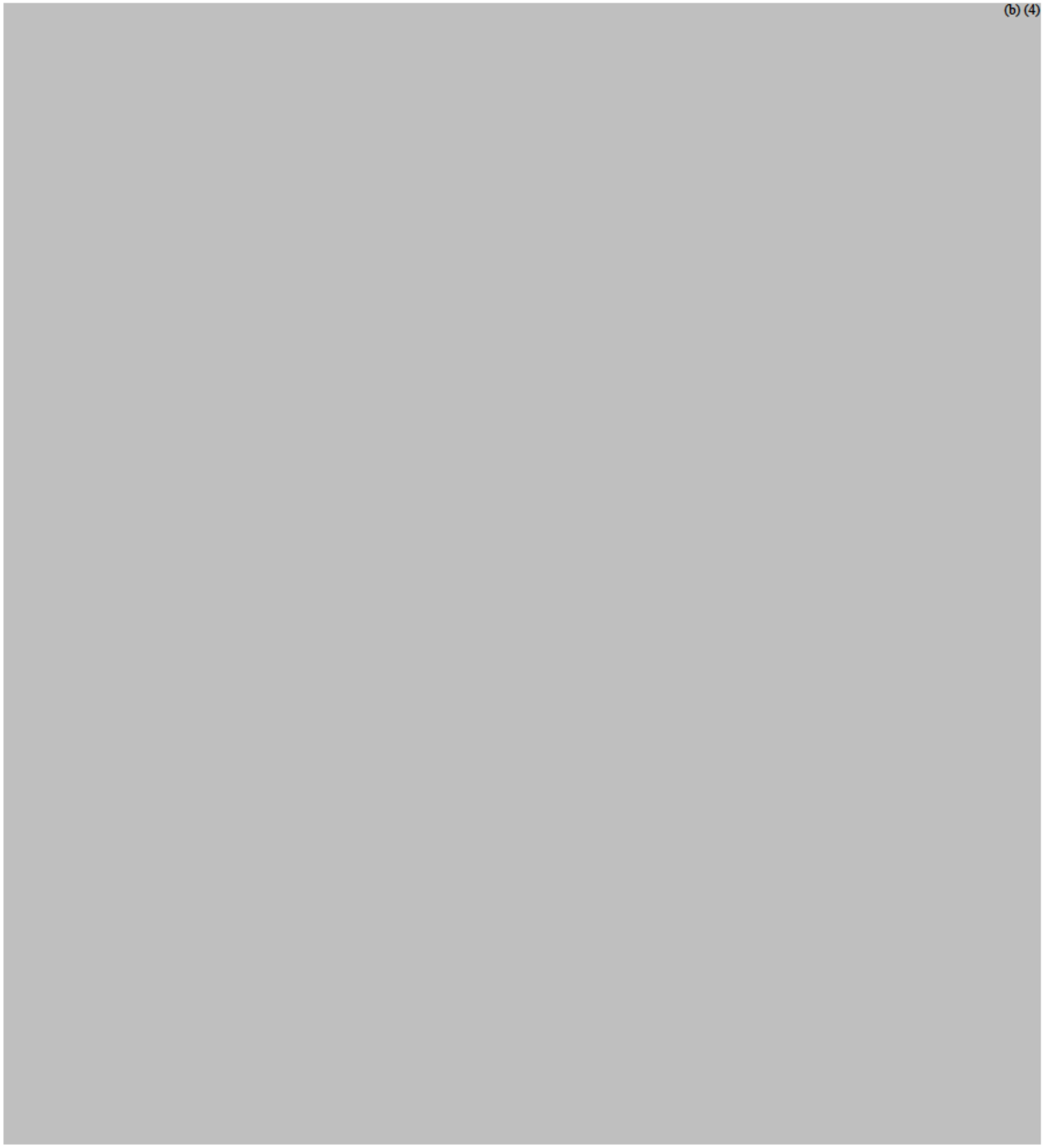
In-process controls implemented during the manufacturing process of the drug product are presented as follows:

(b) (4)

(b) (4)



(b) (4)



Biopharmaceutics

Two strengths (105 mg and 135 mg) of minocycline hydrochloride extended release tablets are included in this NDA. The API of the NDA, Minocycline hydrochloride, is a BCS class I drug (high aqueous solubility and high permeability). The composition of the commercial batches is the same as the one used in the bioequivalence studies. The scale-up batch size of the commercial batches is not more than (b) (4) times of that of the registration batches. The proposed dissolution method is shown below:

- USP apparatus 1
- Rotation speed:100 rpm

- Dissolution medium: degassed HCl and sodium chloride solution at pH 2.1
- Medium volume: 900 mL
- Bath Temperature : 37 ± 0.5°C
- Time Points : 30 minute, 90 minutes and 180 minutes

An UV method is used to determine the concentrations of the drug in the medium of the dissolution test. The wavelength of the UV spectrophotometer was set at 348 nm. The applicant's proposed dissolution method is deemed **acceptable**.

The following dissolution acceptance criteria have been set as agreed upon with the Applicant:

- 0.5 h (30 min): (b) (4)
- 1.5 h (90 min):
- 3 h (180 min): NLT (b) (4)

From the Biopharmaceutics perspective, NDA 209269 for minocycline HCl extended release tablets, 105 mg and 135 mg is recommended for **approval**. The review on the biopharmaceutics of the drug product of the NDA has been conducted by Dr. Hansong Chen (See **CHAPTER V: Review of Biopharmaceutics**).

Quality Microbiology

The applicant provided a comprehensive evaluation of critical control points for microbial load during the drug product manufacturing process. In addition, the applicant provided microbial limits testing results of accelerated (6 months) and long-term (12 months) stabilities on three registration batches of each strength of the drug product packaged in the proposed commercial packs. The results indicated that those batches met specifications and showed no evidence of microbial growth during stability studies.

(b) (4)

The applicant's proposal to exclude routine drug product microbial testing at release and during stability studies is deemed acceptable based on the results of acceptable microbial load and no growth for both the intermediates and the drug

product; (b) (4)

The NDA is recommended for **Approval** from the perspective of quality microbiology. The review on microbiology controls of the drug product of the NDA has been conducted by Dr. Peter Guerrieri (See **CHAPTER VI: Review of Quality Microbiology**).

Facilities

The manufacturing site of the API, minocycline hydrochloride, of this NDA is (b) (4) This site is responsible for the manufacturing and testing minocycline hydrochloride drug substance. The last coverage of the CSN profile class was conducted during the 2/26/2016 inspection and was classified as acceptable.

The API manufacturing site is deemed a lower risk facility based on a solid inspectional history, previous evidence that the firm corrects deficiencies found, and no FARs and Recalls found. No PAI inspection is required, and the firm is listed as **acceptable**.

The drug product manufacturing site of the NDA is Dr. Reddy's Laboratories Limited [FEI: 3009193040 (TTR)] located in India. This site is responsible for the manufacturing, analytical and stability testing, packaging, quality control, and warehousing of the Minolira finished drug product. A limited but acceptable compliance history including a 2016 inspection, the tableting experience available within the firm's global structure, and no FARs and Recalls found provide reasonable assurance that the firm can successfully manufacture the finished drug product, and indicate a low overall risk of this facility. The firm is listed as **acceptable**.

All the facilities are deemed **acceptable** in their identified functions and responsibilities to support approval of NDA 209269. The facility review of the NDA has been conducted by Consumer Safety Officer, Donald Lech (See **CHAPTER VII: Review of Facilities**).

C. Special Product Quality Labeling Recommendations

N/A

D. Final Risk Assessment (Attachment I)

E. List of Deficiencies (Attachment II)

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Risk Assessment for NDA 209269 [Minolira (Minocycline Hydrochloride) Extended-Release Tablets]

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay and related substances	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	4	4	2	32	(b) (4)
						(b) (4)
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	4	4	3	48	(b) (4)

Mirobial Limits Tests	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	3	12	The applicant's proposal to exclude routine drug product microbial testing at release and during stability studies is acceptable based on the results of acceptable microbial load and no growth for both the intermediates and the drug product; (b) (4)
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	4	3	2	24	Dissolution test in pH 2.1 hydrochloric acid solution is included in the drug product specification. Process parameters (b) (4) (b) (4) which potentially affect release characteristics of the drug are evaluated and optimized. (b) (4)

FMECA: Failure Mode, Effects and Criticality Analysis

RPN: Risk Priority Number

$$RPN = \begin{bmatrix}5\\4\\3\\2\\1\end{bmatrix} O \times \begin{bmatrix}5\\4\\3\\2\\1\end{bmatrix} S \times \begin{bmatrix}1\\2\\3\\4\\5\end{bmatrix} D$$

Low Risk- RPN $\leq$ 25

Moderate Risk - 25 < RPN $\leq$ 60

High Risk - RPN > 60

ATTACHMENT II: List of Deficiencies

A. Labeling Deficiencies:

A. **Package Insert**

a) Highlight Section

- The established name should be revised to:
  "(minocycline hydrochloride) extended-release tablets"

- Dosage Forms and Strengths should be revise to:
  "Extended-release tablets: 105 mg and 135 mg of minocycline, functionally scored."

b) Full Prescribing Information

#3: Dosage Forms and Strengths

- Need to add additional tablet descriptive characteristics of functionally scored, with brown or gold color speckles and also the salt equivalency statement as follows:

  MINOLIRA extended-release tablets are white to off-white, functionally scored, rectangular tablets with brown or gold color speckles and a single score line on both surfaces. MINOLIRA are available in the following two strengths.

  - 105 mg extended release tablets: 'M1'debossed on one surface, where 'M' and '1' are on either side of the score line. Each tablet contains 105 mg minocycline, equivalent to 113.4 mg of minocycline hydrochloride.

  - 135 mg extended release tablets: 'M3' is debossed on one surface, where 'M' and '3' are on either side of the score line. Each tablet contains 135 mg minocycline, equivalent to 145.8 mg of minocycline hydrochloride.

#11: Description

- Add the established name and dosage form to this section. The established name and the dosage form should be presented along with the proprietary name as follows:

  "MINOLIRA (minocycline hydrochloride) extended-release tablets"

- Add the salt equivalency statement and revise the extended and immediate release characteristic descriptions as follows:

  MINOLIRA (minocycline hydrochloride) extended-release tablets for oral administration contain 105 mg or 135 mg of minocycline, equivalent to 113.4 mg or 145.8 mg of minocycline hydrochloride, respectively. MINOLIRA extended-release tablets, 105 mg and 135 mg, contain 25% of minocycline as immediate release beads and 75% of minocycline as extended release beads.

- Consider listing the inactive ingredients in alphabetical order (see USP Chapter <1091>).

#16: How Supplied/Storage and Handling

- Revise the strengths and dosage forms to:

  MINOLIRA is supplied as functionally scored extended-release tablets containing (b) (4) minocycline hydrochloride equivalent to 105 mg or 135 mg of minocycline.

- (b) (4)

  The 105 mg extended release tablets are white to off-white, rectangular with brown or gold color speckles. The tablets have a single score line on both surfaces and are debossed with 'M1' on one surface. On the face with debossing, 'M' and '1' are on either side of the score line.

  The 135 mg extended release tablets are white to off-white, rectangular with brown or gold color speckles. The tablets have a single score line on both surfaces and are debossed with 'M3' on one surface. On the face with debossing, 'M' and '3' are on either side of the score line.

- Add the following statement to the Storage Condition:

  Protect from light and moisture.

- (b) (4).

- Provide the Manufacturer/distributor name.

B. Container Label Deficiencies:

- Present the product title as: "MINOLIRA™ (minocycline hydrochloride) extended-release tablets'.

- Revise "Rx" to "Rx only".
- Add the salt equivalency statements:

  For 105 mg strength:

  Revise from (b) (4) to "Each tablet contains 105 mg of minocycline (26.25 mg as immediate release beads and 78.75 mg as extended release beads), equivalent to 113.4 mg of minocycline hydrochloride."

  For 135 mg strength:

  Revise from (b) (4) to "Each tablet contains 135 mg of minocycline (33.75 mg as immediate release beads and 101.25 mg as extended release beads), equivalent to 145.8 mg of minocycline hydrochloride."

- Add the following storage conditions:
  Protect from light and moisture.

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead's Assessment and Signature

From quality perspective, the NDA is not deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
3/10/2017

65 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

MINOLIRA™ (minocycline HCl) Extended Release Tablet, for Oral Use
Initial U.S. Approval: 1971

2) DOSAGE FORMS AND STRENGTHS

Extended release tablets: 105 mg and 135 mg (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary name: **MINOLIRA™** Established Name: (b) (4)	Not Satisfactory. **Revise to:** MINOLIRA™ (minocycline hydrochloride) extended-release tablets, for oral use
Dosage form, route of administration	**Extended Release Tablet, for Oral Use**	**Satisfactory.** See revision above for the presentation.
Controlled drug substance symbol (if applicable)	NA	NA
Dosage Forms and Strengths (201.57(a)(8))	Extended release tablets: 105 mg and 135 mg (3)	**Not Satisfactory.** "functionally scored" should be added per LRT2015. **Revise to:** Extended-release tablets: 105 mg and 135 mg of minocycline, functionally scored (3)
Whether the drug product is scored	Not provided.	**Not Satisfactory.** See the comment above.

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

- 105 mg extended release tablets: (b) (4) 1'debossed on one surface, where

'M' and '1' are on either side of the score line. Each tablet contains (b) (4) of minocycline (b) (4).

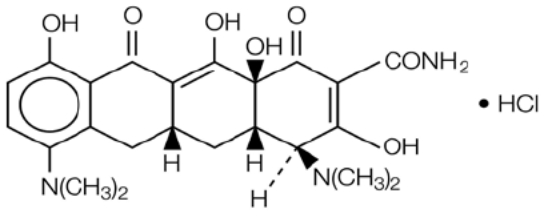
- 135 mg extended release tablets: (b) (4) 'M3' debossed on one surface, where 'M' and '3' are on either side of the score line. Each tablet contains (b) (4) minocycline (b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	extended release tablets	**Satisfactory**. The presentation should be "extended-release tablets".
Strengths: in metric system	105 mg extended release tablets: Each tablet contains (b) (4) minocycline (b) (4) 135 mg extended release tablets: Each tablet contains (b) (4) minocycline (b) (4)	**Not Satisfactory.** No Salt equivalency statement. Revise to: • 105 mg extended release tablets: Each tablet contains (b) (4) equivalent to total of 113.4mg of minocycline hydrochloride. • 135 mg extended release tablets: Each tablet contains (b) (4) equivalent to total of 145.8mg of minocycline hydrochloride. Note: The review team would like to remove the statement of (b) (4) The rationale is that this statement does not describe the identifying characteristics of the dosage form to aid with visual identification of the product. See the comment below: **Comment [XN22]: To the Applicant:** This text does not describe the identifying characteristics of the dosage form to aid with visual identification of the product. Therefore, we deleted it.
Active moiety expression of strength with equivalence statement (if applicable)	Not provided	**Not satisfactory.** The strength was expressed as minocycline with no equivalence statement of hydrochloride salt. See above for the revision.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	105 mg extended release tablets: (b) (4) M1'debossed on one surface, where 'M' and '1' are on either side of the score line. 135 mg extended release tablets:	**Not Satisfactory.** Suggesting the addition of specific identifying characteristics of the appearance as highlighted below. **Revise to:** MINOLIRA extended-release tablets are white to off-white, functionally scored, rectangular tablets with brown or gold color speckles and a single score line on both surfaces. MINOLIRA are available in the following two strengths. *105 mg extended-release tablets:* 'M1'debossed on one

	(b) (4) 'M3' debossed on one surface, where 'M' and '3' are on either side of the score line.	surface, where 'M' and '1' are on either side of the score line. *135 mg extended release tablets:* 'M3' is debossed on one surface, where 'M' and '3' are on either side of the score line. See comments in the Strength (b) (4)

2) #11: DESCRIPTION

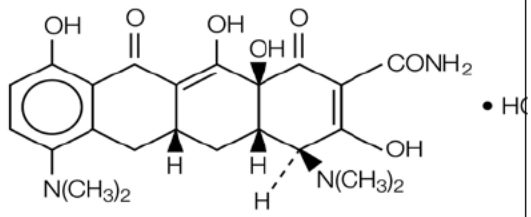
Minocycline hydrochloride, a semi synthetic derivative of tetracycline, is [4S-(4α,4aα,5aα,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a- tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide mono hydrochloride. The structural formula is represented below:



$C_{23}H_{27}N_3O_7$•HCl M. W. 493.95

MINOLIRA for oral administration contain (b) (4) 105 mg (b) (4) of minocycline as extended release beads. In addition, 105 mg and 135 mg tablets contain the following inactive ingredients: microcrystalline cellulose NF, polyethylene glycol 400 NF, ethyl cellulose (b) (4) NF, hypromellose (b) (4) USP, triethyl citrate NF, silicified microcrystalline cellulose NF, sodium stearyl fumarate NF, talc USP, isopropyl alcohol USP and purified water USP.
Both 105 mg and 135 mg tablets also contain Opadry clear (b) (4) which contains hydroxyl propyl cellulose NF and hypromellose (b) (4) USP.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	MINOLIRA	**Not satisfactory.** **Revise to** "MINOLIRA (minocycline hydrochloride) extended-release tablets"
Dosage form and route of administration	MINOLIRA for oral administration	**Not satisfactory.** The dosage form is not presented. See the comment above.
Active moiety expression of strength with equivalence statement (if applicable)	MINOLIRA for oral administration contain (b) (4) 105 mg (b) (4)	**Not Satisfactory.** **Revise to:** MINOLIRA (minocycline hydrochloride) extended-release tablets for oral administration

	(b) (4) f minocycline as extended release beads.	contain 105 mg or 135 mg of minocycline, equivalent to 113.4 mg or 145.8 mg of minocycline hydrochloride, respectively. MINOLIRA extended-release tablets, 105 mg and 135 mg, contain 25% of minocycline as immediate release beads and 75% of minocycline as extended release beads.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	In addition, 105 mg and 135 mg tablets contain the following inactive ingredients: microcrystalline cellulose NF, polyethylene glycol 400 NF, ethyl cellulose (b) (4) NF, hypromellose (b) (4) USP, triethyl citrate NF, silicified microcrystalline cellulose NF, sodium stearyl fumarate NF, talc USP, isopropyl alcohol USP and purified water USP. Both 105 mg and 135 mg tablets also contain Opadry clear (b) (4) which contains hydroxyl propyl cellulose NF and hypromellose (b) (4) USP.	**Not Satisfactory.** Consider listing the inactive ingredients in alphabetical order (see USP Chapter <1091>).
Statement of being sterile (if applicable)	N/A	NA
Pharmacological/ therapeutic class	Minocycline hydrochloride, a semi synthetic derivative of tetracycline,	**Satisfactory.**
Chemical name, structural formula, molecular weight	Minocycline hydrochloride, a semi synthetic derivative of tetracycline, is [4S-(4α,4aα,5aα,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide mono hydrochloride. The structural formula is represented below:  $C_{23}H_{27}N_3O_7$•HCl M. W. 493.95	**Satisfactory.**
If radioactive, statement of important nuclear characteristics.	N/A	NA
Other important chemical or physical properties (such as pKa or pH)	**N/A**	**N/A**

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

MINOLIRA is supplied as scored tablets containing (b) (4) minocycline hydrochloride equivalent to 105 mg and 135 mg of minocycline.

The 105 mg extended release tablets are white to off-white rectangular tablets (b) (4) single score line on both (b) (4) surface and 'M1' (b) (4) on one surface, (b) (4) M' and '1' are on either side of the score line. Each tablet contains 26.25 mg of minocycline as immediate release beads and 78.75 mg of minocycline as extended release beads, supplied as follows:

(b) (4) NDC 43598-540-30 Bottle of 30
(b) (4)

The 135 mg extended release tablets are white to off-white rectangular tablets (b) (4) single score line on both upper and lower surface and 'M3' (b) (4) on one surface, (b) (4) 'M' and '3' are on either side of the score line. Each tablet contains 33.75 mg of minocycline as immediate release beads and 101.25 mg of minocycline as extended release beads, supplied as follows:

(b) (4) NDC 43598-539-30 Bottle of 30
(b) (4)

16.2 Storage

Store at 20ºC - 25ºC (68 ºF - 77ºF); excursions are permitted to 15ºC-30ºC (59º-86ºF) [see USP Controlled Room Temperature].

16.3 Handling

(b) (4)

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

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	MINOLIRA is supplied as scored tablets containing (b) (4) minocycline hydrochloride equivalent to 105 mg and 135 mg of minocycline.	**Not Satisfactory**. **Revise to:** MINOLIRA is supplied as functionally scored extended-release tablets containing (b) (4) minocycline hydrochloride equivalent to 105 mg and 135 mg of minocycline.
Available units (e.g., bottles of 100 tablets)	The 105 mg extended-release tablets are …supplied as follows: (b) (4) NDC 43598-540-30 Bottle of 30 (b) (4) The 135 mg extended-release tablets are…, supplied as follows: (b) (4) NDC 43598-539-30 Bottle of 30 (b) (4)	**Not Satisfactory**. (b) (4).
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	The 105 mg extended release tablets are white to off-white rectangular tablets (b) (4) single score line on both (b) (4) surface and 'M1' (b) (4) on one surface, (b) (4) 'M' and '1' are on either side of the score line. The 135 mg extended release tablets are white to off-white rectangular tablets (b) (4) single score line on both (b) (4) surface and 'M3' (b) (4) on one surface, (b) (4) 'M' and '3' are on either side of the score line. (NDC# information, see the row above.)	**Not Satisfactory.** **Revise to**: The 105 mg extended-release tablets are white to off-white, rectangular with brown or gold color speckles. The tablets have a single score line on both surfaces and are debossed with 'M1' on one surface. On the face with debossing, 'M' and '1' are on either side of the score line. The 135 mg extended release tablets are white to off-white, rectangular, with brown or gold color speckles. The tablets have a single score line on both surfaces and are debossed with 'M3' on one surface. On the face with debossing, 'M' and '3' are on either side of the score line.
Special handling (e.g., protect from light)	(b) (4) Dispense in tight, light-resistant container with child-resistant closure.	**Not Satisfactory.** (b) (4)
Storage conditions	Store at 20ºC - 25ºC (68 ºF - 77ºF); excursions are permitted to 15ºC-30ºC (59º-86ºF) [see USP Controlled Room Temperature].	**Not Satisfactory.** Add "Protect from light and moisture."

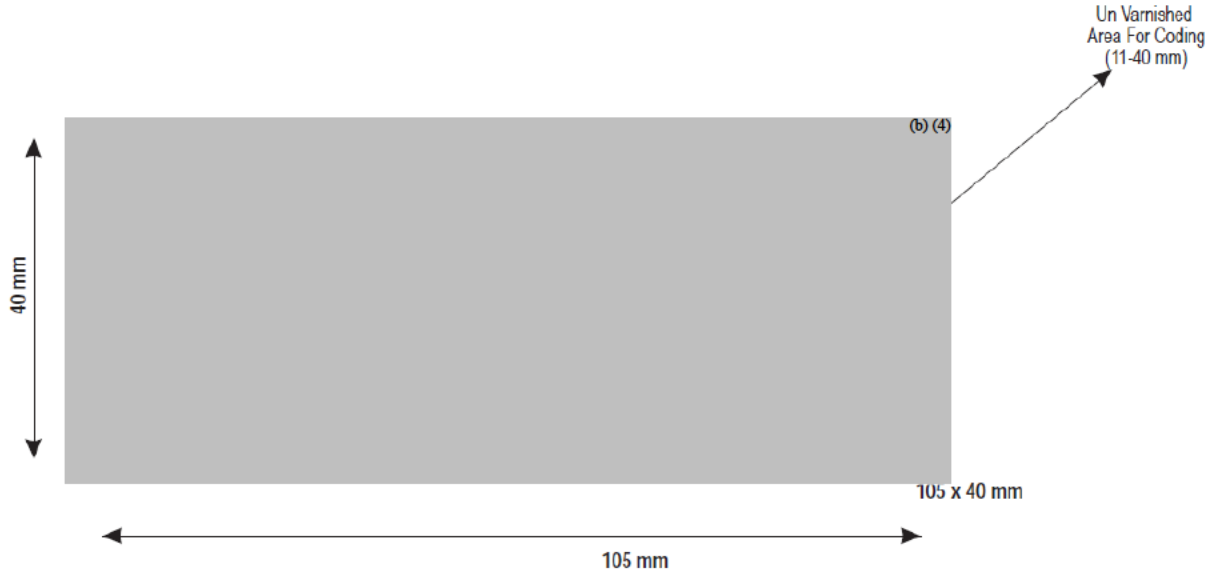
Manufacturer/distributor name (21 CFR 201.1(h)(5))		**Not Satisfactory.** Not provided.

II. Labels

The following Review of Container labels and Cartons are based on the submission by the applicant on September 9, 2016. Only Immediate Container Labels are included in the submission. There is no Carton labels provided.

1. IMMEDIATE CONTAINER

105 mg Physician Sample 10 count container label:



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QUALITY ASSESSMENT

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	MINOLIRA™ (b) (4)	**Not Satisfactory.** **Revise to:** MINOLIRA™ (minocycline hydrochloride) extended-release tablets,
Dosage strength	105 mg* *(Each tablet contains (b) (4) f minocycline (b) (4) 135 mg* *(Each tablet contains (b) (4) f minocycline (b) (4)	**Not Satisfactory.** NO salt equivalency statement. **Revise to:** **105 mg*** *Each tablet contains 105mg of minocycline (26.25mg as immediate release beads and 78.75 mg as extended release beads), equivalent to 113.4 mg of minocycline hydrochloride. **135 mg*** *Each tablet contains 135 mg of minocycline (33.75mg as immediate release beads and 101.25 mg as extended release beads), equivalent to 145.8mg of minocycline hydrochloride.
Net contents	30 Tablets (b) (4)	Satisfactory.
"Rx only" displayed prominently on the main panel	**Rx**	**Not Satisfactory.** **Revise to:** "Rx only"
NDC number (21 CFR 207.35(b)(3)(i))	105 mg , 30 counts: NDC 43598-540-30 (b) (4) 135 mg , 30 counts: NDC 43598-539-30 (b) (4)	**Satisfactory.**
Lot number and expiration date (21 CFR 201.17)	**Lot:** **Exp:**	**Satisfactory.**
Storage conditions	Store at 20 to 25°C (68 to 77°F); excursions permitted to 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]	**Not Satisfactory.** Add the following: Protect from light and moisture.
Bar code (21CFR 201.25)	Specified.	**Satisfactory.**
Name of manufacturer/distributor	Mfg by: Dr. Reddy's Laboratories Limited, FTO-SEZ Process Unit-01 Devunipalavalasa Vilage	**Satisfactory.**

	Srikakulam(District) Andhra Pradesh, INDIA Mfg License No. 38/SK/AP/2012/F/G Marketed by: Promius Pharma, LLC 107 College Road East Princeton, NJ 08540 USA	
And others, if space is available Such as Inactive ingredient information (quantitative, if injectable 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)		**Satisfactory.** Inactive ingredient information is not required to be listed due to its oral route per 21CFR201.100 (b) (5).

2. CARTON LABELS: *N/A*

(b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

The following materials related to labeling/label have been reviewed:

- Highlights of Prescribing Information: Names and Dosage Forms and Strengths.
- Full Prescribing Information: Sections: #3 DOSAGE FORMS AND STENGTHS; #11 (DESCRIPTION) and #16 (HOW SUPPLIED/STORAGE AND HANDLING)
- Container labels for both strengths including the physician samples.
- The Carton Labels are not provided.

The proposed trade name is MINOLIRA. The recommended established name for MINOLIRA is *minocycline hydrochloride extended-release tablets,* which is based on the following reasons:
1. The historical exception prescribed in the CDER salt policy.
2. Retaining the salt in the established name is in line with several existing USP monographs of minocycline hydrochloride for oral dosage forms: "Minocycline Hydrochloride Extended-Release Tablets", "Minocycline Hydrochloride Capsules" and "Minocycline Hydrochloride Oral Suspension".

Although the established name is expressed as salt name, the strengths of MINOLIRA are expressed as minocycline free base form, 105mg and 135mg. Again, this is also consistent with the USP monograph as well as the strength presentation of the RLD, SOLODYN.

The review of the label/labeling of this drug product is performed to make it as much consistent as the previously approved drug product, SOLODYN, unless there is concern about potential medication error.

Recommendation:

From the ONDP perspective, this application is ***not*** recommended for approval per 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Cai's assessment on the labeling and labels with the statement that this application is ***not*** ready for approval until those deficiencies in PI and the Container Labels are resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 2/28/2017 02:53:05PM
GUID: 502d0913000029f9798ca689a802fa55

Hong Cai

Digitally signed by Hong Cai
Date: 2/28/2017 02:34:33PM
GUID: 55919d6500e16bdaad5825645e4f22ff

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 209269

Drug Product Name / Strength: DFD-10 (minocycline HCI) Extended Release Tablets, 105 mg and 135 mg

Route of Administration: Oral

Applicant Name: Dr. Reddy's Laboratories Limited (DRL)

Review Summary:

The Listed Drug SOLODYN (Minocycline Hydrochloride) Extended Release Tablets, 45 mg, 55 mg, 65 mg, 80 mg, 90 mg, 105 mg, 115 mg, and 135 mg, developed by Medicis Pharmaceutical Corporation, Scottsdale, Arizona, USA, was approved by the FDA under NDA 050808 on 5/08/2006. It is indicated for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. However, SOLODYN tablets 45 mg, 90 mg, and 135 mg are no longer distributed or sold by Medicis Pharmaceutical Corporation.

Using SOLODYN as the Listed Drug, Dr. Reddy's Laboratories Limited (DRL) developed DFD-10 (minocycline HCI) Extended Release Tablets, 105 mg and 135 mg and submitted the application under NDA 209269 to seek an approval on 7/8/2016 through 505 (b) (2) regulatory pathway.

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, dissolution specification, biowaiver request, data for split tablets, and in vitro alcohol induced dose dumping study.

The applicant's proposed dissolution method (USP apparatus 1 at 100 rpm using degassed buffer at pH 2.1) is acceptable. The following dissolution specifications have been set as agreed upon with the Applicant:
0.5 h (30 min): (b) (4)%
1.5 h (90 min): (b) (4)%
3 h (180 min): NLT (b) (4)%

From the Biopharmaceutics perspective, NDA 209269 for DFD-10 (minocycline HCI) Extended Release Tablets, 105 mg and 135 mg is reviewed and found adequate for approval.

List Submissions being reviewed (table):

Application 209269 - Sequence 0000 - 0000 (1) 07/08/2016 ORIG-1 /Multiple Categories/Subcategories
Application 209269 - Sequence 0007 - 0007 (8) 12/21/2016 ORIG-1 /Quality/Response To Information Request

Module	Content
1.12.5	Request for a waiver
2..3.P	Quality overall summary- Drug product
2.7.1	Summary of Biopharmaceutic Studies and Associated Analytical Methods (in vitro dissolution data)
3.2.P.1	Description and composition of the drug product
3.2.P.2.2	Pharmaceutical Development-Drug product
3.2.P.5.1	Specifications
3.2.P.5.2	Analytical Procedures
3.2.P.5.2	Validation of Analytical Procedures
3.2.P.5.6	Justification of specifications

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment:

The applicant has stated that Minocycline hydrochloride is a BCS class I drug (high aqueous solubility and high permeability). There is no BCS based biowaiver request.

Solubility:

Soluble in solutions of alkali hydroxides and carbonates
Sparingly soluble in water

Slightly soluble in ethanol (96 %)
Practically insoluble in chloroform and in ether

Table 1. Solubility Data of Minocycline Hydrochloride in Different Physiological pH Media

Medium	Solubility (in mg/mL)					D/S ratio
	Experiment/ Run1	Experiment /Run2	Experiment /Run3	Average	SD	
0.1N HCl	45.3	46.2	46.1	45.9	0.49	3.17
pH 2.1 Simulated gastric fluid (SGF)	9.5	9.5	9.4	9.5	0.06	15.34
4.5 Acetate Buffer	14.8	14.5	14.7	14.7	0.15	9.91
6.8 Phosphate Buffer	20.7	20.6	20.3	20.5	0.21	7.11

Permeability: Minocycline is reported to be almost completely absorbed (95–100%), mainly in upper part of the gastrointestinal tract (stomach, duodenum, and jejunum).

Dissolution: See the Biopharm review below.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

I. Dissolution method

The Applicant used its own dissolution method to conduct dissolution tests, which is different from the USP monograph methods and the Listed Drug's method.

Table 2. The Applicant's proposed dissolution method

	NDA 050808	NDA 209269
Apparatus	USP apparatus I (basket)	USP apparatus I (basket)
Speed	100 rpm	100 rpm
Dissolution media	0.1 N hydrochloric acid	pH 2.1 buffer (Degassed)

Volume	900 mL	900 mL
Sampling times	1, 2, 3, and 4 hours	5, 10, 15, 30, 45, 60. 90, 120, 150, 180, and 240 minutes
Temperature	37 ± 0.5 °C	37 ± 0.5 °C
Specifications	1 h: (b) (4)% 2 h: % 4 h: NLT (b) (4)%	0.5 h (30 min): (b) (4)% 1.5 h (90 min): % 3 h (180 min): NLT (b) (4)%

Table 3. The USP monograph dissolution methods for Minocycline Hydrochloride) Extended Release Tablets

	Test 1	Test 2	Test 3	Test 4
Apparatus	USP Apparatus 2 (paddle)	USP apparatus I (basket)	USP apparatus I (basket)	USP apparatus I (basket)
Speed	50 rpm	100 rpm	100 rpm	100 rpm
Dissolution media	pH 6.8 buffer	0.1 N HCl	0.1 N HCl	0.1 N HCl
Volume	900 mL	900 mL	900 mL	900 mL
Sampling times	1, 2, and 5 hours	1, 2, and 4 hours	0.5, 1.5, and 4 hours	1, 2, and 4 hours
Temperature	37 ± 0.5 °C	37 ± 0.5 °C	37 ± 0.5 °C	37 ± 0.5 °C
Specifications	1 h: 20%-45% 2 h: 40%-70% 5 h: NLT 85%	45 mg 1 h: 40%-60% 2 h: 70%-95% 4 h: NLT 85% 90 mg/135 mg 1 h: 40%-60%	0.5 h: NMT 40% 1.5 h: (b) (4)%-95% 4 h: NLT 85%	45 mg / 90 mg 1 h: 35%-50% 2 h: 63%-78% 4 h: NLT 90% 135 mg 1 h: 35%-50%

		2 h: 70%-90% 4 h: NLT 85%		2 h: 67%-82% 4 h: NLT 90%

II. Dissolution Method Development for Minocycline Hydrochloride

The Applicant developed its own dissolution method for DFD-10 (minocycline HCl) Extended Release Tablets, 105 mg and 135 mg. The difference between the proposed method and the compendial methods is that the former used pH 2.1 SGF as the dissolution medium, and the latter pH 6.8 buffer or 0.1 N HCl.

A. Selection of dissolution medium

(b) (4)

(b) (4)

(b) (4)

[redacted]

III. The Discriminatory Power of the Proposed Dissolution Method

A. The power of the dissolution method to discriminate formulation change

Prototype Formulations MCT-PP-32/031 and MCT-PP-23/034D (formulation similar to that for formulation MCT-PP-23/009, (b) (4) Extended release (b) (4) tablet) have different ratios of (b) (4). The former formulation has a higher concentration of (b) (4) than the latter. The results show MCT-PP-32/031 demonstrates faster dissolution than MCT-PP-23/034D in pH 2.1 SGF (Figure 3) and they have dissimilar dissolution profiles based on calculated similarity factor , f2=36.28.

Figure 3. Dissolution Profile of Prototype Formulations with Change in Formulation Composition In pH 2.1 SGF/100 RPM/USP Apparatus I

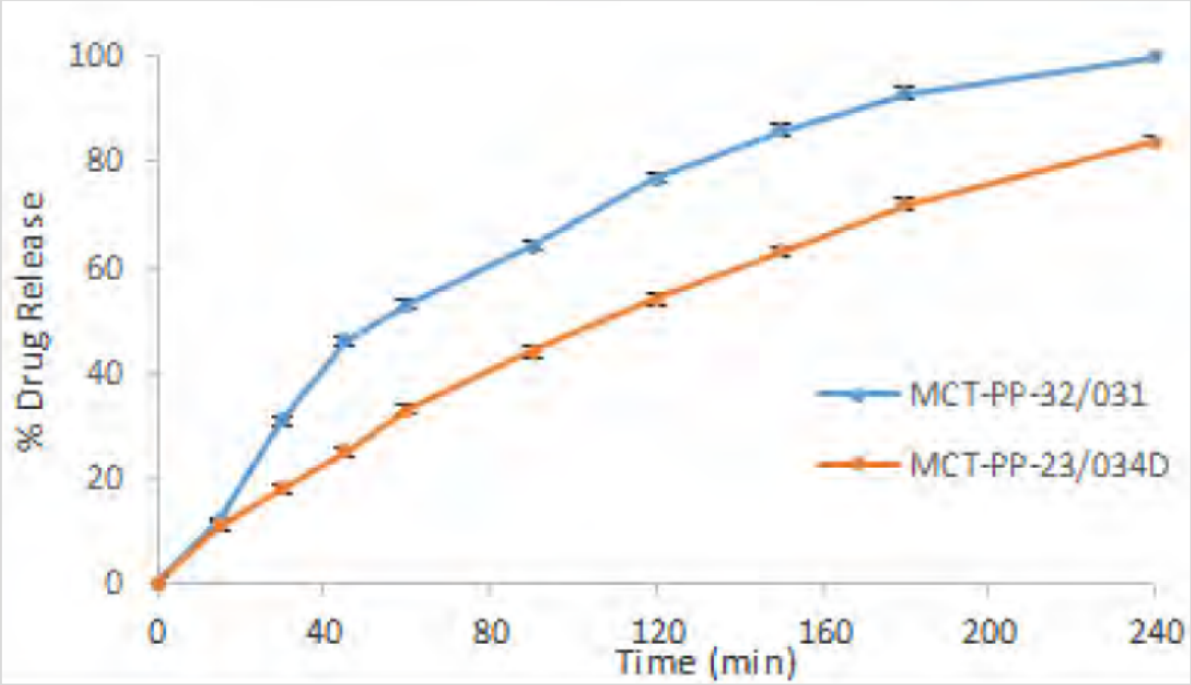


Table 5. Mean dissolution data comparison between MCT-PP-32/031 and MCT-PP-23/034D

Batch Number/ Time (min)	15	30	45	60	90	120	150	180	240
MCT-PP-32/031	12	31	46	53	64	77	86	93	100
MCT-PP-23/034D	11	18	25	33	44	54	63	72	84

B. The power of the dissolution test method to discriminate Changes in Manufacturing Process Conditions

(b) (4)

(b) (4)

Reviewer's comment:

The Applicant used four time points (b) (4) *to conduct the comparison of the dissolution profiles. It is not appropriate to use f2 to determine if they are similar because there are not enough valid time points for f2 calculation per Guidance for Industry- Dissolution Testing of Immediate Release Solid Oral Dosage Form. However, Figure 4 shows that these two batches have significantly different dissolution profiles. If the first three time points are used for f2 calculation, the value is* (b) (4).

IV. Analytical Method for Dissolution

The Applicant used UV analysis to determine the concentrations of the dissolution samples. The UV wavelength was set at 348nm. The percentage of drug release is calculated using the following equations:

For Intact Tablets 105 mg

$$\%\ \text{Release of minocycline at } n^{th} \text{ time intervals} = \frac{AT}{AS} \times \frac{W_S}{100} \times \frac{5}{100} \times \frac{900}{LC} \times \frac{25}{4} \times P$$

For Intact Tablets 135 mg

$$\%\ \text{Release of minocycline at } n^{th} \text{ time intervals} = \frac{AT}{AS} \times \frac{W_S}{100} \times \frac{5}{100} \times \frac{900}{LC} \times \frac{25}{3} \times P$$

Where,
AT is the absorbance from the test solution.
AS is the absorbance from the standard solution.
WS is the weight of minocycline hydrochloride standard taken in mg.
P is the percentage potency of minocycline hydrochloride standard calculated as minocycline on as is basis.
LC = Label claim of minocycline in mg per Intact tablet.
n = 1, 2, 3

For Split Tablets 105 mg

$$\% \text{ Release of minocycline at } n^{th} \text{ time intervals} = \frac{AT}{AS} \times \frac{W_S}{100} \times \frac{5}{100} \times \frac{900}{L.C} \times \frac{10}{3} \times P$$

For Split Tablets 135 mg

$$\% \text{ Release of minocycline at } n^{th} \text{ time intervals} = \frac{AT}{AS} \times \frac{W_S}{100} \times \frac{5}{100} \times \frac{900}{L.C} \times \frac{20}{5} \times P$$

Where,
AT is the absorbance from the test solution.
AS is the absorbance from the standard solution.
WS is the weight of minocycline hydrochloride standard taken in mg.
P is the percentage potency of minocycline hydrochloride standard calculated as minocycline on as is basis.
LC is the Label claim of minocycline in mg per split portion of tablet (52.50mg for 105mg strength and 67.50mg for 135mg strength).
n = 1, 2, 3

Calculation of Correction Factors

% of minocycline present in sampled volume after 1st time interval, F1 = (D1/900) x 10

% of minocycline present in sampled volume after 2nd time interval, F2 = (D2/900) x 10

Calculation of Corrected Results

For 1st time interval = D1 (No correction required)

For 2nd time interval = D1 + F1

For 3rd time interval = D2 + F1 + F2

V. Validation of Analytical procedures for Dissolution

The analytical method for dissolution was validated in Dr. Reddy's Laboratories Limited (DRL), India. The validation includes specificity, linearity & range, accuracy, precision (repeatability and intermediate precision), stability in analytical solution, effect of Filter variation, and robustness. The method is adequate.

VI. Dissolution data and specification

A. Whole tablet data and specification

The Applicant manufactured the following batches of test products. The Applicant provided the complete dissolution data of Batches ET15030, ET 15028, ET 15025, and ET 15031 in pH 2.1 SGF. The data are listed in Appendix I for details.

Table 8. Batch Information – Registration/Clinical Batches of DFD-10 Tablets

Batch number	Strength	Date of Manufacture	Use of Batch
ET15030	135 mg	January 2015	Clinical and stability
ET15028	135 mg	January 2015	Stability
ET15025	135 mg	January 2015	Stability
ET15031	105 mg	January 2015	Stability
ET15027	105 mg	January 2015	Stability
ET15026	105 mg	January 2015	Stability

Table 9. Mean dissolution data of test products in pH 2.1 SGF

Batch Number	5	10	15	30	45	60	90	120	150	180	240
ET15030	16	19	29	37	46	64	81	88	98	104	107
ET15028	8	14	21	39	48	56	68	78	86	92	99
ET15025	8	14	20	37	47	55	67	78	86	91	97
ET15031 1st analysis	11	15	18	29	43	61	67	77	81	92	96
ET15031 2nd analysis	7	12	20	35	45	53	67	78	92	100	104

Initially, the Applicant proposed the following dissolution specifications for their proposed products:

0.5 h (30 min): NMT (b) (4) %

1.5 h (90 min): (b) (4) %

3 h (180 min): NLT (b) (4)%

The above specifications appeared in the following documents:

- 3.2.P.5.1 specifications
- 3.2.P.2 Pharmaceutics development
- 3.2.P.5.4 Batch analyses

However, the Applicant stated they will use another set of specifications for their product based on the ongoing stability studies:

0.5 h (30 min): (b) (4)%

1.5 h (90 min): (b) (4)%

3 h (180 min): NLT (b) (4)%

These specifications are reported in the following documents:

- 3.2.P.5.1 specifications
- 3.2.P.5.6 Justification of Specifications

This Reviewer checked the individual data of Biobatch ET15030 and found it is not able to pass the second proposed specifications, because the average dissolution at 90 minutes is (b) (4)% with a range from (b) (4)%. In addition, based on the data of Biobatch ET15030, the specifications are set liberally. The Applicant was asked to accept the following recommended specifications:

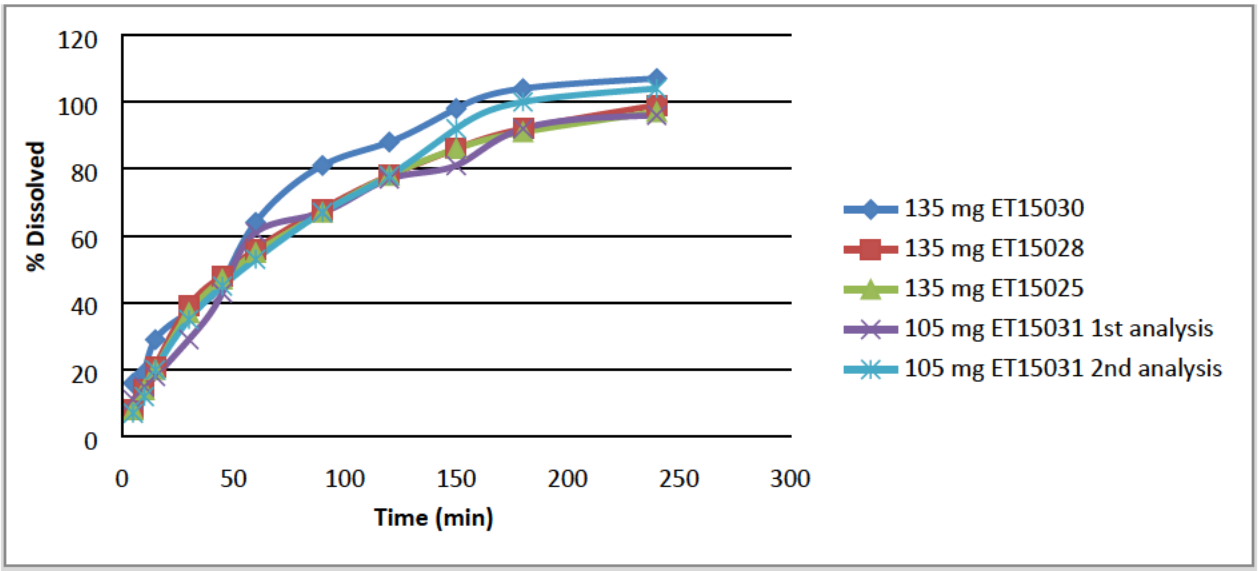
0.5 h (30 min): (b) (4)%

1.5 h (90 min): (b) (4)%

3 h (180 min): NLT (b) (4)%

Batches ET15025, ET15028, and ET15031 are able to meet the above recommended specifications.

Figure 5. Mean dissolution profiles between higher strength and lower strength



B. Half tablet data and specification

The Applicant also provided the complete dissolution data of half tablets for Batches ET15030, and ET 15031 in pH 2.1 SGF. The data are listed in Appendix II for details.

Table 10. Mean dissolution data of half tablets in pH 2.1 SGF

Batch Number/Time points (min)	5	10	15	30	45	60	90	120	150	180	240
ET15030 whole tablet	16	19	29	37	46	64	81	88	98	104	107
ET15030 Manually Split half tablets	13	17	24	41	52	60	74	85	94	100	105
ET15030 Mechanically Split half tablets	11	14	24	39	50	60	74	81	92	97	101
ET15031 whole tablet 1st analysis	11	15	18	29	43	61	67	77	81	92	96
ET15031 whole tablet 2nd analysis	7	12	20	35	45	53	67	78	92	100	104
ET15031 Manually Split half tablets	13	21	28	45	57	65	77	85	94	99	104

ET15031 Mechanically Split half tablets	10	15	22	35	48	55	75	81	91	98	104

The half tablets were generated by both manually and mechanically split. The half tablets from ET15030 and ET 15031 are able to meet the FDA recommended specifications.

This Reviewer also calculated the similar factors between half tablets (both manually and mechanically split) and their respective whole tablets, and the results show the dissolution profiles between half tablets and whole tablets are similar (Table 8, Figures 6 an7)

Table 11. Similarity factor (f2) between half tablets and whole tablets

Comparison	F2
ET15030 whole tablet vs. Manually split half tablets	66.69
ET15030 whole tablet vs. Mechanically split half tablets	64.17
ET15031 whole tablet 1st analysis vs. Manually split half tablets	50.27
ET15031 whole tablet 1st analysis vs. Mechanically split half tablets	61.82
ET15031 whole tablet 1st analysis vs. Manually split half tablets	51.05
ET15031 whole tablet 1st analysis vs. Mechanically split half tablets	72.06

Figure 6. Mean dissolution profiles of half tablets and their respective whole tablets in pH 2.1 SGF, ET 15030, 135 mg

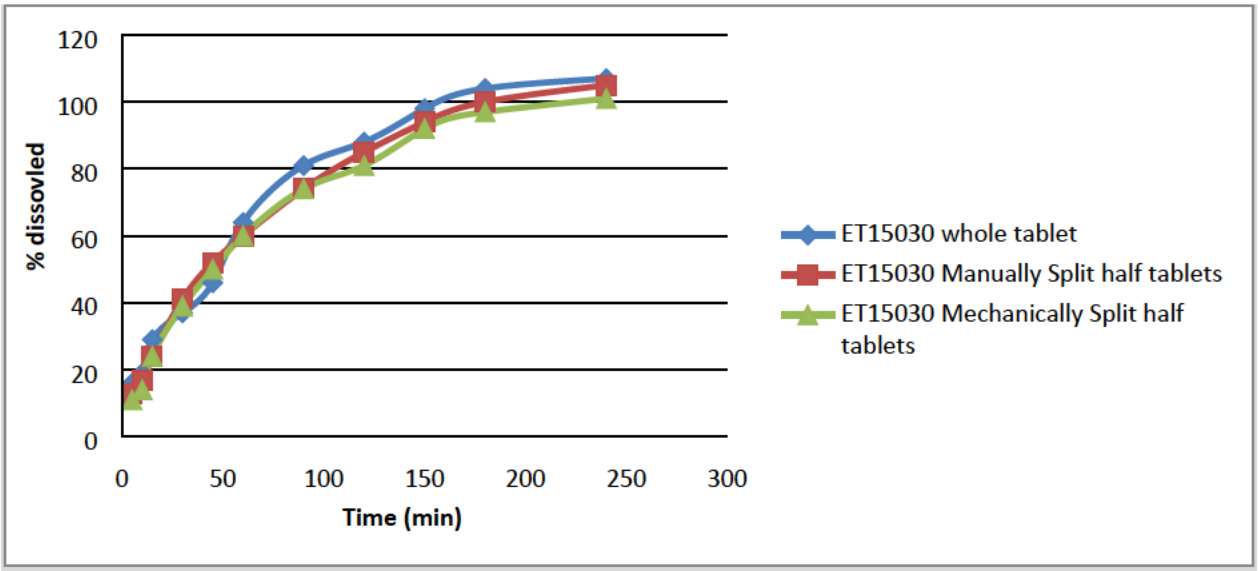
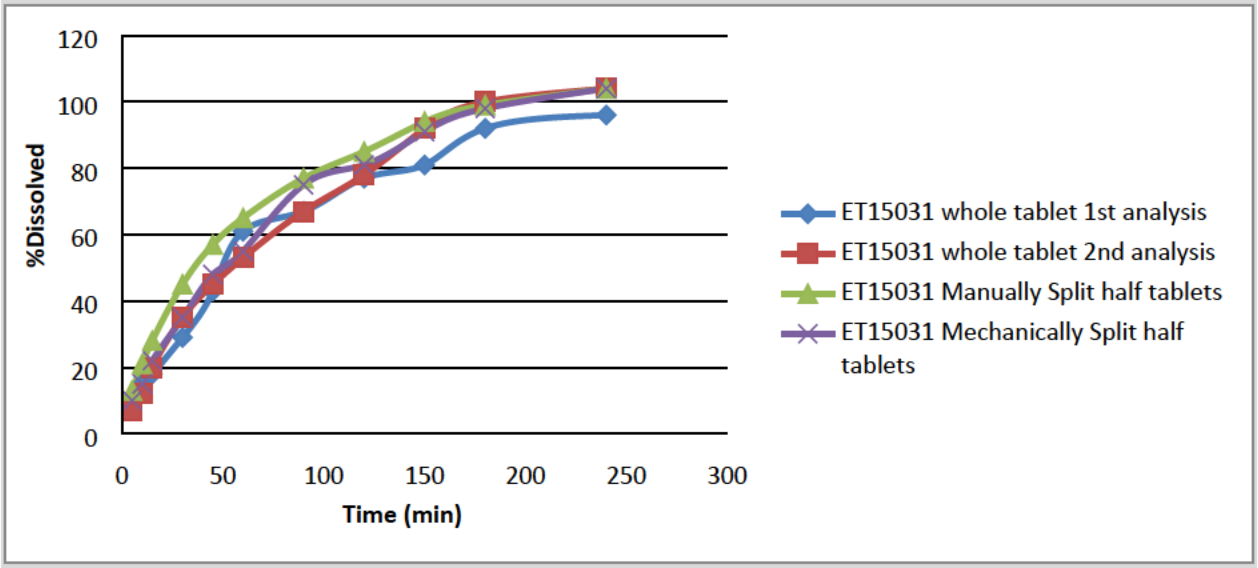


Figure 7. Mean dissolution profiles of half tablets and their respective whole tablets in pH 2.1 SGF, ET 15031, 105 mg



C. Other data required for scored tablets

Because the proposed product is [redacted] (b) (4) film coated extended release tablets, the following data should be included in the submission per Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for evaluation:

- Dissolution should be demonstrated at both ends of the hardness range: data for tablets [redacted] (b) (4) lower hardness and at higher hardness

- Dissolution profile on [redacted] whole and split tablet portions should meet similarity factor (f2) criteria to ascertain the integrity of beads [redacted].

The Applicant provided the above required data in 3.2.P.2.3.5. Process Development [redacted] Coating. The similarity factor f2 for tablets [redacted] and higher hardness was above [redacted] for 135 mg and 105 mg tablets and split tables. Please refer to the Process Review for additional details.

VII. Information request (IR)

After reviewing the submitted dissolution data for both half tablets and whole tablets, we sent an Information Request IR to the Applicant on 12/8/2016. On 12/21/2016, the Applicant responded to the IR. The following are the IR, the Applicant's response to the IR, and this Reviewer's comment of the Applicant's response:

IR

Your proposed dissolution specifications are loose. Based on the data, we request that you acknowledge your acceptance of the following recommended dissolution acceptance criteria and update the drug product specifications accordingly:

0.5 h (30 min): [redacted]%

1.5 h (90 min): [redacted]%

3 h (180 min): NLT [redacted]%

The Applicant's response to the IR

The Applicant acknowledged that they accept the Agency recommended dissolution specifications and updated the drug product specifications in Table 3.2.P.5.1-2 of Module 3.2.P.5.1.

Reviewer's comment

The response is adequate.

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Reviewer's Assessment: *N/A*

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment:

The Applicant used the QC method to conduct the in vitro alcohol induced dose dumping tests in 0.1 N HCl and pH 2.1 SGF dissolution media containing 0%, 5%, 10%, 20%, and 40% (v/v) ethanol.

Table 12. Dissolution Method for Alcohol Dose Dumping Evaluation

Apparatus	USP apparatus I (basket)
Speed	100 rpm
Dissolution media	0.1 N HCl or pH 2.1 SGF
Volume	900 mL
Sampling times	15, 30, 45, 60, 75, 90, 105,120,150 and 180 minutes
Temperature	37 ±0.5 °C

DFD-10 tablets 135 mg batch ET15030 was employed in this study, which was also used in the pivotal studies. The mean dissolution data are listed in Table 10.

Table 13. Mean dissolution data of DFD-10 tablets 135 mg batch ET15030 in 0.1 N HCl or pH 2.1 SGF with 0%, 5%, 10%, 20%, and 40% Alcohol

Time points (min)	15	30	45	60	75	90	105	120	150	180
0.1 N HCl with 0% of alcohol	25	50	72	87	94	98	100	101	102	102
0.1 N HCl with 5%	26	50	71	83	91	94	97	98	99	99

of alcohol										
0.1 N HCl with 10% of alcohol	31	59	80	91	97	100	99	101	101	102
0.1 N HCl with 20% of alcohol	34	64	80	88	93	96	98	99	100	101
0.1 N HCl with 40% of alcohol	19	43	59	70	79	84	88	93	99	102
pH 2.1 SGF with 0% of alcohol	23	40	50	58	64	69	74	80	87	92
pH 2.1 SGF with 5% of alcohol	23	41	52	60	69	75	82	87	94	98
pH 2.1 SGF with 10% of alcohol	21	39	49	58	66	73	80	85	91	95
pH 2.1 SGF with 20% of alcohol	25	42	56	67	76	84	90	93	96	99
pH 2.1 SGF with 40% of alcohol	14	28	38	46	52	58	62	66	74	80

Figure 8. Comparative Dissolution Profile of DFD-10 tablets 135 mg batch ET15030 in 0.1N HCl Containing 0%, 5%, 10%, 20% and 40% Alcohol

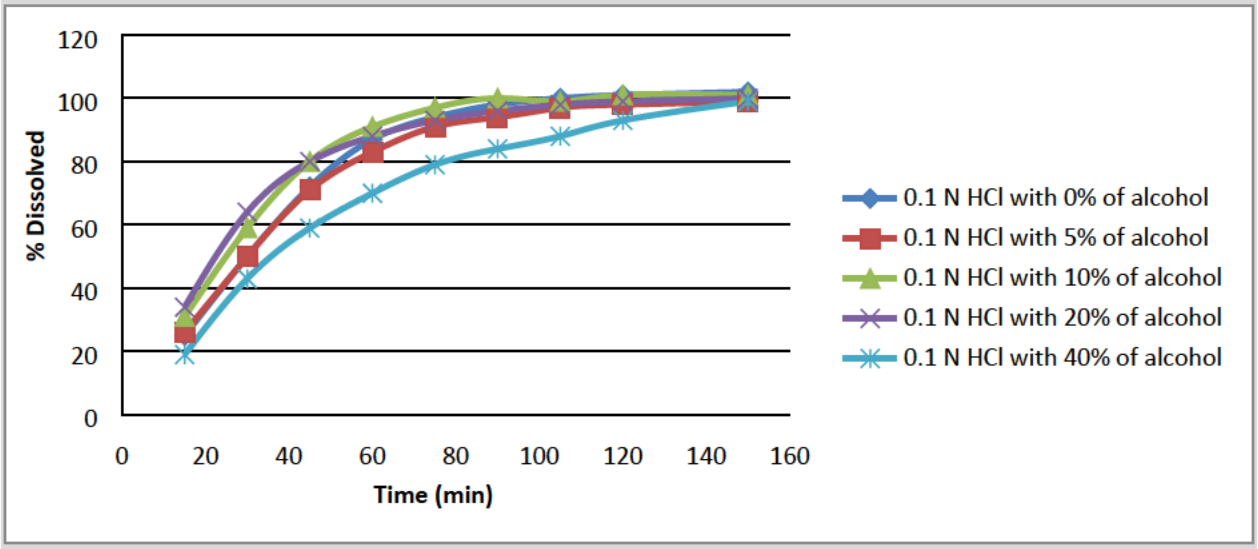


Figure 9. Comparative Dissolution Profile of DFD-10 tablets 135 mg batch ET15030 in 2.1 SGF Containing 0%, 5%, 10%, 20% and 40% Alcohol

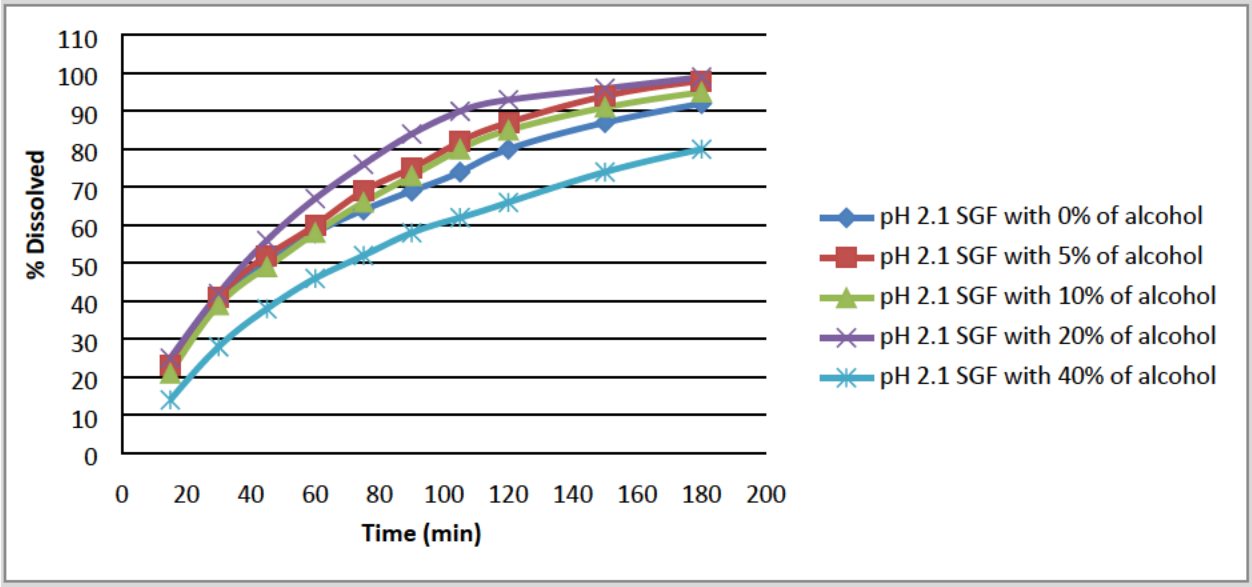


Table 14. The similarity factors between the proposed product's dissolution profiles in medium without alcohol and with alcohol

Comparison	F2 values
0.1 N HCl with 0% of alcohol vs. 0.1 N HCl with 5% of alcohol	81.5
0.1 N HCl with 0% of alcohol vs. 0.1 N HCl with 10% of alcohol	57.5
0.1 N HCl with 0% of alcohol vs. 0.1 N HCl with 20% of alcohol	51.6
0.1 N HCl with 0% of alcohol vs. 0.1 N HCl with 40% of alcohol	46.6
pH 2.1 SGF with 0% of alcohol vs. pH 2.1 SGF with 5% of alcohol	65.6
pH 2.1 SGF with 0% of alcohol vs. pH 2.1 SGF with 10% of alcohol	73.1
pH 2.1 SGF with 0% of alcohol vs. pH 2.1 SGF with 20% of alcohol	49.1
pH 2.1 SGF with 0% of alcohol vs. pH 2.1 SGF with 40% of alcohol	46.0

This Reviewer calculated the similarity factors between the dissolution profiles of minocycline HCl extended tablets in the dissolution media without alcohol and with alcohol, and the f2 values are listed in Table 11. The results demonstrate that alcohol is unlikely to cause dose dumping of DFD-10 (minocycline HCI) Extended Release Tablets.

The results also show that the dissolution of the proposed product is the slowest in the dissolution medium containing 40% of alcohol. Minocycline HCl is freely soluble in water and slightly soluble in 95% of alcohol. When the amount of the alcohol in dissolution medium increases to 40%, the solubility of Minocycline HCl in the medium will drop significantly; consequently, the dissolution of minocycline HCl extended tablets is slower.

The results of this study have been conveyed to the Office of Clinical Pharmacology.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: N/A

Bridging of Formulations

Reviewer's Assessment:

The formulation of the commercial batches is the same as the one of exhibit batches. The scale-up batch size of the commercial batches is not more than (b) (4) times that of the exhibit batches.

Biowaiver Request

Reviewer's Assessment:

The Applicant conducted two bioequivalence studies (under fasting and fed conditions) to compare the higher strength of test product 135 mg (Batch ET 15030) with the Listed Drug-SOLODYN 80 mg + 55 mg (co-administered, Lot No.: 5D5253for 55 mg and Lot No.: 5B4934 for 80 mg), which is pending Clinpharm Review conclusion (for additional details, please refer to clinical pharmacology review. The Applicant requested the biowaiver for the lower strength 105 mg.

A. Formulation of the test products

Table 15. Qualitative and Quantitative Composition of the Drug Products

Components	Function	Quality standard	% w/w	Amount per unit (mg)	
				105 mg	135 mg
Minocycline hydrochloride $*	Drug Substance	USP	12.67	113.369	145.760
Microcrystalline cellulose (b) (4)	(b) (4)	NF	(b) (4)		
Opadry clear (b) (4)		IH			
Polyethylene glycol 400 (b) (4)		NF			
Ethyl cellulose (b) (4)		NF			
Hypromellose (b) (4) (b) (4)		USP			
Triethyl citrate		NF			
Silicified microcrystalline cellulose (b) (4)		NF			
Microcrystalline cellulose (b) (4)		NF			
(b) (4)					
Sodium stearyl fumarate		NF			
Talc		USP			
Isopropyl alcohol+		USP			
Purified water+		USP			
Total weight					

$113.369 mg of minocycline hydrochloride is equivalent to minocycline 105 mg
$145.760 mg of minocycline hydrochloride is equivalent to minocycline 135 mg
+ Does not appear in the final product except in traces.

Table 12 shows that 105 mg strength and 135 mg strength are dose proportional.

B. Comparative dissolution assessment

The Applicant conducted dissolution profiles comparison between Biobatch ET15030 and lower strength 105 mg Batch ET15031 in multiple media: 0.1N HCl, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer. The data are listed in Appendix III for details.

Table 16. Mean dissolution data between the higher strength and lower strength in multimedia

Batch Number	5	10	15	30	45	60	90	120	150	180	240

ET15030 in 0.1 N HCl	9	13	22	44	67	81	92	97	100	104	108
ET15031 in 0.1 N HCl	14	16	24	50	71	81	88	93	96	99	103
ET15030 in pH 4.5 Acetate Buffer	7	11	17	33	44	53	70	85	92	97	103
ET15031 in pH 4.5 Acetate Buffer	10	17	25	42	53	60	79	92	99	102	104
ET15030 in pH 6.8 Phosphate Buffer	8	16	18	36	51	57	64	74	79	84	94
ET15031 in pH 6.8 Phosphate Buffer	7	13	17	29	38	48	63	72	83	88	95

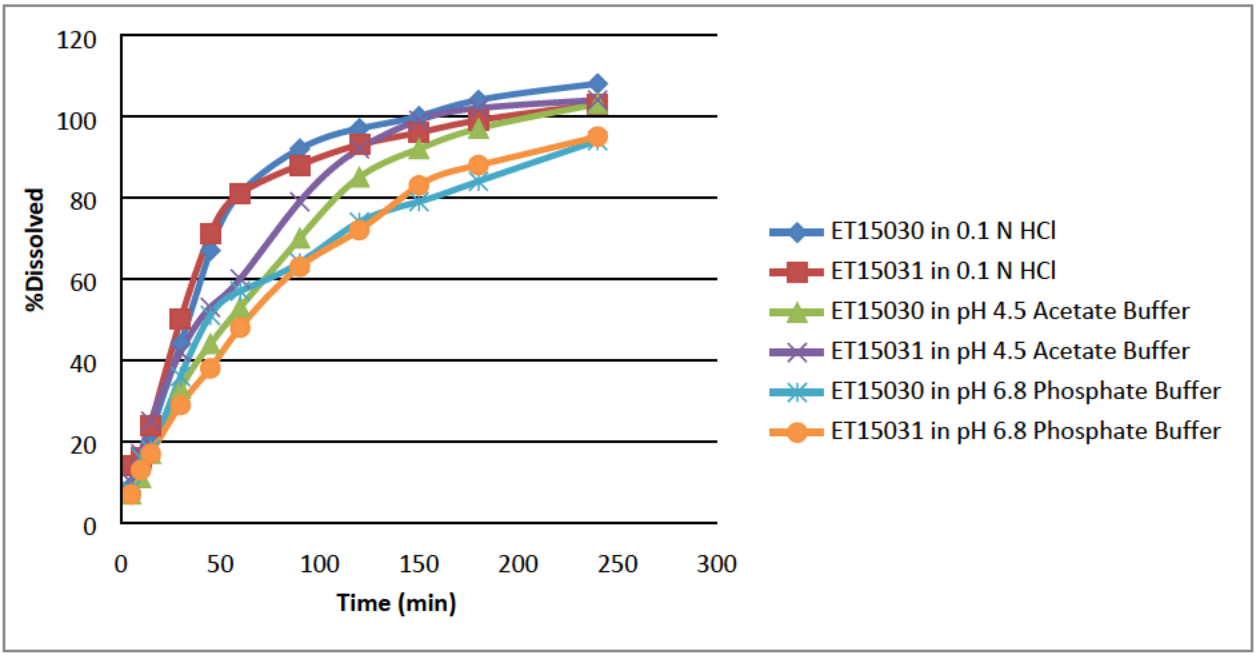
This Reviewer calculated the similarity factors (f2), and the results are listed in Table 14. It was concluded that Biobatch ET15030 and lower strength 105 mg Batch ET15031 are similar on dissolution profiles in multimedia.

Table 17. Dissolution Similarity Factors f2 between Biobatch ET15030 and lower strength 105 mg Batch ET15031 in multimedia

Comparison	F2
Biobatch ET15030 vs. Batch ET15031 in 0.1 N HCl	69.80
Biobatch ET15030 vs. Batch ET15031 in pH 4.5 Acetate Buffer	56.06
Biobatch ET15030 vs. Batch ET15031 in 6.8 Phosphate Buffer	61.18
*Biobatch ET15030 vs. Batch ET15031 in pH 2.1 SGF (1st analysis)	53.70
*Biobatch ET15030 vs. Batch ET15031 in pH 2.1 SGF (2nd analysis)	52.41

*The data are listed in Table 9

Figure 10. Mean Comparative Dissolution Profiles of Biobatch ET15030 and lower strength 105 mg Batch ET15031 in multimedia



C. Biowaiver

Provided bioequivalence is demonstrated for the 135 mg strength product the Biowaiver is granted for the strength 105 mg due to the following reasons:

1) The lower strength product is in the same dosage form, but in different strength
2) The lower strength (105 mg) and the higher strength (135 mg) are proportionally similar in its active and inactive ingredients
3) The lower strength (105 mg) and the higher strength (135 mg) are similar on dissolution profiles in multimedia

R Regional Information

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment:

Lifecycle Management Considerations

List of Deficiencies: *None*

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, 2/17/2017, 2/27/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Vidula Kolhatkar, Ph.D., March 02, 2017

Hansong Chen

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Vidula Kolhatkar

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