CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208711Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: APPROVAL

NDA #208711

Review #1

Drug Name/Dosage Form	EGATEN (Triclabendazole) tablets
Strength	250 mg triclabendazole
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	NOVARTIS Pharmaceutical Corporation
US agent, if applicable	Not Applicable

SUBMISSION(S) REVIEWED		DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Quality Information	SD #0002	*12-Mar-2018*	Biopharmaceutics
New NDA	SD #0008	*14-Jun-2018*	All
Quality Response to IR	SD #0016	*7-Aug-2018*	Process and Facilities
Quality Response to IR	SD #0018	*29-Aug-2018*	Drug Product
Quality Response to IR	SD #0022	*24-Sep-2018*	Biopharmaceutics
Quality Response to IR	SD #0023	*3-Oct-2018*	Drug Product
Quality Response to IR	SD #0028	*11-Oct-2018*	Drug Substance
Quality Response to IR	SD #0029	*15-Oct-2018*	Drug Product
Quality Response to IR	SD #0031	*22-Oct-2018*	Drug Product
Quality Response to IR	SD #0032	*25-Oct-2018*	Drug Product
Labeling	SD #0033	*25-Oct-2018*	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Dr. Mohd Shahjahan Kabir	Dr. Su Tran
Drug Product	Dr. Milton Sloan	Dr. Balajee Shanmugam
Process	Dr. Ying Wang	Dr. Upinder Atwal
Microbiology	Dr. Ying Wang	Dr. Upinder Atwal
Facility	Dr. Ying Wang	Dr. Frank Wackes
Biopharmaceutics	Dr. Gerlie Geiser	Dr. Elsbeth Chikhale
Environmental Assessment	Dr. Milton Sloan	Dr. Balajee Shanmugam
Laboratory (OTR)	-	-
ORA Lead	-	-
Regulatory Business Process Manager	Dr. Anh-Thy Ly	-
Application Technical Lead	Dr. Andrei Ponta	-

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)		Adequate	See DS review	-
	Type III			Adequate	See DP review	-

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
#0008	IND 127946	Triclabendazole
#0008	IND (b) (4)	Triclabendazole

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharm/Tox	NA			
CDRH	NA			
Clinical	NA			
Other (Method Verification)	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for approval from the Product Quality perspective. This document contains the final evaluation of all manufacturing facilities, the final risk assessment, and the summary of all product quality aspects of the NDA.

II. Summary of Quality Assessments

A. Product Overview

The Applicant has submitted this NDA via the 505(b)(1) pathway. Currently, there is no drug approved in the United States for the treatment of fascioliasis. The World Health Organization (WHO) and Center for Disease Control (CDC) treatment guidelines for fascioliasis state that triclabendazole is the recommended drug of choice for the treatment of this condition.

The proposed drug product, EGATEN, is an immediate release tablet containing 250 mg triclabendazole. The tablets are pale red, speckled, capsule shaped, biconvex with a functional score on both sides and with one side imprinted with, "EG EG." The drug product is packaged in blisters containing four tablets.

The drug product is indicated for treatment of fascioliasis (b) (4) in adults and children of 6 years of age and older. (b) (4)

Proposed Indication(s) including Intended Patient Population	EGATEN™ tablet is indicated for treatment of fascioliasis (b) (4) in adults and children of 6 years of age and older.
Duration of Treatment	The proposed dose of EGATEN is (b) (4)
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	Oral use only. Can be taken crushed and administered with (b) (4) applesauce).

B. Quality Assessment Overview

The proposed drug product, EGATEN, is an immediate release tablet containing 250 mg triclabendazole.

The clinical drug substance material was manufactured at Novartis Crop Protection SA (Monthey, Switzerland) but the manufacturing site has since been divested. (b) (4) . The Applicant cross references drug substance

information to DMF # (b) (4) which has been reviewed in concurrence with the NDA and has been found adequate. The quality of the commercial (b) (4) drug substance has been reviewed and it has been determined that it is comparable to Novartis' clinical drug substance material with respect to the impurity profile, polymorph, particle size, specification, test methods, and batch analyses.

The triclabendazole drug substance is a new molecular entity (NME). The Applicant considers triclabendazole as a BCS Class II/IV drug substance, due to its poor water solubility (0.1 mg/L) and inconclusive human permeability data. It is a white to almost white crystalline powder and is known to exhibit polymorphism. The drug substance manufacturing process only produces the polymorph (b) (4) No other polymorph can form using this manufacturing process.

The drug product is an immediate release tablet containing 250 mg triclabendazole and the following compendial excipients: lactose monohydrate, corn starch, methyl hydroxyethyl cellulose, magnesium stearate, silicon dioxide, and red iron oxide.

The manufacturing process for the tablet involves (b) (4). The manufacturing process is adequately described and controlled. The Applicant has manufactured numerous drug product batches to date and provided release results for eight clinical, production, and/or commercial batches. All drug product batches manufactured to date met the proposed release specifications.

The initial risk table identified three aspects as moderate risk: physical stability (solid state); content uniformity, due to functional scoring; and dissolution. All of these aspects have been evaluated and determined to be low risk based on the mitigation strategy.

The dissolution method has been evaluated and was shown to have discriminating power for changes in critical quality attributes) of the drug product (e.g. drug substance particle size. The Applicant has also revised the dissolution acceptance criterion (Q = (b) (4)% at 30 minutes) ensuring that the criterion is sufficient to reject aberrant drug product batches.

The drug product has a score on both sides of the tablet to facilitate splitting into two equal halves. Comparative dissolution profiles of the whole versus split tablets have demonstrated that splitting of the tablets do not significantly impact the dissolution profile. Additional studies performed on split tablets (e.g. assay, degradation products, content uniformity, friability, weight variation) provided further support that the drug product has a functional score. Both manual and mechanical splitting of tablets is recommended as an acceptable means for ease of administering divided dose to patients.

An additional dissolution study demonstrated that crushing the drug product with and without applesauce does not impact *in-vitro* dissolution. Additional stability studies (e.g. assay, degradation products) confirmed that the crushed drug product is stable in applesauce up to four hours.

The drug product, EGATEN 250 mg tablets, is packaged in (b) (4) blister packs commonly used for solid oral dosage forms, contained in a cardboard box. Each

blister pack contains four tablets.

The Applicant has provided 9 months' stability data on three drug product batches representative of the proposed commercial product manufactured in October 2017. The Applicant has also provided 36 months' supportive long-term stability data from three drug product batches and 60 months' supportive long-term stability data from an additional three drug product batches. (b) (4) However, data from the supportive stability studies were manufactured using Novartis Crop Protection drug substance, while the registration batches and the proposed commercial product are manufactured with (b) (4) drug substance. Evaluation of the stability results indicates that drug product is stable at long-term storage conditions and that no significant change occurs at accelerated conditions. Based on the stability data, the proposed shelf life of 24 months is acceptable when stored below 30°C.

Following a review of the application, inspectional documents, and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. All sites are found acceptable upon completion of this review. The Overall Manufacturing Facility Status in Panorama is Approve. For details, see the Facility evaluation within this review.

The Applicant has submitted a claim for categorical exclusion per 21 CFR 25.31(b) as the concentration of the active moiety, triclabendazole, will be significantly less than 1 ppb. A statement of no knowledge of extraordinary circumstances that might significantly affect the quality of the human environment has been submitted for the categorical exclusions, per 21 CFR 25.15(a). The claim for categorical exclusion has been reviewed and deemed acceptable.

C. Special Product Quality Labeling Recommendations

There are no deficiencies which would prevent approval from the product quality perspective. The following recommendations were conveyed to the OND PM for consideration as the labeling is not yet finalized:

1. We recommend adding and revising following statements to the blister container:
    a. Discard unused tablet(s)
    b. Store below 30°C (86°F)

D. Final Risk Assessment (see Attachment)

Andrei Ponta, Ph.D.

Application Technical Lead for NDA #208711

Date: 8-Nov-2018

Comparability Protocols

N/A

Reviewer's Assessment:

N/A

Post-Approval Commitments

Reviewer's Assessment:

N/A

Lifecycle Management Considerations

Reviewer's Assessment:

N/A

List of Deficiencies

N/A

Primary Drug Substance Reviewer Name and Date:

M. Shahjahan Kabir, Ph.D.
FDA/CDER/OPQ/ONDP/DND/API/Branch 1
10-October-2018

Secondary Reviewer Name and Date:

Suong T. Tran, Ph.D. Branch Chief
FDA/CDER/OPQ/ONDP/DND/API/Branch 1
10-October-2018

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Primary Drug Product Reviewer Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
10/29/2018

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

Balajee Shanmugam, PhD
Branch Chief
OPQ/ONDP/Div1/Branch III
10/31/2018

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Milton Sloan

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LABELING

IQA Review Guide Reference

{For NDA Only}

I. Package Insert

1. *Highlights of Prescribing Information*

----------DOSAGE FORMS AND STRENGTHS----------
Tablet: 250 mg, functionally scored (3)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	EGATEN™ (triclabendazole)
Dosage form, route of administration	Tablets for oral use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	250 mg Tablets with functional score on both sides

2. *Section 2 Dosage and Administration*

The recommended dose of Egaten is [redacted] (b) (4) The tablets are functionally scored and divisible into two equal halves of 125 mg [redacted] (b) (4) If the dosage cannot be adjusted exactly, [redacted] (b) (4) round the dose upwards [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4) tablets can be swallowed [redacted] (b) (4) whole [redacted] (b) (4) or crushed and administered with [redacted] (b) (4) applesauce. The crushed tablet mixed with [redacted] (b) (4) (apple sauce) is stable up to 4 hours.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Studies to support food compatibility and tablet crushing were done to support statements.

3. *Section 3 Dosage Forms and Strengths*

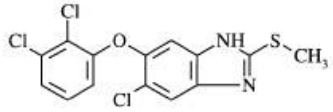
EGATEN™ (triclabendazole) tablet: 250 mg pale red, speckled, (b) (4) biconvex with imprint of "EG EG" on one side and functionally scored on both sides.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablet
Strengths: in metric system	250 mg
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Included with recommended modification

4. *Section 11 Description*

Egaten (triclabendazole) tablet is an orally administered anthelmintic (b) (4) for immediate release. Triclabendazole is designated chemically as benzimidazole derivative, 6-chloro-5-(2, 3-dichlorophenoxy)-2-(methylthio)-1H-benzimidazole (triclabendazole). The molecular formula for triclabendazole is (b) (4) and the molecular weight is 359.65 g/mol.

The chemical structure of triclabendazole is shown below:



Triclabendazole is a white or almost white, crystalline powder.

Egaten tablets are , pale red, speckled, capsule shaped, biconvex tablets, with imprint "EG EG" on one side and functionally scored on both sides. Each tablet contains 250 mg of triclabendazole.

Inactive Ingredients: colloidal silicon dioxide, iron oxide red, lactose monohydrate, maize starch, magnesium stearate, methylhydroxyethylcellulose, , ,.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	N/A
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The USP/NF monograph is under colloidal silicon dioxide
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Yes, anthelmintic
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Non

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

EGATEN (triclabendazole) tablets are supplied as pale red, speckled, (b) (4) biconvex tablets, with imprint "EG EG" on one side and a functional score on both sides. Each tablet contains 250 mg of triclabendazole. . EGATEN (triclabendazole) tablets are available as:

NDC 0078-0937-91 blister packs of 4 tablets

Storage

Store in the original container. Store below 30°C (86°F) (b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	N/A
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer's Assessment of Package Insert: ***{Adequate/Inadequate}***

The prescribing information complies with all regulatory requirements from a CMC perspective. Recommendations for revision has been provided in the text above via tracked changes. Also the dosage and administration is still under discussion (b) (4) .

II. Labels:

1. ***Container and Carton Labels***

{Copy/paste or refer to a representative example of a proposed container}

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Back of Wallet (closed):

(b) (4)

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Yes	
Dosage strength	Yes	
Net contents	Yes	
"Rx only" displayed prominently on the main panel	Yes	
NDC number (21 CFR 207.35(b)(3)(i))	Yes	
Lot number and expiration date (21 CFR 201.17)	Yes	
Storage conditions	Yes	
Bar code (21CFR 201.25)	Yes	
Name of manufacturer/distributor	Yes	
And others, if space is available	N/A	

Reviewer's Assessment of Labels: ***{Adequate/Inadequate}***

1. We recommend adding and revising following statements to the blister container:
   - Take with food
   - Discard unused tablet(s)
   - Store below 30°C (86°F)

2. Consider alternative blister package presentation (post-approval) to facilitate accurate dosing (perhaps 2 and 4 tablet blisters).

List of Deficiencies:

1. We recommend revising following statements to the blister container:
   - Store below 30°C (86°F)

Overall Assessment and Recommendation: The review of the labeling is ongoing. Consideration on revising dosage continues and may impact labeling sections above.

Primary Labeling Reviewer Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
11/07/2018

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

Balajee Shanmugam, PhD
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Milton Sloan

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Balajee Shanmugam

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BIOPHARMACEUTICS

Product Background:

NDA: 208711; 505(b)(1); Priority; NME

Drug Product Name / Strength: EGATEN (triclabendazole) Tablets / 250 mg

Route of Administration: Oral
Proposed Indication: Treatment of fascioliasis (b) (4) in adults and children of six years of age and older
Proposed Dosage: (b) (4) Swallow whole/divided tablets with water; alternatively, crush tablets and administer (b) (4) apple sauce.

Applicant Name: NOVARTIS Pharmaceutical Corporation

Review Recommendation: APPROVAL

Review Summary:
The Applicant submitted this 505(b)(1) NDA to seek FDA approval of Egaten® (triclabendazole) Tablets for the treatment of fascioliasis based on the efficacy and safety findings of ex-US clinical studies involving patients treated with either Fasinex® or Egaten® (triclabendazole) tablets 250 mg. Fasinex® tablet is a veterinary product that was used in the majority of the medical literature clinical trials, as well as clinical PK studies. Egaten® tablet is currently registered for human use in Egypt and France, distributed worldwide by the World Health Organization (WHO), and was used in several investigator initiated clinical trials being used to support approval of this NDA.

Bridging to the To-Be-Marketed Drug Product
The final proposed to-be-marketed triclabendazole tablets has the same formulation and manufacturing process as the triclabendazole tablets used in the key clinical efficacy/safety trials and clinical PK studies. Thus, *in vivo* bioequivalence (BE) or pharmacokinetics (PK) data are not required for bridging purposes.

Based on the combined comparative *in vitro* dissolution profile data generated using the proposed QC dissolution method, and the Reviewer's confirmatory PBPK modeling, the Fasinex tablets and the WHO-Egaten tablets evaluated in medical literature/clinical PK studies and investigator-initiated trials, respectively, and (b) (4) Egaten tablets (which represent the final, proposed to-be-marketed drug product) are expected to be bioequivalent. Note that (b) (4) is the proposed commercial drug substance/active pharmaceutical ingredient (API) supplier.

Biowaiver Request:
The Applicant's request to waive the requirement to conduct an *in vivo* BA/BE study for the proposed to-be-marketed Egaten tablets is GRANTED, based on the overall evaluation of the dissolution profile data and other comparative *in vitro* data provided for the pre-change and post-change drug products and/or drug substances, the virtual BE analysis results using PBPK modeling and simulation, as well as the clinical efficacy and safety data available for Fasinex and WHO-Egaten tablets, and the clinical PK data generated using Fasinex tablets.

Dissolution Method and Acceptance Criteria:
The proposed dissolution method and the revised dissolution acceptance criterion (as tabulated below) are approved for the routine QC of triclabendazole tablets at batch release and during stability testing.

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
2 (paddle)	75 rpm	0.1M HCl with 1% Tween 20; 37 ± 0.5°C	1000 mL	NLT (b)(4)% (Q) of the label claim dissolved in 30 min

List of Submissions reviewed
SDN-9, 6/14/2018 (New NDA)
SDN-19, 8/29/2018 (Response to Early Biopharmaceutics Information Request)
SDN-23, 9/24/2018 (Response to Biopharmaceutics Information Request)
SDN-27, 10/3/2018 (Response to Quality Information Request)
SDN-29, 10/11/2018 (Response to Biopharmaceutics Information Request)
SDN-31, 10/22/2018 (Response to Biopharmaceutics Information Request)

Outstanding Issues Remaining:
None

BCS Designation

The Applicant considers triclabendazole as a BCS Class II/IV drug substance, due to its poor water solubility (0.1 mg/L) and inconclusive human permeability data.

Reviewer's Assessment:

Solubility: *Low*
Triclabendazole exhibits pH-dependent solubility, and low solubility (per BCS criteria). For the solubility of triclabendazole drug substance in various pH buffer media with and without surfactant, see Table 3-7 of the Pharmaceutical Development Report (PDR).

Permeability: *Indeterminate*
The proposed labeling states that (b) (4) However, the Applicant cited that the World Health Organization (WHO) includes triclabendazole in the list of drugs with inconclusive permeability classification (Lindenberg 2004). Per the Applicant, (b) (4)

Dissolution: *Not Rapidly Dissolving (without sufficient surfactant added to the medium)*
In (b) (4) mL biorelevant media, [i.e., simulated gastric fluid (SGF 2.0), simulated fed intestinal medium (FeSSIF 5.8), and simulated fasted intestinal medium (FaSSIF 6.5)], not more than (b) (4) % of the labeled amount of triclabendazole in the tablet dissolves during dissolution testing [USP Apparatus 2 (paddle) at (b) (4) rpm, 37 ± 0.5°C]; see Figure 3-2 of Report PHAD003659A). The Applicant notes that the observed higher dissolution in FeSSIF than in FaSSIF is in line with the observed higher *in vivo* oral bioavailability of triclabendazole and its two active metabolites under fed than under fasted conditions.
In multi-pH media (pH 1.2, pH 4.5, and pH 6.8 buffers) without surfactant, not more than (b) (4) % of the labeled amount of the drug in the tablet dissolves (see Figure 3-1 of the Report, USP Apparatus 2 at 75 rpm, 1000 mL media).
For routine QC testing, a surfactant is added to the dissolution medium to achieve complete drug release from the tablet. Specifically, in 1000 mL of 0.1M HCl with 1% Tween 20 [the proposed QC dissolution medium; using USP Apparatus 2 (paddle) at 75 rpm], at least (b) (4) % of triclabendazole dissolves within 30 min; see Figures 3-3 and 3-4 of the Report.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

Dissolution Method *- ADEQUATE*

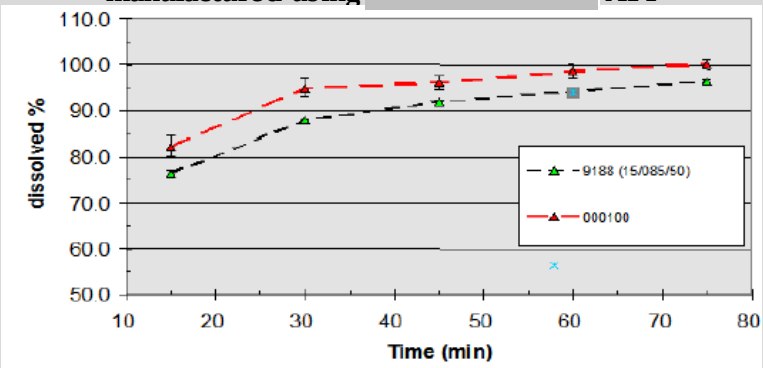
(b) (4)

(b) (4)

Discriminating Power

API particle size distribution is a critical quality attribute for poorly soluble drug substances such as triclabendazole. The proposed QC dissolution method was able to show the correct rank-order relationship between triclabendazole tablets manufactured (using the same formulation and manufacturing process but) with varying API particle size distribution (WHO Egaten vs. Fasinex tablets; see Figure 1 and Table 3-8 of the PDR).

Figure 1
Comparative Dissolution Profiles of Triclabendazole Tablets manufactured using (b) (4) API



Source: Figure 2-1 of IND 127946, SDN-5 dated 5/31/2016

Reviewer Notes: The major difference between the Fasinex and the WHO-Egaten tablets is the API particle size distribution (b) (4) which explains at least in part the faster dissolution rate of the WHO-Egaten tablets. Note that the final proposed to-be-marketed triclabendazole tablet uses (b) (4) API, which also explains at least in part the slightly faster *in vitro* dissolution in the proposed QC dissolution medium of the process validation batches of the (b) (4) Egaten tablets as compared to the Fasinex and WHO-Egaten Tablets (see Figure 2 below). For a detailed comparison of the API particle size distribution of (b) (4) Novartis DS, (b) (4) Novartis DS, and (b) (4) DS, refer to Tables 2-21 to 2-25 of SDN-19.

[This Reviewer does not consider the provided comparative dissolution profile data for the following drug product batches as valid evidence of the proposed dissolution method's discriminating power, for the reason(s) provided:

(1) *Formulation composition differences*: Fasinex and the Interim Human Formulation (IHF) tablet (b) (4) which could partly explain the lack of bioequivalence between the two drug products (see Figure 3-3 of the PDR).

(2) *Different* (b) (4): A consistent trend was not observed (see Figure 3-10 of the PDR).

(3) (b) (4) */viscosity:* The apparent observed trend of (b) (4) dissolution at (b) (4) min for Fasinex/WHO-Egaten/(b) (4) Egaten tablets manufactured using

(b) (4) could have been confounded by API particle size differences among the compared drug products (see Tables 3-13 and 3-14 of the PDR).

Additional comparative dissolution profile data of drug product batches intentionally manufactured with variations (b) (4) were requested but were not available.

Triclabendazole exhibits (b) (4) crystalline forms (b) (4). Polymorphic form could potentially impact drug substance solubility (as shown (b) (4) (b) (4) in Table 2-1 of the PDR); the pH-solubility profile data of (b) (4) are not available.). However, the Applicant (b) (4) *This Reviewer defers to the Drug Substance and Drug Product Reviewers regarding the evaluation of the adequacy of the Applicant's proposed QC specifications with respect to API polymorphic control.*]

The analytical method (RP-HPLC with UV detection at 306 nm) was validated for specificity/selectivity, linearity, accuracy, precision/repeatability, intermediate precision, stability of the solutions, and filter compatibility (b) (4) The Applicant reported that the standard and the sample solutions were stable for up to 2 days and 1 day, respectively, at room temperature. (b) (4) were found to be compatible with the samples. Additionally, the dissolution data at (b) (4) were comparable between automated and manual sampling. Per the Drug Product Reviewer (Dr. Milton Sloan), the methods validation including that for dissolution testing is adequate.

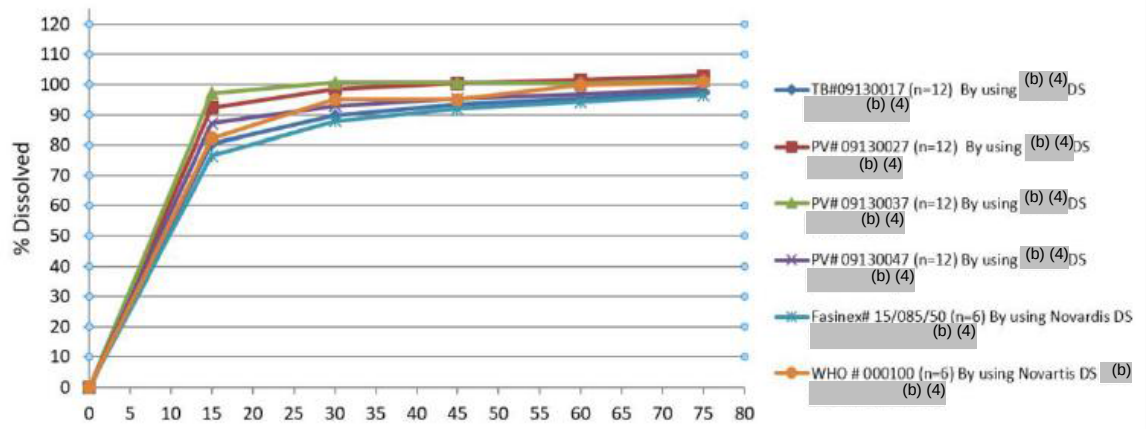
Dissolution Acceptance Criterion *– REVISED ACCEPTANCE CRITERION ADEQUATE*

The proposed dissolution acceptance criterion for the finished drug product is "Not less than (b) (4) % (Q value) of the declared content in (b) (4) minutes according to acceptance table of Ph. Eur. or USP, JP (level 1 and 2 only for release, up to level 3 for stability testing)."

Per the Applicant, the Q value and the specification time point were selected based on the data available to date with production batches of the (b) (4) Egaten tablets. A single-point dissolution acceptance criterion was selected in accordance with the FDA Guidance for dissolution testing of immediate-release solid oral dosage forms. Per the Applicant, with the proposed dissolution acceptance criterion (Q (b) (4)% at (b) (4) min) there is already a 5% probability of failing USP Stage 1 testing.

Based on the dissolution profile data of the Fasinex tablet batch evaluated in key clinical trials and a PK study, the WHO-Egaten tablet batch, as well as one technical batch and all three process validation batches of (b) (4) Egaten Tablets in Figure 2, this Reviewer recommends (b) (4) of the dissolution acceptance criterion to 'NLT (b) (4)% (Q) at 30 min'. Of note, all these batches depicted in Figure 2 pass this Reviewer's recommended dissolution acceptance criterion at USP Stage 1 testing. Additionally, even when considering the dissolution profile data of a commercial WHO-Egaten Batch (2130026; data submitted in the NDA but not included in the Applicant's figure) that required USP Stage 2 testing, the Division of Biopharmaceutics Automation Tool predicts that the passing rate for 50 batches (consisting of (b) (4) ablets each) will still be 100% by USP Stage 2 testing regardless of whether 30 min or (D) (4) min is selected as the specification time point for a Q of (b) (4)%.

Figure 2
Mean dissolution profile comparison of Fasinex, WHO Egaten (000100) and (b) (4) Egaten technical batch and process validation batches in proposed QC dissolution media



Source: Figure 2-3 of the Applicant's Response to Early Biopharmaceutics Information Request (SDN-19, 8/29/2018). *Reviewer Notes:* Fasinex tablet batch 15/085/50 was used in clinical studies/trials involving patients [Studies EGA230B2201 through EGA230B2208, and EGA230B2212 (with PK endpoint), EGA230B2213, and EGA230B2218] and healthy subjects (Study EGA2302B2102). The batch number(s) of the Egaten tablets used in three investigator-initated trials is not known.

Dissolution on Stability

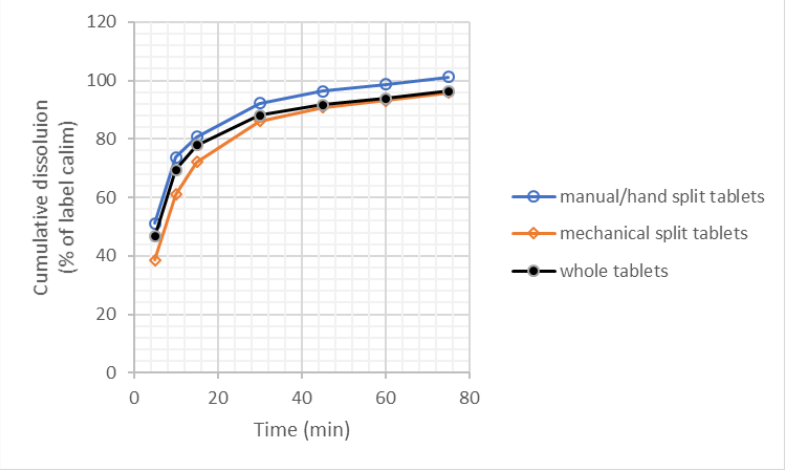
To support the proposed shelf-life of 24 months, up to 9 months of long-term stability (25°C/60%RH) and up to 6 months of accelerated stability (40°C/70%RH) data were provided in the original NDA submission for the three primary registration (process validation) batches of the (b) (4) Egaten tablets. Up to 60 months of supporting long-term stability data were also provided for a total of six WHO-Egaten batches.

The Applicant notes that the dissolution data of the stability samples were initially collected at the (b) (4) min sampling time point. Later on, the Applicant's dissolution acceptance criterion was (b) (4) to 'Q = (b) (4)% at (b) (4) min'. Since the dissolution at (b) (4) min is (b) (4)% for the registration stability lots of the (b) (4) Egaten tablets [and their dissolution profiles at the initial stability time point (T= 0 months) show close to (b) (4)% dissolution at 30 min], it is deemed reasonable for this Reviewer to recommend (b) (4) of the dissolution acceptance criterion to "Q = (b) (4)% at 30 min" for batch release and stability testing of future drug product batches. Additionally, based on the dissolution profile data of the (b) (4) Egaten Process Validation Batches at Months 0 and 9 of long-term stability testing, the proposed commercial drug product is able to conform to this Reviewer's recommended dissolution acceptance criterion (Q = (b) (4)% at 30 min; see Figures 4-7 to 4-9 of 3.2.P.8.1 of SDN-27).

Whole versus Split Tablets

The proposed to-be-marketed drug product ((b) (4) Egaten tablets) has a score on both tablet faces to facilitate splitting of the tablet into two equal halves. To support the functional score on the tablet, comparative dissolution profiles of whole vs. split tablets and other CMC data from one technical batch (as well as from three process validation batches) of the final proposed to-be-marketed Egaten tablets were provided. As shown in Figure 3, manual and mechanical splitting of the double-scored tablet did not significantly impact the dissolution profile of the tablets. The split tablets would pass both the Applicant's and this Reviewer's dissolution acceptance criteria by USP Stage 2 testing.

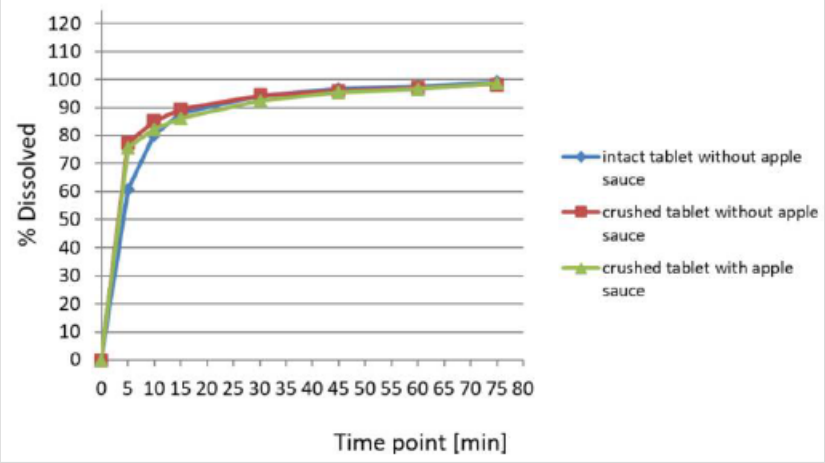
Figure 3
Comparison of dissolution profiles of Egaten tablets: whole versus manually and mechanically split tablets



Source: Tables 1-13 and 14 of 3.2.P.2 Appendix 1; Table 3-9 of 3.2.P.2. Dissolution Comparability Report. *Reviewer Notes:* Per the Applicant, the testing of Technical batch# 09130017 (n=12) was performed in accordance with the March 2013 FDA's Guidance on Tablet Scoring. The calculated profile similarity values for the manually and mechanically split tablets were both greater than 50, relative to the whole tablets.

Whole versus Crushed Tablets With and Without Addition of Apple Sauce
As shown in Figure 4, crushing of the tablets with or without addition of apple sauce did not impact the *in vitro* dissolution profile of triclabendazole in the proposed QC dissolution medium.

Figure 4
Comparison of dissolution profiles of Egaten tablets: intact tablet without apple sauce, crushed tablet with and without apple sauce



Source: Figure 2-6 of the Applicant's Response to Early Biopharmaceutics Information Request (SDN-19, 8/29/2018).
Reviewer Notes: (b) (4) Process Validation Batch 09130027 was used. The crushed tablet was dispersed in apple sauce and stored for 4 hours at room temperature prior to dissolution testing. Assay results for the samples ranged from 99.7% to 102% after 4 hours; the difference in assay results between samples with and without apple sauce was within 2.0%.

Clinical relevance of dissolution method & acceptance criteria

Reviewer's Assessment:

The results of Virtual BE analysis using PBPK (Gastro-Plus 9.5) modeling indicate that the triclabendazole tablets that exhibit cumulative dissolution of at least (b) (4)% at 30 min are expected to be bioequivalent to the Fasinex and Egaten tablets that were evaluated for PK, and/or efficacy and safety in clinical studies. Thus, this Reviewer recommended the (b) (4) of the dissolution acceptance criterion to 'NLT (b) (4)% (Q) at 30 min'. On 10/11/2018, the Applicant adopted the FDA recommended acceptance criterion and updated the finished product QC specifications accordingly.

Bridging to the To-Be-Marketed Drug Product

Reviewer's Assessment: *ADEQUATE*

The proposed US commercial Egaten tablet ("(b) (4) Egaten"), the ex-US commercial Egaten tablet distributed worldwide by the World Health Organization ("WHO-Egaten"), and the Fasinex tablet for animal use are manufactured using the same formulation, process (b) (4) However, the proposed commercial US Egaten tablet will be manufactured using API from a new drug substance supplier ((b) (4) in lieu of Novartis which manufactured the API of the WHO Egaten and the Fasinex tablets. Additionally, the appearances (debossing letters and/or number of scores) of the three tablets are different; see Table 3-2 of the PDR.

Thus, comparative *in vivo* PK data were not submitted nor required to bridge the final proposed to-be-marketed triclabendazole tablets (as represented by the (b) (4) Egaten tablet process validation batches) to the Fasinex and the WHO-Egaten tablets used in key clinical efficacy/safety trials.

To justify the proposed change in the API supplier from Novartis/Switzerland to (b) (4), as well as the change in appearance, i.e., after conducting the clinical studies using Fasinex or WHO-Egaten tablets, the Applicant provided the following data/information:

(1) Comparative CMC (solubility, particle size distribution, crystal morphology, impurity profile, and chemical stability) data for the drug substances manufactured by the two API suppliers. The Applicant reported that (a) since both the Novartis and (b) (4) sourced API materials exhibit Polymorphic (b) (4) their pH-solubility profiles are the same, and (b) although it appears that the (b) (4) drug substance (DS) (b) (4) its API particle size distribution is comparable to that of the (b) (4) API used for the manufacture of the WHO-Egaten Tablets, (b) (4) Novartis DS used for the manufacture of Fasinex tablets. Overall, the Drug Substance Reviewer (Dr. Mohd Shahjahan Kabir) considers the quality attributes of the Novartis DS and the (b) (4) DS equivalent.

(2) Comparative *in vitro* dissolution profile data for the drug product in either the QC dissolution medium (Fasinex vs. WHO-Egaten vs. (b) (4) Egaten), and/or in biorelevant media (WHO-Egaten vs. (b) (4) Egaten). (Note that Fasinex tablets are no longer available for further testing such as dissolution in biorelevant media and multi-pH media.) The Applicant's modeling and simulation predicts that the WHO-Egaten and (b) (4) Egaten tablets will be bioequivalent to Fasinex tablets in terms of triclabendazole Cmax and AUC.

This Reviewer's profile similarity (f_2 and multivariate) analyses revealed that at least one of the three process validation batches of (b) (4) Egaten (especially, Batch #09130037) exhibited a faster dissolution rate as compared to the reference Fasinex tablet batch (15/085/50) and/or one of the two reference WHO-Egaten tablet batches (2130026). As discussed earlier in this review under the section on "Dissolution Acceptance Criteria", such observation could be explained (at least in part) by the QC dissolution method's discriminating power for changes in API particle size distribution. In general, faster dissolution rate is not considered a concern for immediate release drug products, especially when the normal Tmax is not prolonged, such as the case for triclabendazole (2 – 4 hours). However, confirmatory PBPK modeling was still performed by this Reviewer to gain added assurance that relatively faster dissolving immediate release triclabendazole tablets would not result in significant increases in drug exposures as compared to those achieved using the tablets used in clinical studies. Thus, as discussed later in this review under the section on "Biowaiver Request", this Reviewer's Virtual BE analysis using Gastro-Plus 9.5 predicted that under fed conditions (b) (4) Egaten Process Validation Batch #09130037 will still be bioequivalent to both Fasinex and WHO-Egaten tablets in terms of triclabendazole Cmax and AUC, with no observed shortening of the Tmax. Therefore, this Reviewer concludes that the changes in the API supplier (i.e., the (b) (4) in API particle size) and in the appearance (i.e., the increase in the number of scores and the change in the debossing letters) of the tablet that occurred after evaluating triclabendazole PK/efficacy/safety of Fasinex tablets are not anticipated to impact the *in vivo* performance of the proposed to-be-marketed Egaten tablets (which has the same formulation and manufacturing process) as the reference Fasinex tablets.

Biowaiver Request

Reviewer's Assessment: *GRANTED*

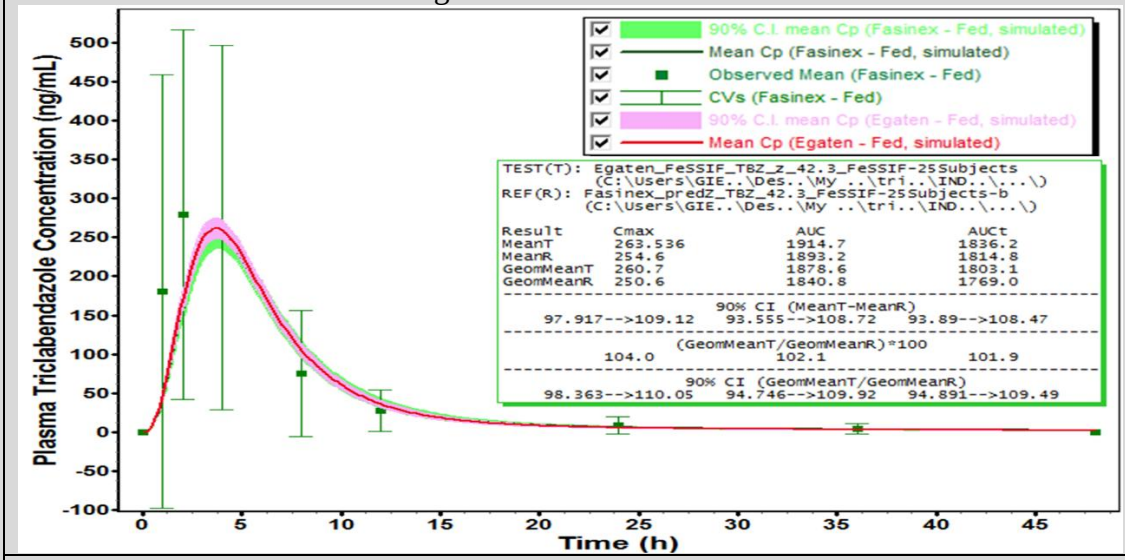
Human PK data are available for the Fasinex (triclabendazole) 250 mg veterinary tablets but not for the Egaten (triclabendazole) 250 mg tablets developed for human use. The Applicant requested a waiver to conduct an *in vivo* BA/BE study for the proposed to-be marketed Egaten (triclabendazole) 250 mg tablets, based on evidence of comparable *in vitro* dissolution profiles and the Applicant's PBPK model predicted bioequivalence results.

The (b) (4) Egaten tablet (the final proposed-to-be-marketed drug product), the WHO-Egaten tablet (used in investigator initiated clinical trials), and the Fasinex tablet (used in majority of the clinical efficacy and safety trials) share a common formulation and manufacturing process. As described in the previous section, these three tablets differ mainly in terms of appearance (i.e., imprint and number of scores), as well as the manufacturing process and/or supplier of the poorly soluble API (i.e., (b) (4) (b) (4) DS vs. (b) (4) Novartis DS vs. (b) (4) Novartis DS). Based on this Reviewer's PBPK modeling and simulation using Gastro-Plus 9.5, the (b) (4) Egaten tablet and the WHO-Egaten tablet were demonstrated to be bioequivalent to the Fasinex tablet, i.e., in terms of triclabendazole Cmax and AUC,

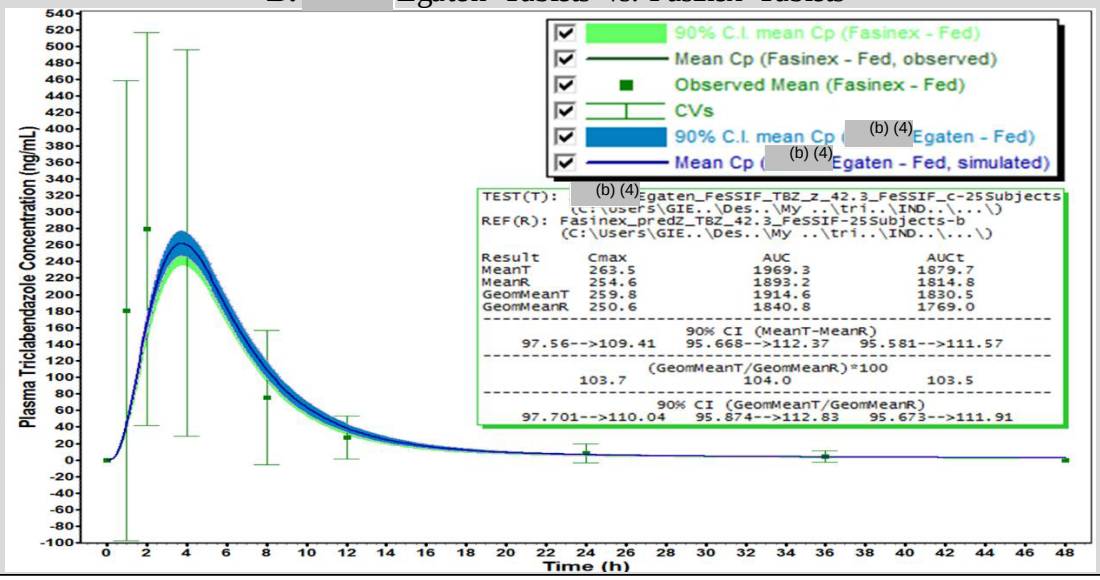
when administered under fed conditions. As shown in Figure 5A, the model-predicted mean plasma triclabendazole concentration-time profiles of the test and the reference treatments were superimposable, and the variability of the observed PK data for the reference product was high. For the details of this Reviewer's PBPK modeling and simulation involving mainly the WHO-Egaten and the Fasinex tablets, refer to the Biopharmaceutics Review of SDN-5 of IND 127946. Since at the time of NDA submission, the Applicant proposed additional CMC changes, i.e., to the API supplier (from Novartis to (b) (4) and the tablet appearance, this Reviewer's PBPK modeling and simulation work under the IND stage had to be extended to cover also the (b) (4) Egaten tablets (the final, proposed-to-be-marketed drug product). The final virtual BE comparisons obtained using this Reviewer's own PBPK model are reflected in Figure 5B.

Figure 5. Virtual Bioequivalence Analysis using GastroPlus 9.5

A. WHO-Egaten Tablets vs. Fasinex Tablets



B. (b) (4) Egaten Tablets vs. Fasinex Tablets



Reviewer Notes: The *in vitro* dissolution profile data and *in vivo* PK data of Fasinex Batch 15/085/50, and the *in vitro* dissolution profile data of WHO-Egaten Batch 000100 and (b) (4) Egaten Process Validation (PV) Batch 09130037 were used in the Reviewer's PBPK Modeling and Virtual BE Analysis. PV Batch 09130037 was selected for simulation because (as shown in Figure 2 above) of the three (b) (4) Egaten PV batches, it showed the greatest separation from (i.e., the fastest dissolution rate as compared to) the reference Fasinex and WHO-Egaten tablets.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date:

Gerlie Gieser, Ph.D. (10/25/2018)

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

Elsbeth Chikhale, Ph.D. (11/2/2018)

Gerlie Gieser

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Elsbeth Chikhale

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Date: 11/02/2018 04:13:03PM
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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

Final Risk Table for EGATEN (Triclabendazole) (NDA #208711)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability		**L**	(b) (4)	Acc	
Physical stability (solid state)		**M**		Acc	
Content uniformity		**M**		Acc	
Microbial limits		**L**		Acc	
Dissolution – BCS Class II & IV		**M**		Acc	
Drug Product Impurity Control		**L**		Acc	

Andrei Ponta

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