

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204412Orig1s000**

**CHEMISTRY REVIEW(S)**

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

**Application:** NDA 204412/000  
**Submission Date:** 01-AUG-2012  
**Regulatory:** 01-FEB-2013

**Action Goal:**  
**District Goal:** 03-DEC-2012

**Applicant:** WARNER CHILCOTT LLC  
 100 ENTERPRISE DR  
 ROCKAWAY, NJ 07866

**Brand Name:** WC3045 (mesalamine) delayed-release caps  
**Estab. Name:**  
**Generic Name:**

**Priority:** 3  
**Org. Code:** 180

**Product Number; Dosage Form; Ingredient; Strengths**  
 001; CAPSULE, DELAYED ACTION, ENTERIC COATED, HARD  
 GELATIN; MESALAMINE; 400MG

**Application Comment:**

<b>FDA Contacts:</b>	C. TRAN-ZWANETZ	Project Manager	(HFD-800)	3017963877
	H. SHROFF	Review Chemist		3017962116
	M. KOWBLANSKY	Team Leader		3017961390

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<b>Overall Recommendation:</b>	ACCEPTABLE	on 01-FEB-2013	by R. SAFAAI-JAZI	( )	3017964463
	PENDING	on 10-AUG-2012	by EES_PROD		

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FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Establishment:



DMF No:

AADA:

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

Establishment

Comment:

Profile:



OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	10-AUG-2012				TRANZWANETZC
OC RECOMMENDATION	14-AUG-2012			ACCEPTABLE BASED ON PROFILE	STOCKM

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Establishment:



DMF No:

Responsibilities:

Establishment Comment: ALTERNATE PACKAGING SITE, APPLICANT LISTS THE FEI AS (b) (4) on (b) (4) by C. TRAN-ZWANETZ  
Profile: TABLETS, DELAYED RELEASE OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	10-AUG-2012				TRANZWANETZC
OC RECOMMENDATION	14-AUG-2012			ACCEPTABLE BASED ON PROFILE	STOCKM

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Establishment:



(b) (4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment  
Comment:

Profile: TABLETS, DELAYED RELEASE

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	10-AUG-2012				TRANZWANETZC
OC RECOMMENDATION	14-AUG-2012			ACCEPTABLE BASED ON PROFILE	STOCKM

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

**Establishment:** (b) (4)

**DMF No:** (b) (4) **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Establishment Comment:**  
**Profile:** (b) (4)

**OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	10-AUG-2012				TRANZWANETZC
SUBMITTED TO DO PROFILE IS IN INITIAL STATUS	14-AUG-2012	<span style="background-color: gray; color: gray;">(b) (4)</span>			STOCKM
UNDER REVIEW	19-AUG-2012				PHILPYE
DO RECOMMENDATION	24-OCT-2012			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	26-OCT-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAJAZIR

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

Establishment:



(b) (4)

DMF No:

AADA:

Responsibilities:

DRUG SUBSTANCE RELEASE TESTER

Establishment  
Comment:

APPLICANT HAS FEI LISTED AS (b) (4) DUNS (b) (4) on (b) (4) by C. TRAN-ZWANETZ (HFD-800)  
3017963877)

Profile:

CONTROL TESTING LABORATORY

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	10-AUG-2012				TRANZWANETZC
SUBMITTED TO DO PROFILE IS IN INITIAL STATUS	14-AUG-2012	(b) (4)			STOCKM
UNDER REVIEW	19-AUG-2012				PHILPYE
DO RECOMMENDATION	20-SEP-2012			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	23-SEP-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

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

**Establishment:**



(b) (4)

**DMF No:**

**AADA:**

**Responsibilities:**

DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE RELEASE TESTER

**Establishment  
Comment:**

**Profile:** CONTROL TESTING LABORATORY

**OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	10-AUG-2012				TRANZWANETZC
SUBMITTED TO DO	14-AUG-2012				STOCKM
ASSIGNED INSPECTION TO IB	19-AUG-2012				PHILPYE
INSPECTION SCHEDULED	03-OCT-2012				IRIVERA
DO RECOMMENDATION AS PER A. MOZZACHIO, BC	29-JAN-2013			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	29-JAN-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

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

**Establishment:** CFN: 9611632 FEI: 3002808032  
 WARNER CHILCOTT DEUTSCHLAND GMBH  
 DR OTTO ROHM STRASSE 2-4  
 WEITERSTADT, HESSEN, GERMANY

**DMF No:** **AADA:**

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

**Establishment Comment:**  
**Profile:** TABLETS, DELAYED RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	10-AUG-2012				TRANZWANETZC
SUBMITTED TO DO	14-AUG-2012	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	19-AUG-2012	GMP Inspection			PHILPYE
INSPECTION SCHEDULED	21-SEP-2012		08-NOV-2012		PHILPYE
INSPECTION PERFORMED See EIR	08-NOV-2012		08-NOV-2012		Michele.PerryWilliams
OC RECOMMENDATION	24-JAN-2013			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	25-JAN-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SHARPT

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

**Establishment:** CFN: WARNER CHILCOTT LIMITED (b) (4)  
FEI: (b) (4)

**DMF No:** (b) (4)  
**AADA:**

**Responsibilities:** FINISHED DOSAGE STABILITY TESTER

**Establishment Comment:**  
**Profile:** CONTROL TESTING LABORATORY

**OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u> SUBMITTED TO OC	10-AUG-2012			<u>Reason</u>	TRANZWANETZC
OC RECOMMENDATION	14-AUG-2012			ACCEPTABLE BASED ON PROFILE	STOCKM

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

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

**DMF No:** (b) (4) **AADA:**

**Responsibilities:** FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Establishment  
Comment:**

**Profile:** CONTROL TESTING LABORATORY

**OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
SUBMITTED TO OC <u>Comment</u>	10-AUG-2012			<u>Reason</u>	TRANZWANETZC
SUBMITTED TO DO	14-AUG-2012	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	01-OCT-2012	GMP Inspection			BRYKMANR
INSPECTION PERFORMED AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING (b) (4)	01-OCT-2012				FACTS_EES
DO RECOMMENDATION A BRIEF REVIEW OF THE (b) (4) INSPECTION REPORT WAS CONDUCTED WITH PRIMARY FOCUS ON THE LABORATORY SYSTEM COVERAGE. NO SIGNIFICANT DEFICIENCIES WERE NOTIFIED DURING THE (b) (4) INSPECTION. ADDITIONALLY, THE (b) (4) INSPECTOR STATED IN AN EMAIL THAT HE COVERED RELEASE AND STABILITY TESTING PERFORMED AT THIS SITE. HE SPECIFICALLY MENTIONS MANUFACTURING AND TESTING OF U.S. PRODUCTS. BASED ON MY REVIEW OF THE AVAILABLE INSPECTION DOCUMENTATION PROVIDED BY THE (b) (4) DIDQ DOES NOT OPPOSE APPROVAL OF THE AFOREMENTIONED APPLICATION.	01-FEB-2013			ACCEPTABLE BASED ON FILE REVIEW BASED ON FOREIGN AUTHORITY REP	CRUZC
OC RECOMMENDATION	01-FEB-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY GRACE LUBAO  
02/12/2013

**Memorandum**

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

**Date:** February 01, 2013

**From:** Hitesh Shroff, Ph.D.

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

**To:** CMC Review #1 of NDA 204412

**Subject:** Final Recommendation

The CMC review #1 has noted the following pending issues:

1. Manufacturer of drug substance is not adequate.
  - The manufacture, [REDACTED] <sup>(b) (4)</sup> needs to be withdrawn.
2. Manufacturing process of the drug product is not adequate.
  - The “original process” needs to be replaced with the “alternative process”.
3. Stability commitment is not adequate.
  - The commitment needs to be revised to test 180-count bottle annually.
4. The label/labeling issues were not resolved.
5. Overall “ACCEPTABLE” site recommendation has not been made from the Office of Compliance for this application.

And because of these deficiencies, in the CMC Review #1, this NDA was not recommended for approval from the ONDQA perspective.

In the amendments dated January 07, 2013 and Jan 11, 2013, the applicant has adequately addressed the issues 1, 2 and 3. (see **Attachment -1**)

The Office of Compliance has made an overall “Acceptable” recommendation for the facilities involved in the NDA (see the **Attachment -2**).

The labels/labeling issues are satisfactorily resolved (see the **Attachment -3**).

**Final Recommendation:**

From the ONDQA's perspective, this NDA is now recommended for "Approval" with an expiration dating period of 18 months.

## Attachments:

### Attachment-1.

#### Applicant's Responses to the Deficiencies noted in Review #1

In response to the IR letter dated Dec 7, 2012 the applicant submitted **adequate** justifications in Jan 07, 2013 and Jan 11, 2013 amendments. The GMP related responses are summarized below.

1. The applicant clarified that Asacol 400 core tablets are manufactured using both the original and alternative manufacturing methods. The alternative method

(b) (4)  
Since January 2010 to November 2012, (b) (4) batches of Asacol 400 core tablets utilizing the original process and (b) (4) batches utilizing the alternative process were manufactured. Both processes produced core tablets capable of meeting specifications. A CMC supplement for the alternative manufacturing process for Asacol core tablets was submitted to NDA 19651 and approved on December 23, 2009.

(b) (4) batches of mesalamine delayed-release capsules were manufactured using the core tablets manufactured by the original manufacturing process and (b) (4) batches were made using the core tablets manufactured by the alternative manufacturing process. The applicant provided satisfactory CoAs of 3 batches of capsules manufactured by each manufacturing method.

**Evaluation:** *The applicant has provided sufficient evidence to demonstrate that both original and alternative manufacturing process can produce comparable drug product that meet the specification. Thus, both original and alternative core tablet manufacturing methods will be acceptable.*

2. The CMC related information regarding the white ink solution used to imprint the capsules is provided in DMF (b) (4). All of the excipients are compendial and meet regulation requirements. Appropriate CFR references were also included.

**Evaluation:** *The applicant has provided adequate information about the white ink.*

3. The applicant agreed to add specification for (b) (4) in the drug product. Based on (b) (4) testing data of 5 batches of capsules the applicant proposed (b) (4) in capsules acceptance limit to NMT (b) (4) using (b) (4) method I USP (b) (4). The updated drug product specification table was submitted in Jan 11, 2013 amendment as shown below.

## Drug Product Specification

Test	Specification	Method
Description *	Red capsule printed with 'WC 400mg' in white ink	Visual Inspection
Identification	Complies with reference spectrum	Infra-Red Spectroscopy
Assay *	(b) (4)	HPLC
Uniformity of Dosage Units (Weight variation)	Meets the requirements of USP <905>	USP <905> Uniformity of Dosage Units (Weight Variation)
Related Substances *	(b) (4)	HPLC
Dissolution *	<p>USP method and apparatus 0.1N HCl (Type II Paddle 100 RPM, 2 hrs) Level 1: No individual value exceeds 1% dissolved Level 2: Average of the 12 units (L1 + L2) is not more than 1% dissolved, and no individual unit is greater than 10% dissolved. Level 3: Average of the 24 units (L1 + L2 + L3) is not more than 1% dissolved, and not more than one individual unit is greater than 10% dissolved</p> <p>pH 6.0 (Type II Paddle 100 RPM, 1 hr) Level 1: No individual value exceeds 1% dissolved Level 2: Average of the 12 units (L1 + L2) is not more than 1% dissolved, and no individual unit is greater than 10% dissolved Level 3: Average of the 24 units (L1 + L2 + L3) is not more than 1% dissolved, and not more than one individual unit is greater than 10% dissolved</p>	UV Spectroscopy USP <711> Dissolution Method

Dissolution *	<p>pH 7.2, Q=80% (Type II Paddle 50 RPM, 1.5 hrs). Level 1: Each unit is not less than (b) (4) Level 2: Average of the 12 units (L1 + L2) is equal to or greater than (b) (4) and no unit is less than (b) (4) Level 3: Average of the 24 units (L1 + L2 + L3) is equal to or greater than (b) (4) and not more than two units are less than (b) (4) and no unit is less than (b) (4)</p>	UV Spectroscopy USP <711> Dissolution Method
(b) (4)	Meets the requirements for: (b) (4)	(b) (4)
(b) (4)	Not more than (b) (4)	(b) (4)

\* Denotes stability indicating parameters

**Evaluation:** The revised specification of the drug product now includes (b) (4) testing and acceptance limits. The proposed drug product specification is adequate to assure the strength, purity and over all quality of the drug product.

4. The applicant revised the post approval commitment to test 180-count bottles annually and 12-count bottles optionally. The applicant also stated that stability failures will be reported to FDA per 21 CFR 314.81 (b)(1)(ii). The post approval stability commitment is provided as shown below.

Stability commitment for first three batches of drug product

Test	25°C ± 2°C/60%RH ± 5%RH	40°C ± 2°C/75%RH ± 5%RH
Description	0, 3, 6, 9, 12, 18, 24, 36	0, 3, 6
Assay	0, 3, 6, 9, 12, 18, 24, 36	0, 3, 6
Related Substances	0, 3, 6, 9, 12, 18, 24, 36	0, 3, 6
Dissolution	0, 3, 6, 9, 12, 18, 24, 36	0, 3, 6
(b) (4)	0, 3, 6, 9, 12, 18, 24, 36	0, 3, 6

Stability commitment for annual testing

Test	25°C ± 2°C/60%RH ± 5%RH
Description	0, 3, 6, 12, 24, 36 <sup>1</sup>
Assay	0, 3, 6, 12, 24, 36 <sup>1</sup>
Related Substances	0, 3, 6, 12, 24, 36 <sup>1</sup>
Dissolution	0, 3, 6, 12, 24, 36 <sup>1</sup>
(b) (4)	0, 3, 6, 12, 24, 36 <sup>1</sup>

<sup>1</sup> Testing is continued yearly through shelflife

**Evaluation:** The proposed stability commitments are adequate to assure the strength, purity and overall quality of the drug product through out the storage period.

5. As recommended by FDA Warner Chilcott has agreed to withdraw (b) (4) (b) (4) as a secondary drug substance supplier in NDA 204412. The to-be marketed capsules will be manufactured from the drug substance from (b) (4)

6. As requested the applicant sent the specification for drug substance, mesalamine as shown below.

## Specification of drug substance, mesalamine

<b>Title</b>		(b) (4) Mesalamine	(b) (4)
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### Component Details

Material Number	(b) (4)
SAP Description	(b) (4) (b) (4)
Material Expiration date	18 months
Technical Grade	USP/NF grade
Storage Conditions	Store in tight, light-resistant containers

### Specification

Test	Specification	Method	Testing Site
Description	(b) (4)		
Identification (IR)			
Identification (UV)			
Identification C			
Appearance of solution			
pH			
(b) (4)			
Residue on Ignition			
(b) (4)			
(b) (4)			
(b) (4)			
Assay			
(b) (4)			
Impurities, single other related			
(b) (4)			
Total impurities			
Bulk density			
Tapped density			
(b) (4)			

**Evaluation:** The proposed drug substance specification manufactured by (b) (4) is adequate to assure the strength, purity and over all quality of the drug substance.

Attachment-2

EES Report

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

<b>Application:</b>	NDA 204412/000	<b>Sponsor:</b>	WARNER CHILCOTT LLC
<b>Org. Code:</b>	180		100 ENTERPRISE DR
<b>Priority:</b>	3		ROCKAWAY, NJ 07866
<b>Stamp Date:</b>	01-AUG-2012	<b>Brand Name:</b>	WC3045 (mesalamine) delayed-release caps
<b>PDUFA Date:</b>	01-FEB-2013	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	
<b>District Goal:</b>	03-DEC-2012	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
			001: CAPSULE, DELAYED ACTION, ENTERIC COATED, (b) (4)
			(b) (4) MESALAMINE, 400MG
<b>FDA Contacts:</b>	C. TRAN-ZWANETZ	Project Manager	(HFD-800) 3017963877
	H. SHROFF	Review Chemist	3017962118
	M. KOWBLANSKY	Team Leader	3017961390

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**Overall Recommendation:** ACCEPTABLE on 01-FEB-2013 by R. SAFAAI-JAZI ( ) 3017964463  
PENDING on 10-AUG-2012 by EES\_PROD

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

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Profile:** (b) (4) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 14-AUG-2012

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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**Establishment:** (b) (4)

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE PACKAGER

**Profile:** TABLETS, DELAYED RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 14-AUG-2012

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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

**Establishment:** (b) (4)

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE PACKAGER

**Profile:** TABLETS, DELAYED RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 14-AUG-2012

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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**Establishment:** (b) (4)

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER

**Profile:** (b) (4) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 26-OCT-2012

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** (b) (4)

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE RELEASE TESTER

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

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 23-SEP-2012

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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

<b>Establishment:</b>	(b) (4)		
<b>DMF No:</b>	AADA:		
<b>Responsibilities:</b>	DRUG SUBSTANCE RELEASE TESTER FINISHED DOSAGE RELEASE TESTER		
<b>Profile:</b>	CONTROL TESTING LABORATORY	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	29-JAN-2013		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	DISTRICT RECOMMENDATION		
<hr/>			
<b>Establishment:</b>	<b>CFN:</b> 9611632	<b>FEI:</b> 3002808032	
	WARNER CHILCOTT DEUTSCHLAND GMBH DR OTTO ROHM STRASSE 2-4 WEITERSTADT, HESSEN, GERMANY		
<b>DMF No:</b>	AADA:		
<b>Responsibilities:</b>	DRUG SUBSTANCE RELEASE TESTER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER		
<b>Profile:</b>	TABLETS, DELAYED RELEASE	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	25-JAN-2013		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	DISTRICT RECOMMENDATION		
<hr/>			
<b>Establishment:</b>	<b>CFN:</b>	<b>FEI:</b> (b) (4)	
	WARNER CHILCOTT LIMITED	(b) (4)	(b) (4)
<b>DMF No:</b>	AADA:		
<b>Responsibilities:</b>	FINISHED DOSAGE STABILITY TESTER		
<b>Profile:</b>	CONTROL TESTING LABORATORY	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	14-AUG-2012		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	BASED ON PROFILE		
<hr/>			



## Attachment-3.

### Final labels/Labeling

#### 1. Package Insert

##### (a) “Highlights” Section

###### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use DELZICOL safely and effectively. See Full Prescribing Information for DELZICOL.

**Delzicol (mesalamine) delayed-release capsules, for oral use**  
**Initial U.S. Approval: 1987**

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

#### #3. Dosage Form and Strength

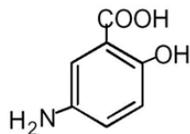
### **3 DOSAGE FORMS AND STRENGTHS**

Delzicol (mesalamine) delayed-release capsules are red capsules containing 400 mg mesalamine and imprinted with “WC 400mg” in white.

#### #11. Description

### **11 DESCRIPTION**

Each Delzicol (mesalamine) delayed-release capsule for oral administration contains 400 mg of mesalamine, an aminosalicylate. Mesalamine is a non-steroidal anti-inflammatory agent. Delzicol (mesalamine) delayed-release capsules contain acrylic based resin, Eudragit S (methacrylic acid copolymer type B, NF), which dissolves at pH 7 or greater and releases mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon. Mesalamine (also referred to as 5-aminosalicylic acid or 5-ASA) has the chemical name 5-amino-2-hydroxybenzoic acid. Its structural formula is:



Molecular Weight: 153.1  
Molecular Formula: C<sub>7</sub>H<sub>7</sub>NO<sub>3</sub>

**Inactive Ingredients:** Each capsule contains colloidal silicon dioxide, dibutyl sebacate, ferric oxide red, ferric oxide yellow, lactose monohydrate, magnesium stearate, methacrylic acid copolymer type B (Eudragit S), polyethylene glycol, povidone, sodium starch glycolate, talc and hydroxypropyl methylcellulose (HPMC).

## #16. How Supplied/Storage and Handling

### 16 HOW SUPPLIED/STORAGE AND HANDLING

Delzicol (mesalamine) delayed-release capsules are available as red capsules containing 400 mg mesalamine and imprinted with “WC 400mg” in white.

NDC 0430-0753-27 Bottle of 180 capsules

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

## 2. Labels

### Sample Bottle

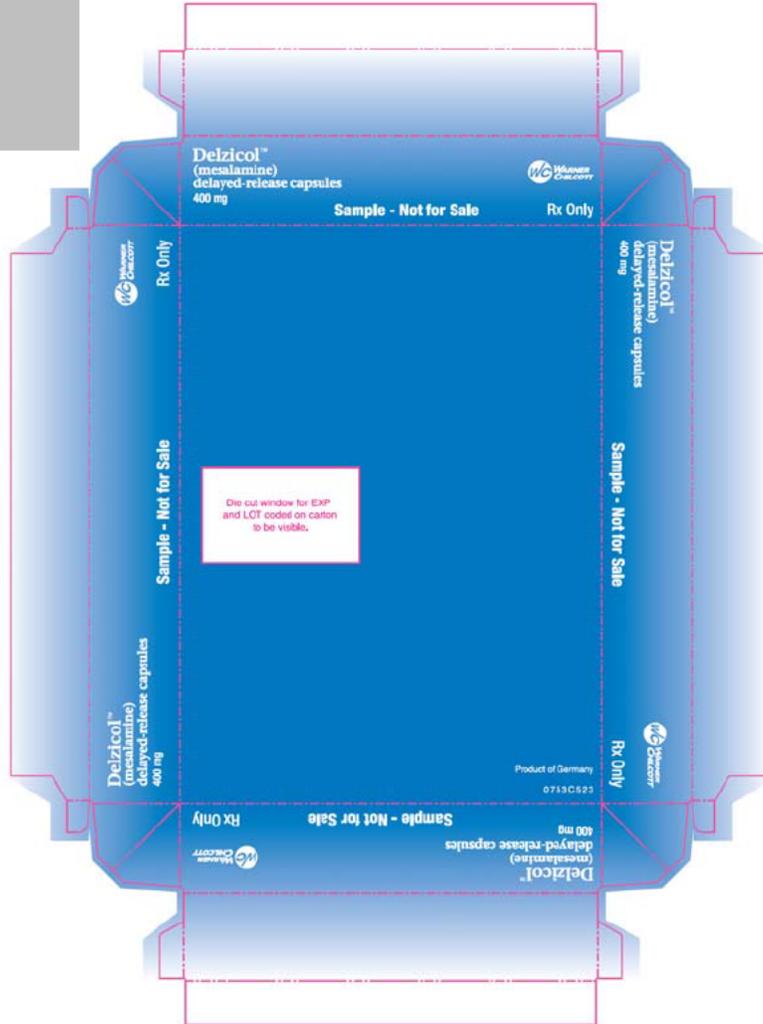
<p>Store at controlled room temperature 20° to 25° C (68° to 77° F); excursions are permitted 15° to 30° C (59° to 86° F). [See USP Controlled Room Temperature]</p> <p>For the treatment of mildly to moderately active ulcerative colitis: The usual dosage in adults is two 400 mg capsules to be taken three times a day for a total daily dose of 2.4 grams for a duration of 6 weeks.</p> <p>For the maintenance of remission of ulcerative colitis: The recommended dosage in adults is 1.6 grams daily, in divided doses.</p> <p>Take each dose at least one hour before or 2 hours after a meal.</p>	<p>NDC 0430-0753-95 <b>SAMPLE-Not for Sale</b></p> <p>Rx Only</p> <p><b>Delzicol™</b> <b>(mesalamine)</b> <b>delayed-release capsules</b> <b>400 mg</b></p> <p><b>Not Bioequivalent to Asacol® HD</b></p> <p><b>12 Capsules</b> 10000804</p> <p>EXP LOT</p>	<p>See Package Outsert for Full Prescribing Information.</p> <p><b>Do not break, crush, or chew the capsules. Swallow whole with water.</b></p> <p>Product of Germany</p> <p>Mfg. by: Warner Chilcott Deutschland GmbH Weiterstadt, Germany 64331 Mkt. by: Warner Chilcott (US), LLC Rockaway, NJ 07866 1-800-621-8813</p> <p>Under license from Medeva Pharma Suisse AG, (registered trademark owner) US Patent Nos. 5,541,170 and 5,541,171 07530844</p> 
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# Sample Carton



(b) (4)

# Sample Tray



## Trade Bottle



**NEW FORMULATION** NDC 0430-0753-27

**Delzicol™**  
(mesalamine)  
delayed-release  
capsules  
400 mg

**Not Bioequivalent to Asacol® HD**

**Rx Only**

180 Capsules

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

**For the treatment of mildly to moderately active ulcerative colitis:** The usual dosage in adults is two 400 mg capsules to be taken three times a day for a total daily dose of 2.4 grams for a duration of 6 weeks.

**For the maintenance of remission of ulcerative colitis:** The recommended dosage in adults is 1.6 grams daily, in divided doses.

**Take each dose at least one hour before or 2 hours after a meal.**

See Package Outsert for Full Prescribing Information.

**Do not break, crush, or chew the capsules. Swallow whole with water.**

Product of Germany  
Mfg. by: Warner Chilcott Deutschland GmbH  
Weiterstadt, Germany 64331  
Mkt. by: Warner Chilcott (US), LLC  
Rockaway, NJ 07866 1-800-521-8813  
Under license from Medeva Pharma Suisse AG,  
(registered trademark owner)  
US Patent Nos. 5,541,170 and 5,541,171

0753G864

EXP  
LOT

10000803

(b) (4)  
N3 0430-0753-27



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/s/  
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HITESH N SHROFF  
02/01/2013

MOO JHONG RHEE  
02/01/2013  
Chief, Branch IV

**NDA 204412**

(b) (4)

**(mesalamine) delayed-release capsules  
400 mg****Warner Chilcott Company, LLC****Hitesh Shroff, Ph.D.**

Review Chemist

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment II  
Branch IV****CMC Review of NDA 204412  
For the Division Gastrointestinal and Inborn Errors  
Products (HFD-180)**

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# Chemistry Review Data Sheet

1. NDA 204412
2. REVIEW:#1
3. REVIEW DATE: 01-Dec-2012
4. REVIEWER: Hitesh Shroff, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	01-Aug-2012
Amendment	25-Sep-2012
Amendment	02-Oct-2012
Amendment	16-Oct-2012
Amendment	16-Nov-2012

## 1. NAME & ADDRESS OF APPLICANT

Name: Warner Chilcott Company, LLC  
Address: Union Street Road  
Fajardo, Puerto Rico 00738-1005

Representative: Alvin Howard  
Senior Vice President, Regulatory Affairs  
Warner Chilcott (US) LLC, Rockaway, NJ 07866

Telephone: 973-442-3233

## 8. DRUG PRODUCT NAME/CODE/TYPE:

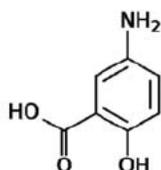
- a) Proprietary Name: (b) (4) (proposed)
- b) Non-Proprietary Name (USAN): Mesalamine
- b) Code Name/# (ONDQA only): None
- c) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Non-steroidal anti-inflammatory agent

11. DOSAGE FORM: Delayed-release capsule
12. STRENGTH/POTENCY: 400 mg Mesalamine per capsule
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product

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



Mesalamine

USAN Name: Mesalamine  
 Chemical name: 5-Amino-2-hydroxy-benzoic acid  
 Common Name: 5-Aminosalicylic acid  
 CAS number: 89-57-6  
 Molecular Formula: C<sub>7</sub>H<sub>7</sub>NO<sub>3</sub>  
 Molecular Weight: 153.14

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENC ED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	12-Dec-2012	Hitesh shroff
	II			3	Adequate		
	III			4			

## Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4			
	III		4			
	III		4			
	III		4			
	III		4			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:** N/A

### 18. STATUS:

#### ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Pending		John Duan
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Claim for categorical exclusion is granted	01-Nov-2012	Hitesh Shroff
Microbiology	N/A		

# The Chemistry Review for NDA 204412

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The NDA has *not* provided sufficient information to assure identity, strength, purity and quality of the drug product.

However, the label/labeling issues are still *not* satisfactorily resolved.

Also, a site recommendation from the Office of Compliance has *not* been made as of the date of this review.

Therefore, from the ONDQA perspective, this NDA is *not* recommended for approval in its present form per 21 CFR 314.125(b)(1),(6) and (13) until these pending issues are resolved.

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

No recommendations at this time.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substance

##### (1) Drug Substance

Mesalamine delayed-release capsules contain mesalamine as an active ingredient. Mesalamine is manufactured at (b) (4). The CMC information for mesalamine is provided in DMF (b) (4). It was reviewed on 12-12-2012 and found to be adequate. Mesalamine is also the active ingredient in previously approved Asacol 400 mg delayed-release tablets (NDA 19651, January 1992) by the Warner Chilcott. The NDA 19651 is cross referenced for the CMC related information of mesalamine.

(b) (4) is designated as a second manufacturer without qualification. It needs to be withdrawn.

##### (2) Drug Product

Mesalamine delayed-release capsules are red capsules imprinted with "WC 400mg" in white ink. Each capsule contains one 400 mg mesalamine enteric coated tablet. In order to avoid potential safety issues associated with dibutyl phthalate (DBP) Warner Chilcott

has developed a new formulation in which DBP used in enteric coating of tablets is replaced with a safer plasticizer dibutyl sebacate (DBS).

Mesalamine delayed-release capsules contain 400 mg mesalamine. The inactive ingredients are lactose monohydrate, sodium starch glycolate, talc, povidone, magnesium stearate, colloidal silicon dioxide, methacrylic acid copolymer, type B, ferric oxide red, ferric oxide yellow, polyethylene glycol (b) (4) and hydroxypropyl methylcellulose. However, the composition of the white ink solution to imprint the capsules is not available.

The tablets are enteric coated so the active ingredient is released at pH greater than 7 in the terminal ileum and beyond for topical anti-inflammatory action in the colon.

The drug product manufacturing process involves (b) (4)

Each mesalamine delayed-release capsule contains one tablet.

Two manufacturing processes were proposed but the registration batches were produced by the only "alternative process". The original process should be withdrawn from this application.

Three clinical and three registration batches of approximately (b) (4) kg each were produced. The release specification of the finished product include appearance, identification, assay, uniformity of dosage units, related substances, (b) (4) and dissolution in acidic, neutral and basic pH, however, (b) (4) test is missing and needs to be added to the specification because of (b) (4).

Based on the stability data from three production scale batches of mesalamine delayed-release capsules at long term (9months) and accelerated (6 months) conditions, the proposed 18 months expiration dating period, when stored at room temperature, is granted. However, the stability protocol should be revised to test 180-count bottles annually (b) (4).

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

Mesalamine delayed-release capsules are indicated for the treatment of mildly to moderately active ulcerative colitis. The capsules are supplied in 180-count bottles. The typical dose consists of up to 2400 mg per day taken orally.

#### **C. Basis for Not-Approval Recommendation**

21 CFR 314.125(b)(1)

## Executive Summary Section

- Manufacturer of drug substance is not adequate.
- Manufacturing process of the drug product is not adequate.
- Stability commitment is not adequate.

## 21 CFR 314.125 (b)(6)

- The label/labeling issues are still pending (see the **List of Deficiencies**, p. 63)

## 21 CFR 314.125 (b)(13)

- No overall “ACCEPTABLE” site recommendation has been made from the Office of Compliance for this application.

(See the **List of Deficiencies** on p. 78)

**III. Administrative****A. Reviewer's Signature**

Hitesh Shroff, Ph.D./ Dec 6, 2012

**B. Endorsement Block**

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, Division 2

**C. CC Block**

Marie Kowblansky, Ph.D.

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/s/  
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HITESH N SHROFF  
12/12/2012

MOO JHONG RHEE  
12/12/2012  
Chief, Branch IV

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

**OND Division:** Division of Gastroenterology and Inborn Errors Products  
**NDA:** 204412  
**Applicant:** Warner-Chilcott  
**Stamp Date:** 8/1/2012  
**Review Date:** 9/10/2012  
**PDUFA Date:** 6/1/2013  
**Filing Meeting:** 9/12/2012  
**Proposed Trademark:** (b) (4)  
**Established Name:** mesalamine  
**Dosage Form:** delayed release capsule  
**Route of Administration:** oral  
**Indication:** ulcerative colitis  
**CMC Lead:** Marie Kowblansky, PhD

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

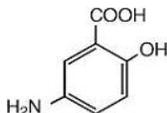
### A. Summary

The proposed product, (b) (4) (mesalamine) Delayed Release Capsules (400 mg) is intended for the treatment of ulcerative colitis. The recommended dosage is two capsules, three times daily for six weeks. The product is a reformulation of Warner-Chilcott's Asacol (mesalamine) Delayed Release Tablets, approved under NDA 19-651. This reformulation was prompted by FDA's concern over the safety of dibutyl phthalate (DBP) which is a component of the Asacol enteric coating.

The currently proposed product has been reformulated as a tablet-in-capsule formulation. The composition of the tablet is (b) (4) to the approved tablet with the exception that DBP has been replaced with (b) (4) amount of dibutyl sebacate (DBS) in the enteric coating. According to the Inactive Ingredients Database, DBS has been used in other approved products and at higher levels than proposed here, so there is no safety concern with this excipient. The capsule is a commonly used hydroxypropyl methylcellulose capsule.

This product was developed under IND 26,093, is submitted as a 505(b)(1) application, and according to MAPP 7500.3 is classified as a Type 3 application.

The drug substance in this product is mesalamine:



Information regarding the manufacture of mesalamine, as well as much of the information regarding manufacture of the drug product is referenced to NDA 19-651, and consequently, will not be described here.

Based on prior agreement with FDA, Warner Chilcott has submitted 6 months of stability data (long term and accelerated) on 3 batches of capsules and will provide an additional 3 months of data (9 months total) during the review clock no later than the midpoint of the clock.

At FDA's request, the firm has amended their original submission with manufacturing batch records, both in the original (b) (4) and with English translations.

The applicant appropriately claims a categorical exclusion from the requirement of filing an Environmental Assessment.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES.

The CMC reviewer for this NDA will be Dr. Hitesh Shroff.

The Biopharmaceutics information will be reviewed by Dr. John Duan.

This application will be reviewed as a priority application with a six month review clock.

### ***B. Critical issues for review***

In view of the applicants extensive history with a closely related product (Asacol, NDA 19-651), which is extensively referenced in this submission, there are no unusual issues that require particular attention in this review.

### ***C. Comments for 74-Day Letter -- None***

### ***D. Recommendation – From the CMC perspective this application is fileable.***

Marie Kowblansky, PhD  
CMC Lead

9/24/2012  
Date

Moo-Jhong Rhee, PhD  
Branch Chief

## Filing Checklist

**NDA Number:** 201-412      **Supplement Number and Type:** original      **Established/Proper Name:** mesalamine  
**Applicant:** Warner-Chilcott      **Letter Date:** July 31, 2012      **Stamp Date:**

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

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

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		Have been entered into EES
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	√		

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

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

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

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	√		Referenced to NDA 19-651
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		Referenced to NDA 19-651
14.	Does the section contain information regarding the characterization of the DS?	√		Referenced to NDA 19-651
15.	Does the section contain controls for the DS?	√		Referenced to NDA 19-651
16.	Has stability data and analysis been provided for the drug substance?	√		Referenced to NDA 19-651
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required Not a filing issue

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?		√	Bioequivalence study conducted
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required; not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required; not a filing issue

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	√		Not required – electronic submission (information in body of submission)

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	NA

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

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

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

*{See appended electronic signature page}*

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Marie Kowblansky, Ph.D.  
 CMC Lead  
 Division of New Drug Assessment #2  
 Office of New Drug Quality Assessment

*{See appended electronic signature page}*

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Moo-Jhong Rhee, Ph.D.  
 Branch Chief  
 Division of New Drug Assessment #2  
 Office of New Drug Quality Assessment

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/s/  
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MARIE KOWBLANSKY  
09/28/2012

MOO JHONG RHEE  
09/28/2012  
Chief, Branch IV