

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**204410Orig1s000**

**CHEMISTRY REVIEW(S)**

## Opsumit (macitentan) Tablets

NDA 204-410

### Summary Basis for Recommended Action Chemistry, Manufacturing, and Controls

**Applicant:** Actelion Pharmaceuticals, Ltd.  
Gewerbstrasse 16  
Allschwil, Switzerland CH-4123

U.S. Representative:  
Actelion Clinical Research, Inc.  
1820 Chapel Avenue West, Suite 300  
Cherry Hill, NJ 08022

**Indication:** For the treatment of pulmonary arterial hypertension.

**Presentation:** The product will be available as film-coated tablets in 10 mg strength. The tablets are packaged in HDPE bottles of 30-count and in 15-count unit-dose PVC/PE/PVDC blisters.

**EER Status:** Overall recommendation is “Pending” as of 21-Aug-2013.

**Consults:** ONDQA Biopharmaceutics – Acceptable as per Dr. John Z Duan’s review dated 18-Jun-2013.

Methods Validation – Acceptable by FDA labs (14-Mar-2013)

EA – Categorical exclusion granted.

**Post-Approval Agreements:** None

**Drug Substance:**

The drug substance, mecitantan, is a new molecular entity. The drug substance is a white to off-white crystalline powder with molecular weight of 588.27. (b) (4)

(b) (4) The manufacturing process described has (b) (4). The drug substance manufacturing process has been described in adequate details. The structure of the drug substance has also been adequately characterized using conventional spectroscopic tools.

Additionally, the drug substance quality is ensured through in-process controls throughout the manufacturing process and appropriate final drug substance specification. The drug substance acceptance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., appearance, identification, assay, impurities, particle size distribution, residual solvents, heavy metals, (b) (4) and microbial controls. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of (b) (4).

**Drug product:**

Opsumit (macitentan) Tablets are immediate release film-coated tablets which will be marketed in a single 10 mg strength. The drug product formulation uses standard compendial excipients. The manufacturing process includes (b) (4)

(b) (4) The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through end product testing. The end product specification includes testing for appearance, identification, assay, content uniformity, (b) (4) dissolution, microbial purity and degradation products. The analytical procedures for the drug product are adequately described and validated. The provided stability data support a 24-month expiration period for this product.

The drug product is stored at 25°C with excursions permitted 15-30°C (59-86°F).

**Conclusion:** Adequate from CMC perspective.

**Additional Items:**

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

**Overall Conclusion:** The application is recommended for “**Approval**” from CMC perspective pending an overall recommendation from the Office of Compliance. The facility recommendation from Office of Compliance was not available at the time of writing this memorandum. An additional memorandum will be written by the reviewer with final recommendation after an overall recommendation from OC about facilities.

Ramesh K. Sood, Ph.D.  
Acting Director, DPA I/ONDQA

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/s/  
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RAMESH K SOOD  
08/21/2013

# **NDA 204-410**

**Opsumit<sup>®</sup> (Macitentan) 10 mg Film-Coated Tablet**

**Actelion Pharmaceuticals, Ltd.**

**Thomas M. Wong, Ph.D.**

**Division of New Drug Quality Assessment I**

**Office of New Drug Quality Assessment**

**Division of Cardiovascular and Renal Products**

**Review of Chemistry, Manufacturing, and Controls**

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## Chemistry Review Data Sheet

**Chemistry Review Data Sheet**

1. NDA: 204-410

2. REVIEW #: 1

3. REVIEW DATE: May 23, 2013

4. REVIEWER: Thomas M Wong, Ph.D.

## 5. PREVIOUS DOCUMENTS:

Previous Documents

IND 77,258

Document Date

Jun 3, 2008

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original submission

Amendment #0004

Amendment #0007

Amendment #0010

Amendment #0013

Document Date

Oct 19, 2012

Jan 24, 2013

Feb 26, 2013

Mar 29, 2013

May 10, 2013

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Actelion Pharmaceuticals, Ltd.

Address: Gewerbestrasse 16  
Allschwil, Switzerland CH-4123Actelion Clinical Research, Inc.  
Representative: 1820 Chapel Avenue West, Suite 300  
Cherry Hill, NJ 08022

Telephone: 856-773-4782

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

a) Proprietary Name: Opsumit®

## Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): Macitentan  
c) Code Name/# (ONDC only): ACT-064992  
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1) Macitentan film-coated tablets 10 mg

10. PHARMACOL. CATEGORY: Treatment of pulmonary arterial hypertension

11. DOSAGE FORM: Film-coated tablet

12. STRENGTH/POTENCY: 10 mg

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:

USAN: Macitentan

CAS Name: *N*-[5-(4-bromophenyl)-6-{2-[(5-bromopyrimidin-2-yl)oxy]ethoxy}pyrimidin-4-yl]-*N'*-propylsulfuric diamide  
*N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-*N'*-propyl-sulfamide  
*N*-[5-(4-bromophenyl)-6-[2-(5-bromopyrimidin-2-yloxy)ethoxy]pyrimidin-4-yl]-*N'*-propylsulfamide

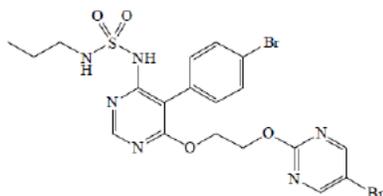
CAS registry number: 441798-33-0

Molecular weight: 588.27

## Chemistry Review Data Sheet

Molecular formula: C<sub>19</sub>H<sub>20</sub>Br<sub>2</sub>N<sub>6</sub>O<sub>4</sub>S

## Structure



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	4			Sufficient information in application

<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)

Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 77,258	Commercial IND

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Pending		
LNC	N/A		
Methods Validation	Acceptable	Mar 1, 2013	Laura C. Mecker
DMEPA	N/A		
EA	N/A		
Microbiology	N/A		

## Executive Summary Section

## The Chemistry Review for NDA 204-410

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

NDA 204-410 for Opsumit® (macitentan) 10 mg Tablets cannot be approved from the CMC standpoint due to the following pending issue:

The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections.

Final Biopharmaceutics recommendation has not yet been provided. However, there is no pending Biopharmaceutics issue as per conversion with Dr. John Duan.

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

None as per this review.

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)****Drug product**

The applicant has developed an immediate release film-coated tablet once daily oral administration for the long-term treatment of pulmonary arterial hypertension in adult (b) (4). The trade name for macitentan tablet is Opsumit® and the tablets are white to off white, biconvex, round, film-coated and debossed with 10 on one side. Each tablet contains 10 mg macitentan and the following excipients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone, and sodium starch glycolate Type A and coating material which contains polyvinyl alcohol, soya lecithin, talc, titanium dioxide, and xanthan gum. The tablets will be manufactured by (b) (4) and commercial batch size is (b) (4) tablets equivalent to (b) (4) of core tablets. Tablets are packaged in HDPE bottles with 30 counts per bottle. They are also packaged into 15 count unit dose PVC/PE/PVDC blister with one tablet per cavity. Tablets are stored at 20°C – 25°C (68°F – 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). Available 12 months stability data supports 24-month expiration dating period for the tablets when packaged in the proposed commercial packages and stored in the afore-mentioned storage conditions

**Drug substance**

Macitentan, a new molecular entity, is a dual ETA and ETB endothelin receptor antagonist. Macitentan is a small molecule with molecular formula C<sub>19</sub>H<sub>20</sub>Br<sub>2</sub>N<sub>6</sub>O<sub>4</sub>S and molecular weight 588.27. It is a white to off-white crystalline powder and is not soluble in water and in aqueous solution of pH 1.2 through pH 9. The molecule is achiral (b) (4)

## Executive Summary Section

(b) (4)  
anufacturing process is (b) (4)  
by (b) (4). The (b) (4) the drug substance will be conducted by (b) (4)  
The finished drug substance will be released by Acetlion Pharmaceuticals, Ltd. The established commercial process has been validated for approx. (b) (4) of macitentan which is considered representative for an increase of batch size up to a factor of ten times of this validated scale.  
The applicant provided adequate information regarding structure elucidation and confirmation and impurity profile. Available 12 months stability data at 30°C/65% RH storage conditions supports a (b) (4) re-test dating when stored at 30°C/65% RH when packaged into (b) (4)

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

The recommended dose is 10 mg once daily. Tablets can be administered with or without food. Tablets should not be split, crushed, or chewed.

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

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. From the CMC point of view NDA 204-410 for Opsumit® (macitentan) 10 mg Tablets cannot be approved due to pending issues mentioned in Section I A above.

**III. Administrative**

- A. Reviewer's Signature: See DARRTS
- B. Endorsement Block: See DARRTS
- C. CC Block See DARRTS

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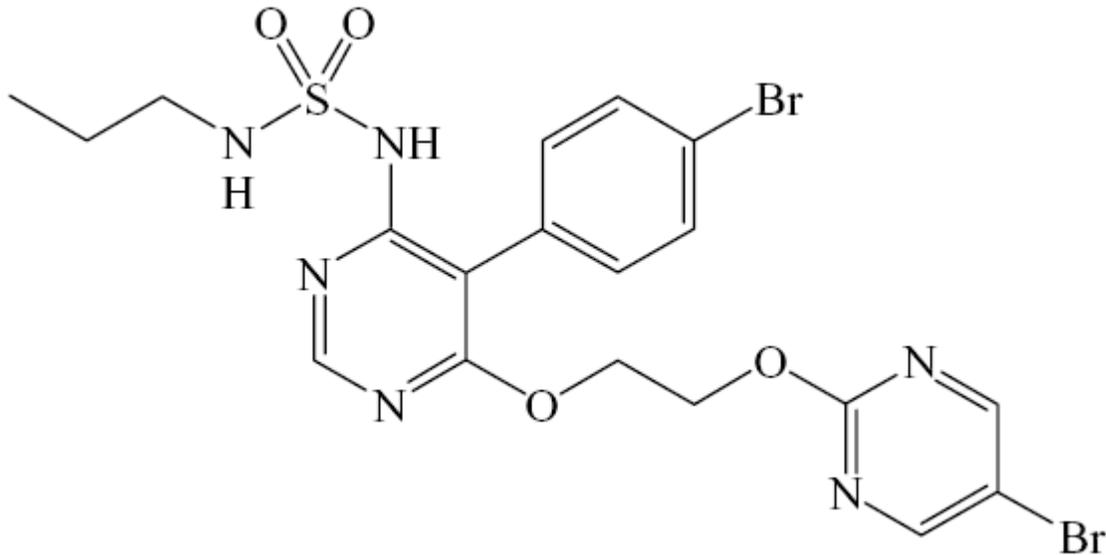
/s/  
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THOMAS M WONG  
05/23/2013

RAMESH K SOOD  
05/24/2013

Initial Quality Assessment  
Branch I

**OND Division:** Division of Cardiovascular and Renal Products  
**NDA:** 204410  
**Applicant:** Actelion Pharmaceuticals, Ltd.  
**Letter Date:** Oct 19, 2012  
**Stamp Date:** Oct 19, 2012  
**PDUFA Date:** Aug 19, 2013 (Standard Review)  
**Tradename:** Opsumit  
**Established Name:** Macitentan  
**Dosage Form:** Tablets, 10 mg  
**Route of Administration:** Oral  
**Indication:** Treatment of pulmonary arterial hypertension  
**Assessed by:** Kasturi Srinivasachar  
**ONDQA Fileability:** Yes



## Summary

This is an e-CTD 505(b)(1) NME NDA application for macitentan 10 mg film coated tablets. Macitentan is an orally active, nonpeptide, dual endothelin (ET<sub>A</sub> and ET<sub>B</sub>) receptor antagonist. This is the second endothelin receptor antagonist developed by Actelion for pulmonary arterial hypertension; the first, Tracleer (bosentan) was approved under NDA 21,290 in 2001. Clinical development of macitentan was carried out under IND 77,258. The tradename Opsumit has been conditionally accepted by DMEPA. Macitentan has received orphan drug designation. After IND submission there were no CMC specific meetings or multidiscipline meetings involving CMC with the Applicant. [REDACTED] (b) (4)

[REDACTED] Actelion has requested Priority Review status and provided justification which is being evaluated by DCRP.

## Drug Substance

Macitentan is a white to off-white crystalline powder with mp 135°C. It is soluble in many non-alcoholic solvents, slightly soluble in methanol and ethanol, and insoluble in aqueous media with pH in the range 1.2 to 9. The molecule is achiral [REDACTED] (b) (4)

[REDACTED] Macitentan is manufactured by [REDACTED] (b) (4)

[REDACTED] The Applicant has justified these starting materials on the basis of ICH Q11 and provided specifications and batch analysis data for these compounds. Specifications and batch analysis data have also been submitted for [REDACTED] (b) (4) [REDACTED] (b) (4)

[REDACTED] These process improvements have described in 3.2.S.2.6 Manufacturing Process Development. [REDACTED] (b) (4)

[REDACTED]

The drug substance specification contains the standard test attributes. Particle size and microbial tests are included. Batch analysis data for 3 registration batches as well as numerous other batches produced during development have been submitted. Stability data for the registration batches for 12 months under long term storage and 6 months at accelerated conditions are available. In addition, supportive stability data (6 months accelerated and 48 months long term) for 3 clinical batches produced at the same site and by the same manufacturing procedure are provided. Based on these data, a retest period of [REDACTED] (b) (4) is proposed.

## Drug Product

The drug product will be marketed in only one strength, 10 mg, as white to off-white, biconvex, round, immediate release film-coated tablets debossed with “10” on one side. Standard compendial excipients for solid oral dosage forms are used in the formulation. Polysorbate 80 is included (b) (4) and the film coat is (b) (4) (b) (4)

(b) (4) the film coated tablet formulation was developed and used in Phase 1, 2 and 3 trials. The (b) (4) and tablet formulations were compared in a clinical pharmacology biocomparison study of the 10 mg strength. The PK of macitentan and its active metabolite were comparable for the two formulations, however,  $C_{max}$  for the tablet was about 19 % lower than the (b) (4). The Applicant argues that since macitentan is intended for chronic multiple-dose use, the difference in  $C_{max}$  is not considered relevant and that no dose adjustment was needed when switching from the (b) (4) to the tablet formulation during development of the product. Comparative dissolution profiles of the two dosage forms show that dissolution rates of macitentan in both are equivalent. The composition of the to-be-marketed 10 mg film-coated 10 mg tablets is the same as used in the pivotal Phase 3 clinical study.

Macitentan is considered a BCS Class 2 drug substance, hence particle size and dissolution rate are critical attributes. (b) (4)

(b) (4) The particle size acceptance criteria were justified on the basis of a study of the effect of particle size distribution on bioavailability. The development of the dissolution method for release and stability testing of the tablets is described and justification for the use of a cationic surfactant, CTAB, in the dissolution medium provided.

(b) (4)

Clinical batches were manufactured at (b) (4) but the process was transferred to (b) (4), for the registration batches. The (b) (4) site is also the proposed commercial manufacturing location. The same type of equipment is used at both sites for each unit operation.

The manufacturing process development from small scale to pilot scale to registration and commercial scales has been described in 3.2.P.2.3. During process development, (b) (4)

(b) (4)

The Applicant

claims to have a thorough process understanding based on the experience gained during optimization studies and the manufacture of 3 registration batches and one commercial pre-validation batch in addition to 3 commercial scale placebo batches simulating the final manufacturing process.

The product specification covers the usual test attributes for a solid oral dosage form and includes a microbial limits test. (b) (4)

(b) (4) A number of the methods are referenced to Ph. Eur. with a footnote stating interchangeability with the corresponding USP general chapter.

Macitentan 10 mg tablets are packaged in blisters and HDPE bottles:

- polyvinyl chloride/polyethylene/polyvinylidene chloride blisters with a push through (b) (4) aluminum foil
- 50 mL HDPE bottle with heat induction seal and (b) (4) cap containing 2g of silica gel in desiccant canister and cotton plug

Stability data are provided for the 3 registration batches stored at long term and accelerated conditions for 12 and 6 months respectively, in both packaging configurations. Based on these data a shelf-life of 24 months is proposed.

### Critical Review Issues

#### Drug Substance

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(b) (4)

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### Drug Product

- Has the compatibility of the excipients with the drug substance been adequately established?
- The dissolution method development report and the proposed specifications should be evaluated by the Biopharmaceutics reviewer as well as the claim that macitentan belongs to BCS Class 2.
- The Product Development section, including formulation development and manufacturing process development, should be evaluated in-depth to confirm that high quality product can be reproducibly manufactured at commercial scale.
- Has the manufacturing process in 3.2.P.3.3 been described in sufficient detail? In lieu of this, is there a Master Batch Record?
- Are the in-process controls for unit operations satisfactory?
- Regarding the specification
  - Is the limit of Max. (b) (4) for total impurities justified?
  - (b) (4) This should be confirmed by the Pharm/Tox reviewer.
  - Skip lot testing for microbial quality is proposed. Is this acceptable?
- Is the minimal information provided on the 2 container closure systems acceptable? Do they meet USP <661> and <671>?
- No DMF references are provided for the container closure systems. Is equivalent information submitted in the NDA application? Similarly, is there adequate information for the desiccant canisters used with the HDPE bottles since again no DMF reference is provided?
- Regarding Stability
  - It is not clear why long term studies are performed at both 25°C/60%RH and 30°C/75% RH. It should be noted that ICH conditions for long term or intermediate storage are 30°C/65%RH and not 75% RH. In addition, the Applicant has arbitrarily skipped some testing time points for the 30°C/75% storage condition.
  - Has photostability testing in accordance with ICH Q1B been performed?
  - Do the submitted data allow extrapolation to a 24 month expiration date?

- The Methods Validation package in section 3.2.R does not contain any drug substance information

### **Comments and Recommendations**

The application is fileable -- see attached Filing Check List. Facilities have been entered into EES and the overall recommendation is currently "Pending"; the reviewer should confirm the completeness and accuracy of the entries. A categorical exclusion from environmental assessment has been requested. A Methods Validation request will be initiated shortly; three analytical procedures will be submitted: 1) Particle size distribution of the drug substance by laser diffraction, 2) determination of [REDACTED]<sup>(b) (4)</sup> in the drug substance by ion chromatography and 3) determination of macitentan content and related substances in the drug product by HPLC. This does not preclude the reviewer from identifying other analytical procedures for validation later in the review timeframe. A single CMC reviewer is recommended since the drug product section is not very extensive or complex.

Kasturi Srinivasachar  
Pharmaceutical Assessment Lead

Nov. 15, 2012  
Date

Ramesh Sood  
Branch Chief

Nov. 15, 2012  
Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS  
FILING REVIEW FOR NDA

**NDA Number:** 204410      **NDA Type:** 1      **Established/Proper Name:** Macitentan/Opsumit  
**Applicant:** Actelion Pharmaceuticals      **Letter Date:** October 19, 2012      **PDUFA Goal:** TBD depending on Priority or Standard Review  
**Stamp Date:** October 19, 2012

**CMC Reviewer:** Thomas Wong

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

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

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

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

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		
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\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

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

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

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

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

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			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?	X		DMF (b) (4)

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

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	X		Fileable for Product Quality. See Biopharmaceutics Filing Review for fileability of the Biopharm Section
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.			NA
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			See Biopharm filing review

37.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X	Request DMF references for Container Closure and desiccant canisters. Request photostability studies on drug product.
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/s/  
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KASTURI SRINIVASACHAR  
11/15/2012

RAMESH K SOOD  
11/15/2012