CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-081

CHEMISTRY REVIEW(S)

Letairis
(ambrisentan)
Tablets

NDA 22-081

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Gilead Sciences, Inc.
7575 W. 103rd Avenue, #102
Westminster, CO 80021-5426

Indication: treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening [redacted].

Presentation: Letairis is supplied as a film-coated, immediate release tablet. Two strengths are available, packaged as 30 count blister [redacted]:

5 mg of ambrisentan per 6.6 mm square convex, pale pink, tablet imprinted with "5" on one side and "GSI" on the other side

10 mg of ambrisentan per 9.8 mm x 4.9 mm oval, deep pink, tablet imprinted with "10" on one side and "GSI" on the other side

EER Status: Acceptable – 12-JUN-2007

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(b).
Methods Validation – Revalidation by Agency not requested.

Original Submission: 18-DEC-2006

Post-Approval Agreements: None

Drug Substance:

The drug substance, ambrisentan, is a small, synthetic, new molecular entity (NME) and is a Biopharmaceutics Classification System (BCS) Type 2 drug. It is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist that is highly selective for the endothelin type-A (ETA) receptor. It contains a single chiral center determined to be the (S)configuration and has a chemical name which is (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid. Ambrisentan is a white to off-white, crystalline [redacted] has a molecular formula of $C_{22}H_{22}N_2O_4$, has a molecular weight of 378.42 grams/mole, and has a melting point of [redacted].

Ambrisentan is a carboxylic acid with a pKa of 4.0. It is practically insoluble in water [redacted] mg/mL) and in aqueous solutions at low pH. Solubility increases in aqueous solutions of higher pH ([redacted] . In the solid state, ambrisentan [redacted] is not hygroscopic, and is not light sensitive.

Ambrisentan is manufactured in [redacted] steps to obtain the stereospecific ambrisentan. [redacted] is the intended commercial manufacturing site for ambrisentan drug substance.

The chemical structure of ambrisentan has been confirmed [redacted] The physicochemical properties of ambrisentan, including the solid-state form, have been determined [redacted]. The reference standard for drug substance is Lot 3109.F.04.602 synthesized in 2004 [redacted] using the same synthetic pathway as that intended for commercial manufacturing.

The proposed release specification for ambrisentan includes appearance, identification by [redacted] and by [redacted] high performance liquid chromatography (HPLC), water content by Karl Fischer, assay by HPLC, impurities by HPLC, enantiomeric purity by [redacted] HPLC, residual solvents by gas chromatography (GC), heavy metals, residue on ignition, and particle size [redacted] .

Adequate stability data was provided to support the requested retest date of [redacted] months for bulk drug substance stored at controlled room temperature (15-25°C), [redacted] . Applicant proposes to continue long-term (25°C/60% RH) stability testing for a minimum of [redacted] to support extension of the retest period.

Conclusion: Drug substance is acceptable.

Drug Product:

Letairis is available as 5 mg and 10 mg immediate release, film-coated tablets for once-daily, oral administration.

In addition to the active ingredient, each tablet contains croscarmellose sodium [redacted] , lactose monohydrate [redacted] , magnesium stearate [redacted] and microcrystalline cellulose [redacted] for a core tablet weight of [redacted] . The tablets are film-coated with [redacted] for a total tablet weight of 147.0 mg.

Specification of the drug product includes: appearance, identification by [redacted] high performance liquid chromatography [redacted] HPLC), dissolution, content uniformity by [redacted] -HPLC, degradation products by [redacted] HPLC, and strength by [redacted]-HPLC.

Adequate stability data were provided to support the proposed expiration dating of 24 months at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F) for Letairis tablets, 5 mg and 10 mg, packaged in either [redacted] or [redacted] and aluminum foil blisters.

Conclusion: Drug product is acceptable.

Additional Items:

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval**.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
6/13/2007 05:44:45 AM
CHEMIST

NDA 22-081
Letairis
(Ambrisentan) Tablets

Gilead Sciences, Inc.

Haripada Sarker, Ph.D.
ONDQA, DPA I

Reviewed for DCRP (HFD-110)

Chemistry Review Data Sheet

1. NDA 22-081

2. REVIEW #2:

3. REVIEW DATE: 6-12-2007

4. REVIEWER: Haripada Sarker, Ph.D.

5. PREVIOUS DOCUMENTS:

NDA 22-081	13-December-2006
Amendment N-12(BC)	01-May-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment N-00(BC)	01-June-2007
Amendment N-00(BC)	11-May-2007
Amendment	12-June, 2007 (via e-mail)

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	7575 W. 103rd Avenue, #102 Westminster, CO 80021-5426
Representative:	Michael Gerber, MD, Senior Vice President, Clinical Research
Telephone:	(303) 464-3988

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LETAIRIS™
b) Non-Proprietary Name: Ambrisentan
c) Code Name/#: 1
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1 (for NME)
- Submission Priority: P

e) Proposed Trade Name: LETAIRIS™

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

10. PHARMACOL. CATEGORY: LETAIRIS™ is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening and [redacted].

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5mg and 10mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

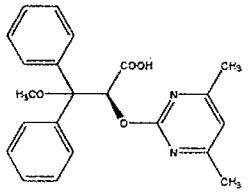
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Structure:



Name (drug substance) (USAN) Ambrisentan

Chemical Name	(+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid

The Chemistry Review for NDA 21-649

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

APPROVAL is recommended for the application from a chemistry, manufacturing and controls standpoint. Office of compliance has provided acceptable overall recommendation. Agreement has been reached with the company to resolve the remaining CMC issues. The CMC issues in the review cycle #2 include revision of acceptance criteria and control of [redacted], as well as dissolution specification of drug product. Drug product shelf-lives of 24 months have been granted for ambrisentan tablets, 5 mg and 10 mg, packaged in [redacted] blisters, stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F). For detail see review cycle #1, which was recommended as approvable from CMC standpoint.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Letairis™ (Ambrisentan) is formulated for oral administration as immediate-release film coated tablets in 5mg and 10mg strengths (development stage strengths, 1mg, 2.5mg, 5mg and 10mg). The active ingredient of the drug is Ambrisentan. All the excipients used in drug product manufacture have standard compendial monograph, except coating agent. The film coating is non-functional and is used to provide a distinctive tablet color to aid in the identification of various strengths. Each strength of commercial tablets is differentiated by color, shape, and markings. Ambrisentan has low solubility and high permeability. The drug product formulation has varied only slightly [redacted] over the course of development in going from Phase 1 [redacted]), Clinical [redacted], to Commercial [redacted]. The drug product is manufactured by [redacted] Some changes [redacted] are observed in going from development stage to commercial stage. Applicant proposes new DP dissolution specification of Q = [redacted] in 30 minutes.

The drug product is stored at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F). [See USP Controlled Room Temperature]. Based on 24 months long term and 6 months accelerated storage conditions, a 24-month expiration dating period is proposed for ambrisentan tablets, 5 mg and 10 mg; packaged in [redacted] blisters, stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F)), [See USP Controlled Room

Temperature]. Based on test data, the DP shelf-life of 24 months has been granted for DP of all the packaging configurations and strengths.

The chemical name for Ambrisentan is (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid. Ambrisentan has a chiral center at the C-2 position of the propanoic acid core structure. It is manufactured as the (*S*)-enantiomer. The DS has pKa of 4.0, and is practically insoluble in water. [redacted]. DS is manufactured in [redacted] steps to obtain the steriospecific ambrisentan. Ambrisentan has been manufactured at [redacted] to supply the DS during the development stages. [redacted] is the intended commercial manufacturing site for ambrisentan DS. The product related impurities for ambrisentan are presented. [redacted]. In this review cycle, the company has agreed to control [redacted] at NMT [redacted] using [redacted], and also to control particle size at [redacted] microns. Applicant proposes DS retest period of [redacted] months, which is supported by 24-month long-term stability data and the [redacted] accelerated stability data for the 3 primary stability batches.

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

Ambrisentan is film coated tablets in 5 mg and 10 mg strengths for oral administration. Each commercial tablet strength is differentiated by color, shape, and markings. Ambrisentan tablets are available in [redacted] blister packs. The same container closure systems are used for the 5 mg and 10 mg tablets. Letairis treatment will be initiated at a dose of 5 mg once daily and may be increased to 10 mg once daily, if necessary.

C. Basis for Approvability Recommendation

Number of issues (specifically dissolution related) were communicated to the company. The applicant has addressed all the issues satisfactorily. The applicant has validated the analytical methods for specified impurities and degradants. The office of compliance has provided an overall acceptable recommendation.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Haripada Sarker, Ph.D.
ChemistryBranchChief/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: Melissa Robb

C. CC Block

16 Page(s) Withheld

6 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

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/s/

Haripada Sarker
6/12/2007 04:44:47 PM
CHEMIST

Ramesh Sood
6/12/2007 04:53:25 PM
CHEMIST

NDA 22-081

Letairis

(Ambrisentan) Tablets

Gilead Sciences, Inc.

Haripada Sarker, Ph.D.
ONDQA, DPA I

Reviewed for DCRP (HFD-110)

Table of Contents

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Chemistry Review Data Sheet

1. NDA 22-081

2. REVIEW #1:

3. REVIEW DATE: 5-16-2007

4. REVIEWER: Haripada Sarker, Ph.D.

5. PREVIOUS DOCUMENTS:

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-081	13-12-2006
Amendment N-12(BC)	01-05-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	7575 W. 103rd Avenue, #102 Westminster, CO 80021-5426
Representative:	Michael Gerber, MD, Senior Vice President, Clinical Research
Telephone:	(303) 464-3988

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LETAIRIS™
b) Non-Proprietary Name: Ambrisentan
c) Code Name/#: 1

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1 (for NME)
- Submission Priority: P

e) Proposed Trade Name: LETAIRIS™

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

10. PHARMACOL. CATEGORY: LETAIRIS™ is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening [redacted]

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5mg and 10mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

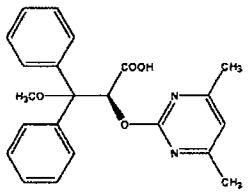
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Structure:



Name (drug substance) (USAN)	Ambrisentan
Chemical Name	(+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid

N22-081 CR#1

CAS number	177036-94-1
Molecular Weight	378.42
Molecular Formula	$C_{22}H_{22}N_2O_4$
Structural formula	As above

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COM-PLETED	COMMENTS (LOA date)
	IV			3	Adequate	N/A	June-7-2006
	III			3	Adequate	N/A	Aug.-24-2006
	III			3	Adequate	N/A	May-18-2006
	III			3	Adequate	N/A	July-11-2006
	III			3	Adequate	N/A	July-18-2006
	III			3	Adequate	N/A	July-24-2006
	III			3	Adequate	N/A	
	III			3	Adequate	N/A	Nov.-25-2002
	III			3	Adequate	N/A	Oct.-1-2003

[1] 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")

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

B. Other Documents: None

18. STATUS:

ONDQA: To be filled later

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	As of 16-May-2007	J. D. Ambrogio
Biopharm	Deficient	7-May.-2007	Haripada Sarker
DMETS/DDMAC	Deficient	23-April.-2006	Edward Fromm
Methods Validation	N/A	N/A	N/A
EA (Categorical Exclusion)	Acceptable	30-Mar.-2007	Haripada Sarker
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-649

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVABLE from a chemistry, manufacturing and controls standpoint. Proposed shelf-lives of 24 months for ambrisentan tablets, 5 mg and 10 mg, packaged in [redacted] blisters, stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F) can't be granted due to absence of dissolution and relevant test data on stability samples based on proposed dissolution specification. An IR (information request at the end of the review) has been sent to the company, and they have responded, which will be reviewed as review #2.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Letairis™ (Ambrisentan) is formulated for oral administration as immediate-release film coated tablets in 5mg and 10mg strengths (development stage strengths, [redacted] 5mg and 10mg). The active ingredient of the drug is Ambrisentan. All the excipients used in drug product manufacture have standard compendial monograph, except coating agent. The film coating is non-functional and is used to provide a distinctive tablet color to aid in the identification of various strengths. Each strength of commercial tablets is differentiated by color, shape, and markings. Ambrisentan has low solubility and high permeability. The drug product formulation has varied only slightly (specifically coating) over the course of development in going from Phase 1 [redacted], Clinical [redacted] to Commercial [redacted].

[redacted]

[redacted] Applicant proposes new DP dissolution specification; however, no stability test data is generated with this specification. A list of IR has been sent to the company, and they have responded, which will be reviewed as review #2.

The drug product is stored at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F). [See USP Controlled Room Temperature]. Depending on 18 months long term and 6 months

accelerated storage conditions, a 24-month expiration dating period is proposed for ambrisentan tablets, 5 mg and 10 mg, packaged in [redacted] blisters, stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F)), [See USP Controlled Room Temperature]. Without satisfactory dissolution test data, the DP shelf-life can't be granted at this time.

The chemical name for Ambrisentan is (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid. Ambrisentan has a chiral center at the C-2 position of the propanoic acid core structure. It is manufactured as the (*S*)-enantiomer. The DS has pKa of 4.0, and is practically insoluble in water.

[redacted]

[redacted]. DS is manufactured in [redacted] steps to obtain the steriospecific ambrisentan. Ambrisentan has been manufactured at [redacted], to supply the DS during the development stages. [redacted] is the intended commercial manufacturing site for ambrisentan DS. The product related impurities for ambrisentan are presented.

[redacted]

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

Ambrisentan is film coated tablets in 5 mg and 10 mg strengths for oral administration. Each commercial tablet strength is differentiated by color, shape, and markings. Ambrisentan tablets are available in [redacted] blister packs. The same container closure systems are used for the 5 mg and 10 mg tablets. Letairis treatment will be initiated at a dose of 5 mg once daily and may be increased to 10 mg once daily, if necessary.

C. Basis for Approvability Recommendation

Number of issues (specifically dissolution related) was communicated to the company. The applicant needs to address all the issues satisfactorily. The applicant has validated the analytical methods for specified impurities and degradants. The office of compliance is yet to provide an overall acceptable recommendation. Applicant proposes DS retest period of [redacted] months, which is supported by 24-month long-term stability data and the [redacted] accelerated stability data for the 3 primary stability batches. No DP shelf-life is granted at this time due to absence of dissolution and relevant test data on stability samples based on proposed dissolution specification.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Haripada Sarker, Ph.D.
ChemistryBranchChief/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: Melissa Robb

C. CC Block

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/s/

Haripada Sarker
5/16/2007 03:56:11 PM
CHEMIST

Ramesh Sood
5/16/2007 05:37:26 PM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assesment Division I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	22-081
Applicant:	Gilead Sciences, Inc.
Letter Date:	13 December, 2006
Stamp Date:	18 December, 2006
PDUFA Date:	18 June, 2007
Tradename:	Letairis
Established Name:	Ambrisentan
Dosage Form:	Tablets -- 5mg and 10 mg
Route of Administration:	Oral
Indication:	Treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening [redacted].

Assessed by: Haripada Sarker

	Yes	No
ONDQA Fileability:	x	
Comments for 74-Day Letter:		x

Summary
The application introduces ambrisentan film-coated tablets and is available in two dosage strengths, 5mg and 10mg. The active ingredient is a new molecular entity, ambrisentan, which is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist that is selective for the endothelin type A (ETA) receptor. This application for ambrisentan tablets is submitted by Gilead Sciences, Inc. The sponsor for related IND 64,915 was Myogen (later named as Gilead Sciences). In IND stage four different tablet strengths, [redacted] 5mg and 10mg were proposed for clinical trials, however, two strengths, 5mg and 10mg tablets are planed for current marketing. In a pre-NDA meeting dated July 26, 2006, number of CMC issues was discussed. Some of the issues were agreed, however, applicant committed to address the other issues, e.g. equivalence of DS from different suppliers, acceptance criterion [redacted] and impurities from excipients, in the NDA submission.

Drug Substance (DS)
Ambrisentan has a chiral center at the C-2 position of the propanoic acid core structure. It is manufactured as the (*S*)-enantiomer. Even though ambrisentan is indicated to be the USAN name, the name does not appear in USP dictionary, and needs to be verified. The crystal structure of this solid

is a white to off-white crystalline solid. The DS has pKa of 4.0, and is practically insoluble in water.

DS is manufactured in steps to obtain the steriospecific ambrisentan. Ambrisentan has been manufactured at to supply the DS during the development stages. is the intended commercial manufacturing site for ambrisentan DS. The product related impurities for ambrisentan are presented

the bioequivalence study during the development stages. Several variations in Cmax values are observed for different DS batches .

DS Critical Issues

- Two different sites (for DS clinical batches and stability batches are indicated, however, DS validation batches are obtained from . These DS sources need to be evaluated for comparison with respect to manufacturing and specification.
- Closer examination of analytical methods related to specifications of impurities including of DS is essential.
- The acceptance criterion of .

Drug Product (DP)

Ambrisentan is formulated for oral administration as immediate-release film coated tablets in 5mg and 10mg strengths (development stage strengths, , 5mg and 10mg). All the excipients used in drug product manufacture have standard compendial monograph, except coating agent. The film coating is non-functional and is used to provide a distinctive tablet color to aid in the identification of various strengths. Each strength of commercial tablets is differentiated by color, shape, and markings. Ambrisentan has low solubility and high permeability and is classified as a biopharmaceutics classification system (BCS) Class II drug. The drug product is manufactured by ; therefore, the solubility of ambrisentan does not affect the product formulation or the manufacturing process. The drug product formulation has varied only slightly over the course of development in going from Phase 1 to Commercial

degradants from excipients are reported (pre-NDA meeting), however, there are no excipient related degradation products specified in the drug product specifications. Applicant conducted various changes in DP dissolution method to meet the recommendation during pre-NDA meeting. Ambrisentan tablets are available in blister packs. The same container closure systems are used for the 5mg and 10mg tablets. routinely occur in both commercial drug product and historical (clinical) lots when the film-coated tablets are stored in blister packaging at accelerated conditions. Based on primary and accelerated stability data, a 24 months expiration dating is proposed for the DP. Information on carton, container and package inserts are provided.

DP Critical Issues

- Even though the applicant claimed some degradants from excipients, compatibility of excipients with DS, and monitoring the degradants throughout shelf-life of the DP appear to be essential.
- In-process controls, sampling [redacted] need to be evaluated to find any interrelation.
- Justification of dissolution method and specification including the dissolution media that will discriminate the DP.

[redacted]

- Monitor the integrity of blister packaging with respect to the stability of DP.
- Exclusion of [redacted] from DP specification in release and stability studies needs to be justified.

Comments and Recommendations

The application is fileable and no 74-Day Letter issue has been identified at this point. Facilities have been entered into EES. The review of the dissolution method and specification will be conducted by the CMC reviewer to evaluate the critical aspects of drug quality. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex. Because of the critical issues of DS particle size, DP blend uniformity, DP dissolution and other related attributes, the application could be a good candidate for discussion in ONDQA forum.

Haripada Sarker
Chemistry Reviewer

January 31, 2007
Date

Ramesh Sood, Ph.D.
Branch Chief

January 31, 2007
Date

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/s/

Haripada Sarker
1/31/2007 04:16:39 PM
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Ramesh Sood
1/31/2007 04:31:10 PM
CHEMIST