CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202992Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 202-992, [redacted] (teriflunomide) Tablets, 7 mg and 14 mg
Date: 05-JUN-2012

Introduction

The [redacted] Tablet is an immediate release tablet formulation to be marketed in one strength – 14 mg. The application also includes supporting information for a second strength, 7 mg. Both strengths were reviewed for adequacy as part of the current review. All excipients are commonly used in solid oral dosage forms. The two tablet strengths are qualitatively similar, but differ slightly in the composition of the film coat. The quantitative formulations differ in the relative amounts of the active ingredient, [redacted].

The recommended dose of [redacted] is 14 mg taken orally with or without food.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation from the Office of Compliance was issued on 22-JAN-2012.

All CMC review issues have been resolved, and ONDQA recommends approval of this NDA.

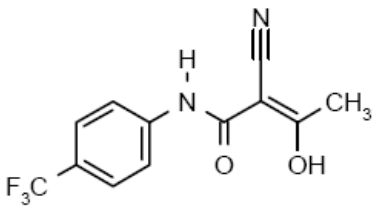
Administrative

The original submission of this 505(b)(1) NDA was received on 12-AUG-2011 from Sanofi-Aventis, Inc. Four (4) solicited CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (12-APR-2012, Dr. P. Shiromani) and the Biopharmaceutics Review (11-APR-2012, Dr. T. Chen).

The NDA is supported by IND 67,476 and two (2) drug master files (DMFs). Both DMFs were assessed for adequacy in the chemistry review.

Drug Substance (teriflunomide)

Chemical Name: (Z)-2-Cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl) amide

Chemical structure	
Molecular formula	$C_{12}H_9F_3N_2O_2$
Relative molecular mass	270.21

Teriflunomide is a new molecular entity. It contains no chiral centers. Teriflunomide is weakly acidic (pKa 3.1), which results in pH-dependent solubility. It is practically insoluble in water (0.02 mg/mL at 25°C). In aqueous buffers at 25°C, the solubility of teriflunomide increases from 0.02 µg/mL at pH 1.2 to 8 mg/mL at pH 7.6. The octanol/water partition coefficient of teriflunomide (log Ko/w) is 2.7. The Applicant indicates that (b) (4) was found in extensive screening experiments. Teriflunomide is a BCS class 2 compound due to its low solubility and high permeability.

During the review, the Applicant was asked to verify whether included spiking studies on the proposed starting materials to confirm the absence of genotoxic impurities (GTIs) in the final drug substance were conducted on at least six (6) consecutive pilot scale or three (3) consecutive production scale batches. As stated in the 12-APR-2012 Chemistry Review, "*…the Applicant has demonstrated with data…that the level of the 6 GTIs , tested in 6 consecutive industrial scale batches, are* (b) (4) *in the drug substance.*" The Applicant's response satisfactorily resolved the deficiency.

Teriflunomide is relatively stable; no extraordinary storage precautions are required. The proposed **re-test period of** (b) (4) when stored in the recommended container closure system and under the proposed storage conditions (b) (4) is granted.

Drug Product (teriflunomide tablets, 14 mg)

The drug product is an immediate release, film-coated tablet to be marketed in one strength – 14 mg. Excipients used in the 14 mg formulation are conventional for solid oral dosage forms and include lactose monohydrate, corn starch, hydroxypropylcellulose, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. Components of the film coat are standard and include hypromellose, titanium dioxide, macrogol, talc, and FD&C Blue #2. The 7 mg dosage strength was included in Module 3 and, while not intended for marketing, the dosage strength was reviewed as part of this application. There are minor differences in the qualititative compositions of the two tablet strengths, including slight variations in the compositions of the film coats. The quantitative formulations differ in the relative amounts of the active ingredient. (b) (4)

Teriflunomide tablets are manufactured via (b) (4) The manufacturing process development report is outlined in Chemistry Review #1 and represents a traditional approach to process development.

Identified review issues center around the proposed drug product specifications, particularly the proposed specifications for two specified impurities (b) (4) the proposed testing frequency for microbial contamination, and acceptance criteria for dissolution testing. Of particular note is the Applicant's proposal of slightly different release and stability specifications. Variations in specifications are noted in the levels of (b) (4) (NMT (b) (4) for release, NMT (b) (4) for stability) and total degradation products (NMT (b) (4) for release, NMT (b) (4) for stability). As captured in the Chemistry Review, (b) (4) was determined to be toxicologically qualified up to a level of (b) (4) (see Pharmacology/Toxicology Review and page 207 of the Chemistry Review); therefore, the proposed shelf life specification for (b) (4) was determined to be adequately and scientifically justified.

(b) (4) is a genotoxic impurity and is controlled at (b) (4) The proposed frequency of microbial contamination testing was satisfactorily

negotiated during the review clock, and the final dissolution criteria was established as Q= (b) (4) in 30 minutes.

Teriflunomide tablets will be packaged in (b) (4) blisters. The Applicant proposes a 24 month expiry for this product when stored in the commercial packaging at 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C to 30°C (59°F to 86°F). Based on the stability data provided and in accordance with ICH Q1E, the Agency grants the proposed expiry. There is no need for additional confirmatory language in the action letter as there is no disagreement between the Applicant's proposed expiration dating period and that granted by the Agency.

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/s/

SARAH P MIKSINSKI
06/05/2012

NDA 202-992

(b) (4) (teriflunomide) Tablets, 7 mg & 14 mg

Sanofi-aventis

Prafull Shiromani Ph.D.

Division of Pre-Marketing Assessment 1
Division of Neurology Products
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-992

2. REVIEW #: 1

3. REVIEW DATE: 12-Apr-2012

4. REVIEWER: Prafull Shiromani, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA	12-Aug-2011
Amendment # 0030; Applicant's Responses to CMC IR Letter	31-Jan-2012
Amendment # 0033; Amended Module 3 incorporating applicant's responses to CMC IR Letter (amendment #30)	17-Feb-2012
Amendment #0044; Applicant's acceptance of FDA-CMC dissolution specification recommendation	06-Apr-2012
Amendment # 0047: Applicant's acceptance of FDA-CMC analytical method for the drug product recommendation.	12-Apr-2012

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Sanofi-aventis U.S. Inc.

Address: 55 Corporate Drive, Bridgewater, NJ 08807

Representative: Cyntyia Psaras, PhD

Telephone: 908-304-6507

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Teriflunomide
c) Code Name/# (ONDC only): HMR1726
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of relapsing forms of multiple sclerosis

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 7 mg & 14 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

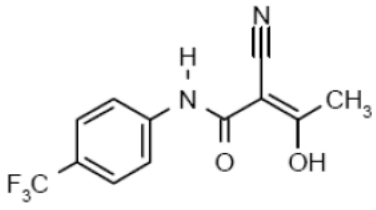
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x__Not a SPOTS product

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

(Z)-2-Cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl) amide

Chemical structure



Molecular formula	$C_{12}H_9F_3N_2O_2$
Relative molecular mass	270.21

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: N/A

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		(b) (4)		4			LOA: 11/29/2010
	3			4			LOA: 2/3/2011

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Recommendation: Acceptable	22-Jan-2012	D. Smith
Pharm/Tox	Pending		
Biopharm	Applicant accepts Biopharm's dissolution acceptance criterion	11-Apr-2012	T. Chen
LNC			
Methods Validation- Consult to Division of Pharmaceutical Analysis, St. Louis, MO. Suitability evaluation of the proposed analytical methods.	The analytical methods were evaluated and are acceptable for quality control and regulatory purposes.	8-March-2012	Wie Ye
DMEPA	Proprietary name (b) (4)	29-Feb-2012	J. Lee
EA	Their submission of a categorical exclusion from preparation of an	27-Dec-2011	P. K. Shiromani

	environmental assessment is granted		
Microbiology	N/A		

The Chemistry Review for NDA 202-992

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate responses to the FDA CMC IR letters. Additionally, the ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS; revised drug product dissolution specifications are recommended therein, which are acceptable to the applicant. There are no CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective.

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

N/A

II. Summary of Chemistry Assessments

This is an e-CTD NDA application for the NME, Teriflunomide, which is a novel immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for de novo pyrimidine synthesis.Teriflunomide is the active, predominant metabolite of leflunomide (Arava®), which has been approved in the US and worldwide for oral treatment of rheumatoid arthritis (RA) since 1998.

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

DRUG SUBSTANCE

The active ingredient, teriflunomide [chemical name: (Z)-2-cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethyl-phenyl)amide], is a well characterized small molecule with molecular formula C12H9F3N2O2 and molecular weight 270.21. Teriflunomide is weakly acidic (pKa 3.1), which results in pH dependant solubility. The drug substance is practically insoluble in water (0.02 mg/mL at 25°C). In aqueous buffers at 25°C, the solubility of teriflunomide increases from 0.02 µg/mL at pH 1.2 to 8 mg/mL at pH 7.6. The octanol/water partition coefficient of teriflunomide (log Ko/w) is 2.7. The applicant indicates that (b) (4) was found in extensive screening experiments. The API is a BCS class 2.

The active ingredient, teriflunomide, is not a salt. Therefore there are no issues of consistency between the established name "teriflunomide tablets" and the labeled potency.

The bulk drug substance is manufactured by Sanofi-aventis Deutschland in Frankfurt am Main, Germany and (b) (4) at Sanofi Chemie in Vertolaye, France. The synthesis involves two chemical steps from the designated starting materials, (b) (4)

Potential genotoxic chemicals were essentially not detected (b) (4) in the API in their spiking studies performed at levels equal to/greater than their acceptance criteria in the starting materials (b) (4) specification [as per EMEA guidance on Limits of Genotoxic Impurities (GTIs), 2008]. One of the comments in the IR letter was for the applicant to verify if the spiking studies' on the impurities in the starting materials were obtained for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition was not fulfilled, a routine test for these impurities in the drug substance specification is needed. This condition is stated in *EMA Guideline. In their response to the IR letter (amendment #0030), the applicant has demonstrated with data (presented in this review) that the level of the 6 GTIs , tested in 6 consecutive industrial scale batches, are* (b) (4) *in the drug substance. Accordingly, the routine test for these impurities in the drug substance specification is not required, as per the EMA guidance.*

The specification for teriflunomide includes test parameters that are typical for a small molecule. There are two specified impurities. (b) (4) is controlled at NMT (b) (4) as a genotoxic impurity. The proposed limit for (b) (4) is consistent with the maximum daily dose of teriflunomide, which is 14 mg. The synthetic intermediate and potential degradant, (b) (4), is controlled to NMT (b) (4); this limit is also applied to individual unspecified impurities.

The drug substance primary stability package includes 18 months of long-term data and six months of accelerated data (40°C/75% R. H.) for three production scale batches of drug substance manufactured at the commercial site. The submitted 18- month primary stability data can qualify for a maximum of (b) (4) retest period as per ICH Q1E and not the proposed (b) (4) *However, in their response to the IR letter (amendment #0030), the applicant presented 24-month primary stability data which became available in the meantime (updated stability data presented in this review). The data confirm the stability of teriflunomide up to 24-month of storage at long term storage conditions of +25°C±2°C/60%±5% RH. Based on the available 24-month long term data of 3 batches and considering the ICH Q1E guidance, their proposed* (b) (4) *retest period for teriflunomide drug substance is acceptable. This* (b) (4) *retest period is further supported by statistical analysis of the assay up to the 12-month time point.* The updated drug substance stability data is provided in Amendment #33 (amended module 3).

DRUG PRODUCT

The proposed dosage form is an immediate release tablet. Two tablet strengths (7 mg and 14 mg) are described in the application. Although the firm proposes marketing of teriflunomide as 14 mg tablets, the application includes supporting CMC documentation for a 7 mg tablet; both the strengths have been reviewed. The 7 mg tablets are very light greenish-bluish grey to pale greenish-blue, hexagonal film-coated tablets. The 14 mg tablets are pale blue to pastel blue, pentagonal film-coated tablets. Both strengths are engraved with the tablet strength on one side

and a corporate logo on the other side. Teriflunomide Tablets will be packaged in (b) (4) blisters.

All excipients in Teriflunomide Tablets are commonly used in solid oral dosage forms. The two tablet formulations are qualitatively similar; however, only the 7 mg formulation includes ferric oxide (yellow iron oxide) in the film-coat. Quantitatively, the tablets core formulations differ in the relative amounts of the active ingredient, (b) (4).

The formulation development history of Teriflunomide Tablets is described in some detail in Module 3.2.P.5. Clinical formulations, (b) (4), were determined to be bioequivalent in BE study BEQ10169; (b) (4) is noted that the physical presentation of batches used in stability studies differs slightly from the commercial image tablets; the former is (b) (4), whilst the latter is (b) (4) Similar changes were made during development of the 7 mg tablet formulation. Prior to the submission of the NDA, the applicant sought agreement to use comparative dissolution data for bridging the clinical formulation and the commercial tablets, with which the Agency agreed.

Teriflunomide Tablets will be manufactured by Sanofi Winthrop Industrie in Compiénge, France (b) (4)

The proposed specification for Teriflunomide Tablets, 14 mg is given in the applicant's Module 3.2.P.5.1. With the exception of appearance, specifications for the 7 mg strengths are the same. There are two specified impurities, (b) (4) which are both process impurities and potential degradation products. (b) (4) a genotoxic impurity, is controlled at (b) (4). The applicant proposes separate release and shelf-life criteria (NMT (b) (4) and NMT (b) (4), respectively) for (b) (4). Their proposal was reviewed to be acceptable. In response to an IR comment they have revised the drug product specification, which now stipulates that the microbiological contamination test will be performed on every tenth batch and at least once a year (b) (4) The revised specification has been captured in their amendment #0033.

A CONSULT REQUEST was sent to the Division of Pharmaceutical Analysis (St. Louis, MO), to evaluate the applicant's HPLC method for the identity, determination of assay and uniformity of content of teriflunomide, and determination of degradation products in film-coated tablets, (b) (4) *is a known genotoxic impurity and there was concern with the adequacy of the method to quantify this impurity).*

DPA sent their report (Wei Ye, Chemist, HFD-920) on 3/8/2012 stating that methods were evaluated and are acceptable for quality control and regulatory purposes. However, DPA did have some comments on the analytical method, which were conveyed to the applicant via an IR Letter. The applicant provided adequate responses (captured in this review to this IR letter in their amendment # 0047; the applicant's HPLC method has more than adequate sensitivity

(LOQ = 60ppm) to implement the (b) (4) *acceptance criterion of NMT* (b) (4) *in the drug product specification.*

An in vivo comparative bioavailability study has proven that tablets manufactured with drug substances of different specific surface areas (b) (4) are bioequivalent (sanofi-aventis study number BDR6639). Following these findings, the dissolution method has been optimized to better align the BEQ data/in vivo performance. Phosphate buffer pH 6.8 provided the most appropriate in vitro dissolution condition that reflected the in vivo similarity of the batches, (b) (4)

The ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS (4-11-2012); the following revised drug product dissolution acceptance criterion is recommended therein:

Q = (b) (4) in 30 minutes.

The revised drug product specifications are included in the applicant's supplement 0044, dated 4/6/2012 and are included in this review.

The NDA stability package contains data for 3 production scale registration batches in Al/Al blister per tablet strength manufactured at the commercial facility. The applicant used the ICH intermediate stability condition (30°C/65% R. H.) for longterm studies and provided data through 12 months. Accelerated stability data through 6 months are also provided. A 24 month shelf life is proposed based on statistical analysis of the longterm data. As per ICH Q1E 2.4.1.1 (long-term and accelerated data showing little or no change over time and little or no variability) their proposed shelf life of 24 months (shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data) is acceptable.

The firm has submitted a claim for categorical exclusion under 21 CFR 25.31(b) which states that the estimated concentration of the active moiety at the point of entry into the aquatic environment will be below one part per billion (1 ppb). Their request is granted by this reviewer.

Compliance issued an overall recommendation for approval on 22-Jan-2012; their summary report is attached to this review.

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

1. Indication and Usage

The drug is indicated for the treatment of patients with relapsing forms of multiple sclerosis (b) (4)

Recommended dose: 14 mg orally once daily, with or without food.

2. Dosage and Administration

Recommended dose: 14 mg orally once daily, with or without food.

The proposed dose can be achieved using the proposed commercial strength.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate responses to the FDA CMC IR letters. Additionally, the ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS; revised drug product dissolution specifications are recommended therein, which are acceptable to the applicant. There are no CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani Ph.D.
ChemistryTeamLeaderName/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: H. M. Toure

C. CC Block

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/s/

PRAFULL K SHIROMANI
04/12/2012

RAMESH K SOOD
04/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Prafull Shiromani, Ph.D., CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Prafull.Shiromani@fda.hhs.gov
Phone: (301)-796-2133
Fax: (301)-796-9747

FROM: FDA
Division of Pharmaceutical Analysis
James Allgire, Team Leader
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3813

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 202992

Name of Product: Aubagio (teriflunomide)Tablets

Applicant: sanofi-aventis U.S.

Applicant's Contact Person: Cynthia Psaras

Address: 55 Corporate Drive, Mail Stop:55D-225A, Bridgewater, NJ 08807

Telephone: 908-981-4874 Fax: 877-332-5512

Date Methods Validation Consult Request Form Received by DPA: 10/06/11

Date Methods Validation Package Received by DPA: 10/06/11

Date Samples Received by DPA: 1/12/12

Date Analytical Completed by DPA: 3/8/12

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments:

Cover memo and Summary of Results are attached

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/s/

JAMES F ALLGIRE
03/08/2012

BENJAMIN J WESTENBERGER
03/08/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Prafull Shiromani, Ph.D., CMC Reviewer
Martha R. Heimann, Ph.D., CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Prafull.Shiromani@fda.hhs.gov
Phone: (301)-796-2133
Fax.: (301)-796-9747

Through: Ramesh Sood, Ph.D., Branch Chief
Phone: (301)-794-1466

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 202992

Name of Product: Aubagio (teriflunomide) Tablets

Applicant: sanofi-aventis U.S.

Applicant's Contact Person: Cynthia Psaras

Address: 55 Corporate Drive, Mail Stop: 55D-225A, Bridgewater, NJ 08807

Telephone: 908-981-4874 Fax: 877-332-5512

Date NDA Received by CDER: **8/12/2011**

Date of Amendment(s) containing the MVP: **8/12/2011**

DATE of Request: **10/3/2011**

Requested Completion Date: **1/12/2012**

PDUFA User Fee Goal Date:

Submission Classification/Chemical Class: 1S

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA #

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
Teriflunomide drug substance Teriflunomide primary standard, batch Sm 299-1.03 (PS) Teriflunomide working standard/secondary standard, batch 0500024551.02 (SS) Teriflunomide film-coated tablets 7 and 14 mg. (b) (4) (impurity) reference standard (b) (4) (impurity) reference standard	TBD by laboratory	

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	N/A (electronic)
Specifications/Methods for New Drug Substance(s)	N/A (electronic)
Specifications/Methods for Finished Dosage Form(s)	N/A (electronic)
Supporting Data for Accuracy, Specificity, etc.	N/A (electronic)
Applicant's Test Results on NDS and Dosage Forms	N/A (electronic)
Other:	N/A

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
QUA-FR-2011-04280	HPLC method for the identity, determination of assay and uniformity of content of teriflunomide, and determination of degradation products in film-coated tablets	3.2.5.2	**0**	Please perform assay and determination of degradation products.

Additional Comments: (b) (4) **is a known genotoxic impurity and we are concerned with the adequacy of the method to quantify this impurity.**

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

MARTHA R HEIMANN
10/03/2011

RAMESH K SOOD
10/03/2011

JEANNIE C DAVID
10/06/2011
ONDQA Methods Validation Project Manager

Initial Quality Assessment
Branch I
Division of New Drug Quality Assessment I

OND Division:	Division of Neurology Products
NDA:	202-992
Applicant:	Sanofi-aventis
Stamp Date:	12-Aug-2011
PDUFA Date:	12-Jun-2011 (priority review expected to be denied)
Trademark:	Aubagio (b) (4)
Established Name:	Teriflunomide
Dosage Form:	Tablet
Route of Administration:	Oral
Indication:	Treatment of relapsing forms of multiple sclerosis
CMC Lead:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

Summary

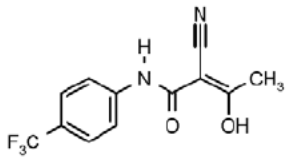
Teriflunomide (codename HMR1726) is a novel immunomodulatory agent with anti-inflammatory properties that is reported to selectively and reversibly inhibit the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH) required for de novo pyrimidine synthesis. It is the active metabolite of leflunomide (Arava®), which was approved in the US for treatment of rheumatoid arthritis in 1998. Teriflunomide was identified and developed by Hoechst Marion Roussel (later part of Sanofi-aventis) under IND 67,476.

The current NDA provides for an immediate release teriflunomide tablet formulation. A single strength, 14 mg, is proposed for marketing; however, the application also contains CMC information for a 7 mg tablet. The product is intended for use in the treatment of patients with relapsing forms of multiple sclerosis (MS (b) (4) The recommended dose is 14 mg/day taken with or without food.

Drug Substance

The active ingredient, teriflunomide [chemical name: (Z)-2-cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethyl-phenyl)amide], is a well characterized small molecule with molecular formula $C_{12}H_9F_3N_2O_2$ and molecular weight 270.21. Teriflunomide is weakly acidic (pKa 3.1), which results in pH dependant solubility. The drug substance is practically insoluble in water (0.02 mg/mL at 25°C). In aqueous buffers at 25°C, the solubility of teriflunomide increases from 0.02 µg/mL at pH 1.2 to 8 mg/mL at pH 7.6. The octanol/water partition coefficient of

teriflunomide (log $K_{o/w}$) is 2.7. The applicant indicates that [redacted] (b) (4) was found in extensive screening experiments. The chemical structure of teriflunomide is:



The bulk drug substance is manufactured by Sanofi-aventis Deutschland in Frankfurt am Main, Germany and [redacted] (b) (4) at Sanofi Chemie in Vertolaye, France. The synthetic route is outlined in the applicant's **Figure 1** [Module 3.2.S.2.2]. The synthesis involves two chemical steps from the designated starting materials, [redacted] (b) (4)

Figure 1 - Flow diagram of the teriflunomide drug substance synthesis

[redacted] (b) (4)

The proposed drug substance specification is given in applicant's **Table 1** [Module 3.2.S.4.1], which is reproduced below.

Table 1 - Specifications for teriflunomide drug substance

Test	Analytical procedure	Acceptance criteria	Retest
(b) (4)			

The specification for teriflunomide includes test parameters that are typical for a small molecule. Assay and Related Substances are determined by a (b) (4) HPLC method using an acetonitrile/ammonium acetate buffer (pH 5.5) as mobile phase and UV detection at 249 nm. There are two specified impurities. (b) (4) is controlled at NMT (b) (4) as a genotoxic impurity. The proposed limit for (b) (4) is consistent with the maximum daily dose of teriflunomide, which is 14 mg. The synthetic intermediate and potential degradant, (b) (4), is controlled to NMT (b) (4); this limit is also applied to individual unspecified impurities.

The drug substance primary stability package includes 18 months of long-term data and six months of accelerated data (40°C/75% R. H.) for three production scale batches of drug substance manufactured at the commercial site. A (b) (4) retest date is proposed.

Drug Product

Reviewer note: Although the firm proposes marketing of teriflunomide as 14 mg tablets, the application includes supporting CMC documentation for a 7 mg tablet. Both tablet strengths are discussed below. The clinical division may require marketing of a lower strength for safety reasons. Therefore, it is recommended that information related to the 7 mg tablets be reviewed.

The proposed dosage form is an immediate release tablet. Two tablet strengths (7 mg and 14 mg) are described in the application. The 7 mg tablets are very light greenish-bluish grey to pale greenish-blue, hexagonal film-coated tablets. The 14 mg tablets are pale blue to pastel blue, pentagonal film-coated tablets. Both strengths are engraved with the tablet strength on one side and a corporate logo on the other side. Teriflunomide Tablets will be packaged in (b) (4) blisters.

The components and composition of Teriflunomide Tablets are summarized in the applicant's **Table 1** and **Table 2** [Module 3.2.P.1]. All excipients in Teriflunomide Tablets are commonly used in solid oral dosage forms. The two tablet formulations are qualitatively similar; however, only the 7 mg formulation includes ferric oxide (yellow iron oxide) in the film-coat. Quantitatively, the tablets core formulations differ in the relative amounts of the active ingredient (b) (4).

Table 1 - Composition of the 7 mg dosage strength

Components [a]	Composition		Function	Reference to standards [b]
	Percentage [%]	Per unit (1 film-coated tablet) [mg]		
Tablet core				
Teriflunomide	(b) (4)	7.0	Drug substance	In-house
Lactose monohydrate		(b) (4)		Ph. Eur., NF
Maize starch [Corn starch]				Ph. Eur., NF
Hydroxypropylcellulose				Ph. Eur., NF
Microcrystalline cellulose				Ph. Eur., NF
Sodium starch glycolate (b) (4) [Sodium starch glycolate]				Ph. Eur., NF
Magnesium stearate				Ph. Eur., NF
(b) (4)				
Film-coating				In-house [c]
Hypromellose [d]				Ph. Eur., USP
Titanium dioxide (b) (4)				Ph. Eur., USP
(b) (4)				
Talc [d]				Ph. Eur., USP
Macrogol [d] [Polyethylene glycol]				Ph. Eur., NF
Indigo carmine aluminum lake (b) (4) [FD&C Blue #2], (b) (4)				EC directive 2008/128, CFR 82.51 and 82.102
Ferric oxide [d] [Iron oxide yellow (b) (4)				NF EC directive 2008/128, CFR 73.1200
(b) (4) (b) (4)				
Mass of film-coated tablet	100	155.0		
(b) (4)				

a Components are listed according to their pharmacopoeial names. If more than one monograph exists, other names are given in brackets, along with the compendial reference.

b Reference is made to the current edition of the Pharmacopoeia.

c (b) (4)

d

Table 2 - Composition of the 14 mg dosage strength

Components [a]	Composition		Function	Reference to standards [b]
	Percentage [%]	Per unit (1 film-coated tablet) [mg]		
Tablet core				
Teriflunomide	(b) (4)	14.0	Drug substance	In-house
Lactose monohydrate		(b) (4)		Ph. Eur., NF
Maize starch [Corn starch]				Ph. Eur., NF
Hydroxypropylcellulose				Ph. Eur., NF
Microcrystalline cellulose				Ph. Eur., NF
Sodium starch glycolate (b) (4) [Sodium starch glycolate]				Ph. Eur., NF
Magnesium stearate				Ph. Eur., NF
(b) (4)				
Film-coating				In-house [c]
Hypromellose [d]				Ph. Eur., USP
Titanium dioxide (b) (4)				Ph. Eur., USP
(b) (4)				
Talc [d]				Ph. Eur., USP
Macrogol [d] [Polyethylene glycol]				Ph. Eur., NF
Indigo carmine aluminum lake (b) (4) [FD&C Blue #2], (b) (4)				EC directive 2008/128, CFR 82.51 and 82.102
(b) (4)				
Mass of film-coated tablet	100	155.0		
(b) (4)				

a Components are listed according to their pharmacopoeial names. If more than one monograph exists, other names are given in brackets, along with the compendial reference.

b Reference is made to the current edition of the Pharmacopoeia.

c (b) (4)

d

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The formulation development history of Teriflunomide Tablets is described in some detail in Module 3.2.P.5. The proposed 'final" commercial formulations are designated as HMR1726/FT/00007/__/07 and HMR1726/FT/00014/__/07 ("…/07" formulations). The differences between the final commercial formulation of the 14 mg tablet and earlier formulations are summarized in the applicant's **Table 2** [Module 3.2.P.2]. It is noted that the physical presentation of batches used in stability studies (…/06) differs slightly from the commercial image tablets (…/07). The …/06 formulation used in stability studies is a (b) (4) , while the final commercial image (…/07) is (b) (4) Similar changes were made during development of the 7 mg tablet formulation.

Table 2 - Composition with formulation identifier reference of the 14 mg dosage strength of teriflunomide film-coated tablets

Components	14 mg [mg]						
Tablet core							
Teriflunomide	14.0				14.0		
Lactose monohydrate	(b) (4)						
Maize starch							
Hydroxypropylcellulose							
Microcrystalline cellulose							
Sodium starch glycolate (b) (4)							
Magnesium stearate							
(b) (4)							
(b) (4)							
Film-coating							
Hypromellose	(b) (4)						
Titanium dioxide (b) (4)							
Talc							
Macrogol							
Indigo carmine aluminum lake (b) (4)							
(b) (4)							
Mass of film-coated tablet	153.5		155.0	153.5	155.0	155.0	
(b) (4)							
Use of batches	Clinical study	Clinical study	Not used	Clinical study	Clinical study	Primary stability	Parameter justification
Image	Clinical	Clinical	Commercial	Clinical	Clinical	Commercial	Commercial (final image)
Formulation identifier	HMR1726/ FT/00014/ _ _/01	HMR1726/ FT/00014/ _ _/02	HMR1726/ FT/00014/ _ _/03	HMR1726/ FT/00014/ _ _/04	HMR1726/ FT/00014/ _ _/05	HMR1726/ FT/00014/ _ _/06	HMR1726/ FT/00014/ _ _/07

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With respect to bridging, the …/04 and …/05 clinical formulations were compared in BE study BEQ10169. Prior to submission of the NDA, the applicant sought agreement to use an in vitro approach (i.e., comparative dissolution data) for bridging the …/05 clinical formulation and the commercial tablets. Agency agreement with this approach was communicated on 19-May-2010.

Teriflunomide Tablets will be manufactured by Sanofi Winthrop Industrie in Compiénge, France. (b) (4)

The proposed specification for Teriflunomide Tablets, 14 mg is given in the applicant's **Table 1** [Module3.2.P.5.1]. With the exception of appearance, specifications for the 7 mg strengths are the same. There are two specified impurities, (b) (4) a genotoxic impurity, is controlled at (b) (4). The applicant proposes separate release and shelf-life criteria (NMT (b) (4) and NMT (b) (4), respectively) for (b) (4)

Analytical procedures are straightforward. Assay, Related Substances and Content Uniformity are determined using the same (b) (4) HPLC method as used for the bulk drug substance. Dissolution is determined using USP Apparatus 2 with pH 6.8 phosphate buffer as the medium and paddle speed 50 rpm. Dissolution is quantitated by UV.

Table 1 - Specifications for teriflunomide film-coated tablets 14 mg

Test	Analytical procedure	Acceptance criteria
(b) (4)		

The NDA stability package contains data for 3 production scale registration batches per tablet strength manufactured at the commercial facility. As noted above, the only difference between the registration batches and the proposed commercial product is (b) (4) The applicant used the ICH intermediate stability condition (30°C/65% R. H.) for long-term studies and provided data through 12 months. Accelerated stability data through 6 months are also provided. A 24 month shelf life is proposed based on statistical analysis of the long-term data.

Critical issues for review

The designated starting materials for teriflunomide, (b) (4), are commercially available, structurally simple molecules; however, there are only two chemical steps from the starting materials to the drug substance. Controls for the starting materials are therefore considered critical to the quality of the final drug substance.

(b) (4) is reported as a confirmed genotoxic impurity and controlled in the drug substance. A number of impurities in (b) (4) are also reported either be genotoxic or have an in-silico mutagenicity alert. Similarly, impurities in (b) (4) which may be carried over into the drug substance (b) (4), the applicant's rationale for not including testing for starting material impurities in the drug substance should be evaluated carefully.

No critical issues related to the drug product were identified in the initial assessment.

Additional issues

Administrative: The firm has submitted a claim for categorical exclusion under 21 CFR 25.31(b) which states that the estimated concentration of the active moiety at the point of entry into the aquatic environment will be below one part per billion (1 ppb).

Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing of teriflunomide and Teriflunomide Tablets is provided in the submission. Facilities requiring compliance evaluation were submitted in EES on 18-Aug-2011.

Labeling/Established Name: The active ingredient, teriflunomide, is not a salt. Therefore there are no issues of consistency between the established name "teriflunomide tablets" and the labeled potency.

Comments for 74-Day Letter

There are no comments for the 74-Day Letter.

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective.

The drug substance is a well-characterized small molecule and the drug product is a simple immediate release tablet. There are no QbD aspects to the submission. It is recommended that the review team include a single CMC reviewer and a Biopharmaceutics reviewer. The drug substance is a new molecular entity; therefore, a Division-level regulatory briefing would be appropriate.

{See appended electronic signature page}

Martha R. Heimann, Ph.D.
CMC Lead, DNDQA-1, ONDQA

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief, DNDQA-1, ONDQA

ATTACHMENT 1

Manufacturing Establishments for Teriflunomide Tablets

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Manufacturing information is reproduced from the attachment to Form 356h.

Table 1 - Establishment information for drug substance manufacturers

Name and address	Responsibilities	Contact person	Establishment registration number	Readiness for inspection
Sanofi-Aventis Deutschland GmbH Industriepark Höchst 65926 Frankfurt am Main Germany	Manufacture of the drug substance, step 1 and step 2 Testing and release of the drug substance Stability testing of the drug substance	Florian BLUME Head Quality Assurance Frankfurt Chemistry Florian.Blume@sanofi-aventis.com Tel: +49 (0)69-305-28221 Fax: +49 (0)69-305-80639	3002807197	Yes
Sanofi Chimie Le Bourg 63480 Vertolaye France	(b) (4) Packaging and labeling of the drug substance	Thomas LAGRUE Quality Assurance Production thomas.lagrue@sanofi-aventis.com Tel: +33 4.73.82.51.43 Fax:+33 4.73.82.52.07	(9610721) 1463-FCFR048	Yes

Table 2 - Establishment information for drug product manufacturers

Name and address	Responsibilities	Contact person	Establishment registration number	Readiness for inspection
Sanofi Winthrop Industrie 56 route de Choisy au Bac 60205 Compiègne France	Manufacturing Primary and Secondary Packaging Control testing and release of drug product packaged in blisters and in carton boxes Stability testing	Chantal Marsh Qualified Person Quality Control Manager chantal.marsh@sanofi-aventis.com Tel: +33 3 44 38 74 03 Fax: +33 3 44 38 44 24	3003492806	Yes
(b) (4)				Yes

All facilities except the (b) (4)) have been submitted in EES.

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number:	**Supplement Number and Type:**	**Established/Proper Name:**
202-992	N/A	Teriflunomide Tablets
Applicant:	**Letter Date:**	**Stamp Date:**
MAP Pharmaceuticals	25-May-2011	25-May-2011

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?	N/A		

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? **This question is not applicable for synthesized API.**	N/A		
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* 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 ASSESSMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion claimed.

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 biowaivers 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?	N/A		

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 #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV		(b) (4)	29-Nov-2010	
(b) (4)	III			03-Feb-2011	

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.	**Is the product quality section of the application fileable?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	N/A		Describe filing issues here or on additional sheets
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			Describe potential review issues here or on additional sheets

{See appended electronic signature page}
Martha R. Heimann, Ph.D.
CMC Lead, DNDQA-1, ONDQA

{See appended electronic signature page}
Ramesh Sood, Ph.D.
Branch Chief, DNDQA-1, ONDQA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTHA R HEIMANN
08/24/2011

RAMESH K SOOD
08/24/2011