CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s000

CHEMISTRY REVIEW(S)

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

DATE: 16-AUG-2012

TO: N203214 File

FROM: Craig M. Bertha, Ph.D.
Chemist
ONDQA, Division III, Branch VIII

THROUGH: Prasad S. Peri, Ph.D.
Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: CMC review of label and labeling revisions, EES status, and overall CMC recommendation for NDA 203214

SUMMARY:
The CMC sections of the package insert and the carton and container labels were reviewed (see review dated 02-AUG-2012). The comments were sent to the firm in a telephone facsimile on 06-AUG-2012. The applicant submitted a revised package insert and revised container labels on 13-AUG-2012, and 14-AUG-2012, respectively. These items are the subject of the first part of this review.

Package Insert - Comments of 06-AUG-2012

1. Revise the DOSAGE FORMS AND STRENGTHS section of the package insert to include the information required by 21 CFR 201.57(c)(4)(ii), rather than referencing the DESCRIPTION section.

2. Revise the DESCRIPTION section so that it is clear that the strengths of the tablets, i.e., 5 and 10 mg, are in terms of the tofacitinib free-base. We recommend that you state the tofacitinib citrate equivalence in parentheses for added clarity.

3. Revise the molecular formula in the DESCRIPTION section to a standard format, i.e., with subscripts for numeric designations.

4. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert to include a description of the imprinting of the tablets as per 21 CFR 201.57(c)(17)(iii).

5. Revise the storage and handling statement to include the following reference "[see USP Controlled Room Temperature]," after the excursion temperature ranges.

Container and Carton Labels – Comments of 06-AUG-2012

1. Revise the established name of the drug product to "tofacitinib tablets" while retaining the strength as 5 or 10 mg and include a footnote stating "each tablet contains 8 mg tofacitinib citrate equivalent to 5 mg tofacitinib," (b) (4)

2. Submit revised bottle and carton label mock-ups that indicate the placement of the expiration date and lot number of the drug product (as per 21 CFR 201.1).

A revised package insert has been submitted to address the comments above, as well as revised container labels. As an example, the mock-up for the container label for the 10 mg strength with 180 count presentation is reproduced below.

(b) (4)

Evaluation: Adequate. In compliance with 21 CFR 201.57(c)(4)(ii), the applicant has revised the DOSAGE FORMS AND STRENGTHS section of the package insert to include descriptions of the identifying characteristics of the dosage form for each strength of the drug product (i.e., color, shape, debossed information). The DESCRIPTION section is revised such that it is now clear that strengths are given in terms of the free base amount of drug (i.e., 5 and 10 mg), and the tofacitinib citrate equivalent amounts have been included in parentheses as suggested. Also in that section, the molecular formula has been corrected as requested. The HOW SUPPLIED/ STORAGE AND HANDLING section now includes a description of the imprinting (debossing) of the tablets and the reference to USP Controlled Room Temperature is included following the recommendations for storage and handling.

The applicant has submitted revised container labels to address the two comments above. Specifically, the established name has been revised so the strength and the name match and the footnote is included to indicate salt equivalency. Also the black area is space available for the expiry and lot number.

Establishment Evaluation Request – Office of Compliance Recommendation Status
The Office of Compliance has entered an "Acceptable" recommendation into the EES on 16-AUG-2012.

Overall CMC Recommendation for NDA 203214
The application is recommended to be **approved**.

_____
Craig M. Bertha, Ph.D.
Chemist, ONDQA

cc:

ONDQA/DIV III/EDuffy
OND/DPARP/NNikilov
OCP/DCPII/LJain
OND/DPARP/LLeshin
OB/DBIII/YKim
OND/DPARP/PBowen
OPS/OMPT/DHenry
ONDQA/Biopharm/JDuan
ONDQA/DNDQA3/ASchroeder
ONDQA/DNDQA3/CBertha/8/16/2012
ONDQA/DNDQA3/YWang
ONDQA/DNDQA2/BKurtyka
ONDQA/DNDQA3/PPeri

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/s/

CRAIG M BERTHA
08/16/2012

PRASAD PERI
08/16/2012
I concur

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

DATE: 02-AUG-2012

TO: N203214 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VIII

THROUGH: Prasad S. Peri, Ph.D.
Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: CMC review of labels and labeling for NDA 203214

SUMMARY:

<u>Package Insert</u>

The DOSAGE FORMS AND STRENGTHS section currently provides a reference to the DESCRIPTION section for the information complying with 21 CFR 201.57(c)(4)(ii). The presentation of the strength in terms of the tofacitinib free base is not clear in the DESCRIPTION section. The molecular formula should be modified to a standard format (with subscript numerical designations). The HOW SUPPLIED/STORAGE AND HANDLING section does not include a description of the tablet imprinting as per 21 CFR 201.57(c)(17)(iii). The storage and handling statement should be modified to include "[see USP Controlled Room Temperature]" to be consistent with recommended practice.

Deficiency: *Revise the DOSAGE FORMS AND STRENGTHS section of the package insert to include the information required by 21 CFR 201.57(c)(4)(ii), rather than referencing the DESCRIPTION section.*

Deficiency: *Revise the DESCRIPTION section so that it is clear that the strengths of the tablets, i.e., 5 and 10 mg, are in terms of the tofacitinib free-base. It is recommended that you state the tofacitinib citrate equivalence in parentheses for added clarity.*

Deficiency: *Revise the molecular formula in the DESCRIPTION section to a standard format, i.e., with subscripts for numeric designations.*

Deficiency: *Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert to include a description of the imprinting of the tablets as per 21 CFR 201.57(c)(17)(iii).*

Deficiency: *Revise the storage and handling statement to include the following reference "[see USP Controlled Room Temperature]," after the excursion temperature ranges.*

Carton and Container Labels

The product of both strengths is to be packaged in 180 and 60 count HDPE bottles with induction seal liners. The application provides carton and container labels for each bottle presentation (2 strengths in 2 bottle presentations).

The most current labels have the name for the drug product as (b) (4) ® (tofacitinib citrate) Tablets and the strength as 5 or 10 mg. However, there is an asterisk after the 5 or 10 mg strength that states that "*Each tablet contains tofacitinib citrate equivalent to 5 mg tofacitinib" and "*Each tablet contains tofacitinib citrate equivalent to 10 mg tofacitinib." Therefore, the strength and the established name do not match as currently proposed. The established name being used for the product is tofacitinib citrate. However, the strength is provided in terms of the free base. To be consistent with the policy promoted by the USP and the Agency to not include the salt forms in the established names of drug products, the "citrate" should be removed from the established name and a footnote added onto the label stating that the actual form of the drug substance is the citrate salt as well as the strength of 8 or (b) (4) in terms of that form.

Deficiency: *Revise the established name of the drug product to "tofacitinib tablets" while retaining the strength as 5 or 10 mg and include a footnote stating "each tablet contains 8 mg tofacitinib citrate equivalent to 5 mg tofacitinib,"* (b) (4)

None of the bottle or carton label mock-ups would appear to include any indication of where the expiration date or the lot number would be located (21 CFR 201.17, 201.18, and 201.100(b)(6)). The labels only list Pfizer as the distributor, but this is in compliance with 21 CFR 201.1(h)(5). Because the dosage and administration instructions in the package insert are relatively extensive, the DOSAGE AND USE instructions on the bottle labels and cartons merely state that the patient or practitioner is to see the accompanying prescribing information. That approach is consistent with 21 CFR 201.55. The bottle labels and cartons state that the product should not be repackaged, thus, this complies with the requirements of 21 CFR 201.100(b)(7). Other information included appears to be consistent with labeling regulations.

Deficiency: *Provide revised bottle and carton label mock-ups that indicate the placement of the expiration date and lot number of the drug product (as per 21 CFR 201.17, 201.18, 200.100(b)(6)).*

DMEPA Labeling Review and Comments

The DMEPA has provided a consult review for the labeling date 12-JUN-2012, (b) (4) The only container closure systems currently proposed are the 60 and 180 count HDPE bottles with foil induction lidding, for both strengths. With regard to the DMEPA comments for the applicant, comment B.1 should be revised to account for the discrepancy between the established name and the product strengths, as discussed above. Therefore, the DMEPA comments could be revised as such:

B. Container Labels

1. The established name includes the active ingredient and the finished dosage form. Relocate the dosage form, 'tablets', to appear after (Tofacitinib). For example:

Tradename
(Tofacitinib)
Tablets
10 mg

Remove DMEPA comment D as [redacted] (b) (4)

RECOMMENDATION: The following labeling comments are to be forwarded to the applicant. Also, refer to the suggested revisions for the DMEPA labeling recommendations immediately above.

Draft CMC Labeling Comments

1. The following comments pertain to the package insert.

    a. Revise the DOSAGE FORMS AND STRENGTHS section of the package insert to include the information required by 21 CFR 201.57(c)(4)(ii), rather than referencing the DESCRIPTION section.

    b. Revise the DESCRIPTION section so that it is clear that the strengths of the tablets, i.e., 5 and 10 mg, are in terms of the tofacitinib free-base. It is recommended that you state the tofacitinib citrate equivalence in parentheses for added clarity.

    c. Revise the molecular formula in the DESCRIPTION section to a standard format, i.e., with subscripts for numeric designations.

    d. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert to include a description of the imprinting of the tablets as per 21 CFR 201.57(c)(17)(iii).

    e. Revise the storage and handling statement to include the following reference "[see USP Controlled Room Temperature]," after the excursion temperature ranges.

2. The following comments pertain to the container and carton labels.

    a. Revise the established name of the drug product to "tofacitinib tablets" while retaining the strength as 5 or 10 mg and include a footnote stating "each tablet contains 8 mg tofacitinib citrate equivalent to 5 mg tofacitinib," [redacted] (b) (4)

    b. Provide revised bottle and carton label mock-ups that indicate the placement of the expiration date and lot number of the drug product (as per 21 CFR 201.1, 201.18, 200.100(b)(6)).

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:

ONDQA/DIV III/EDuffy
OND/DPARP/NNikilov
OCP/DCPII/LJain
OND/DPARP/LLeshin
OB/DBIII/YKim
OND/DPARP/PBowen
OPS/OMPT/DHenry
ONDQA/Biopharm/JDuan
ONDQA/DNDQA3/ASchroeder
ONDQA/DNDQA3/CBertha/8/2/2012
ONDQA/DNDQA3/YWang
ONDQA/DNDQA2/BKurtyka
ONDQA/DNDQA3/PPeri

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/s/

CRAIG M BERTHA
08/02/2012

PRASAD PERI
08/02/2012
I concur

Memorandum

Department of Health and Human Serviced
Food and Drug Administration
Center for Drug Evaluation and Research

Date: **23-Jul-2012**

From: **Bogdan Kurtyka, Ph.D.**
CMC Reviewer

Through: **Prasad Peri, Ph.D.**
Chief, Branch VIII ONDQA Division III
Eric Duffy
Director, ONDQA Division III

To: **CMC Review #1 for NDA 203-214**

CC: **Ying Wang, Ph.D.**
Craig Bertha, Ph.D.

Subject: **Update of NIR methods**

Inspection team members participating in inspection of drug product manufacturing plant reported that NIR methods were updated following a major repair of NIR analyzer after CMC Review #1 that recommended approval of NIR methods was finalized. The details of the update were submitted to the application on 20-Jul-2012. See "Attachment" for detailed information.

Recommendation:

The submitted information demonstrates that updated NIR methods are adequate.

2 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

Reference ID: 3162729

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/s/

BOGDAN KURTYKA
07/23/2012

PRASAD PERI
07/24/2012

ERIC P DUFFY
07/24/2012

[redacted] (b) (4) ® (tofacitinib) Tablets, 5 &10 mg

NDA 203214
Chemistry, Manufacturing, and Controls
Division Director's Summary Basis of Action

Applicant: Pfizer Inc.
445 Eastern Point Road
Groton, CT 06340

Indication: For the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs. The recommended starting dose of the drug is 5 mg two times a day taking orally and may increase to 10 mg two times a day for some patients.

Presentation: [redacted] (b) (4) ® Tablets are packaged in 60 and 180 count HDPE bottles.

EER Status:	Recommendations:	**Pending as of July 2, 2012.**
Consults:	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation –	See assessment by John Kauffman of St. Louis Lab on the [redacted] (b) (4) and [redacted] (b) (4)
	DMETS-	Acceptable
	Biopharm–	Acceptable
	Microbiology –	Acceptable
	Pharm/toxicology –	Acceptable

Background: This drug development has progressed since late 2004 when Pfizer submitted their IND for rheumatoid arthritis. Note this same active has been studied for multiple indications such as immunosuppressive agent for development in human transplantation [redacted] (b) (4) treatment of Crohn's disease [redacted] (b) (4) for treatment of chronic plaque psoriasis [redacted] (b) (4) [redacted] (b) (4) for treatment of ulcerative colitis [redacted] (b) (4) and for treatment of dry eye [redacted] (b) (4)

The drug substance and drug product are developed using a Quality by Design (QbD) Strategy for better assurance of quality from a manufacturer and patient perspective. A CMC only EoP2 meeting was held with Pfizer on March 7, 2011 where several aspects of the control strategy for Identity, Assay (potency), Real Time Release Testing, Content Uniformity, and Disintegration were discussed.

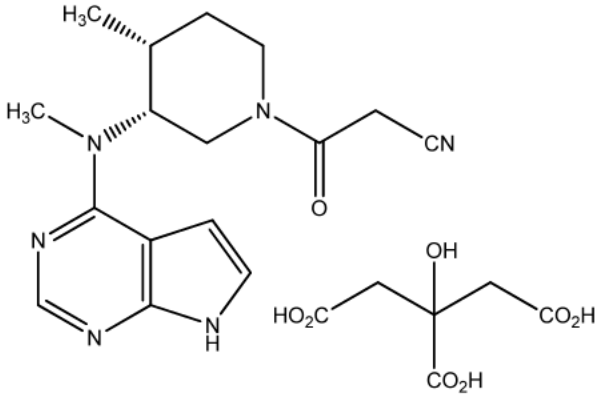
The CMC part of the NDA is in a pilot program with parallel reviews between FDA and European Medicinal Agency (EMA). There have been extensive discussions between the two agencies on major CMC issues particularly in Quality by Design (QbD) areas. Some of the comments and approaches were harmonized between the two agencies. Due to the differences in

Reference ID: 3154370

regulations and precedents some of the comments and approaches have not been harmonized.

Drug Substance:

The drug substance tofacitinib citrate (CP-690,550-10) is a white to off-white crystalline (b) (4) that is (b) (4) and it is non hygroscopic. Tofacitinib citrate is highly soluble as per the Biopharmaceutics Classification System and the applicant indicates that it has low permeability (BCS class 3). The structure of tofacitinib citrate includes an arylamine function, which is a structural alert for potential mutagenicity. The firm performed a series of genetox tests which were negative, as well as QSAR analysis which was also negative. Note that the impurities also have the same structural alert for mutagenicity, and are therefore by extension negative for mutagenicity. The drug substance is not photosensitive and the stability data provided supports both the proposed retest period of (b) (4), as well as the post-approval stability protocol proposed.



tofacitinib citrate

3-((3*R*,4*R*)-4-methyl-3-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile, 2-hydroxypropane-1,2,3-tricarboxylic acid

Molecular Formula: $C_{16}H_{20}N_6O \cdot C_6H_8O_7$ (citrate salt)
Molecular Weight: 504.50 g/mol (312.37 g/mole for free base)

The applicant has also followed Quality by Design (QbD) principles in their development of the manufacturing process for the drug substance and the method that will be used for the determination of drug substance assay and impurities. These approaches included the use of risk-based assessment to identify drug substance quality attributes and process parameters that had potential to impact drug product safety and efficacy. Critical quality attributes (CQAs) of the drug substance were identified and process parameters were categorized as critical or non-critical (CPPs or NCPPs). The applicant performed multivariate experiments and modeled output data to establish links between synthesis process parameters and the quality attributes of intermediates and the final drug substance. In this way they defined the acceptance criteria for the material attributes of the synthesis materials (starting materials, reagents, etc.) and "operational boundaries" for process parameters, optimizing the process and providing greater assurance of the

Reference ID: 3154370

production of acceptable drug substance. In conjunction with these studies the applicant gained an understanding of the fate of, and process parameters that affected the synthetic impurities in the drug substance. Overall, the applicant has presented additional information and data demonstrating enhanced process understanding of the drug substance synthesis process (b) (4) (b) (4) (b) (4) The Agency is also still developing regulatory standards for using QbD approaches for analytical methods and is not taking any regulatory action with respect to the proposed (b) (4), which has been acknowledged by Pfizer.

The final drug substance specifications include the following parameters: Description, Identity (IR, LC), Particle Size, Assay, Counter Ion, Impurities, Residue on Ignition, Heavy Metals, Residual Solvents, and Water Content.

Drug substance retest period is (b) (4).

The drug substance is manufactured at Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland (GMPs acceptable based upon profile). The drug substance is packaged in (b) (4) (b) (4)

Drug Substance: Satisfactory

Drug Product:

Tofacitinib Citrate is formulated as film-coated round immediate release tablets available in two strengths, 5 mg and 10 mg (based on the equivalent amount of Tofacitinib base). The 5 mg tablets are white to off-white, film-coated, round tablets debossed with "Pfizer" on one side and "JKI5" on the other side. (b) (4)

(b) (4) Risk assessment and quality by design (QbD) approaches have been utilized for formulation and manufacturing process development. (b) (4), tablet content uniformity is defined as a critical quality attribute (CQA) and drug substance particle size is defined as a critical quality attribute (CQA). The acceptance criteria for the drug substance particle size distribution have been discussed extensively during the review cycle and were found acceptable. Comprehensive pharmaceutical development information is provided in the submission. Design space for the process parameters has been established through risk

Reference ID: 3154370

assessment, design of experiments, prior knowledge and modeling.

Real time release tests of identification, assay and dosage content uniformity by NIR have been proposed for the drug product. This is a relatively novel approach and has only been used in a few recently approved products. Comprehensive model development and validation information (for the proposed analytical methods) have been submitted in the application which were reviewed in depth. The methods have been deemed adequate for their intended purposes. In conjunction with the NIR method, a large sample size and its associated acceptance criteria have been proposed for the dose content uniformity test at release. The same acceptance criteria have been accepted for other drug products. The proposed acceptance criteria for dose content uniformity using the large n sample size have been deemed acceptable at this point.

The final drug product specifications include the following parameters: Appearance, Identity (NIR or UV, LC), Assay (NIR or LC at release and HPLC on stability), Uniformity of Dosage Units (NIR or LC at release and HPLC on stability), Individual Specified Degradation Products, Individual Unspecified Degradation Products, Total Degradation Products, Disintegration, (b) (4). Note that the disintegration specification was negotiated (b) (4)

The drug product is packed in high-density polyethylene (HDPE) bottles with desiccant and closures with induction seal liners. (b) (4)

The Drug Product is manufactured and packaged in Frieburg, Germany and is also being packaged in Puerto Rico. On the PAI inspection of the Frieburg facility it was noted that a change was made to the NIR calibration model following instrumentation malfunction. The change is considered potentially significant. Pfizer will be asked for information supporting the adequacy of the revised model, with re-validation. Review will be the subject of an addendum to the CMC review.

The submitted drug product stability data include 12 months at the long term storage condition of 25°C/60%RH and 6 month at the accelerated storage condition of 40°C/75%RH for 3 batches of each strength. The stability data support the proposed 24 month shelf life for the drug product when stored at the proposed 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

Drug Product: Satisfactory.

Overall Conclusion:
From a CMC perspective, the application is recommended for approval pending an acceptable recommendation from the Office of Compliance. Finalized labels are not yet provided and hence not included in this review.

Reference ID: 3154370

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/s/

ERIC P DUFFY
07/03/2012

CHEMISTRY REVIEW

NDA 203214

(b) (4) ® (tofacitinib) Tablets, 5 &10 mg

Pfizer Inc.

Craig M. Bertha, Ph.D.
Donghao (Robert) Lu, Ph.D.
Ying Wang, Ph.D.
Bogdan Kurtyka, Ph.D.

ONDQA/DNDQA III/Branch VIII, DNDQA II/Branch IV, and DNDQA I/Branch I
for
Division of Pulmonary, Allergy, and Rheumatology Products

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Reference ID: 3151040

Chemistry Review Data Sheet

1. NDA 203214

2. REVIEW #: 1

3. REVIEW DATE: 26-JUN-2012

4. REVIEWERS: Craig M. Bertha, Ph.D. (drug substance)
Donghao (Robert) Lu, Ph.D. ([redacted] (b) (4) for drug substance impurities method)
Ying Wang, Ph.D. (drug product)
Bogdan Kurtyka, Ph.D. (near infrared methodology)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	21-OCT-2011 (assigned 31-OCT-2011)
Amendment	13-JAN-2012 (response to 74-day letter)
Amendment	30-APR-2012 (response to 16-MAR-2012 information request)
Amendment	11-JUN-2012 (response to 1-JUN-2012 information request)

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Inc.
Address:	445 Eastern Point Road Groton, CT 06340
Representative:	Nickie V. Kilgore, DVM, Director Worldwide Regulatory Strategy
Telephone:	(860)-441-5030

Reference ID: 3151040

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4) ® (proposed)
b) Non-Proprietary Name (USAN): tofacitinib citrate
c) Code Name/# (ONDQA only): CP-690,550-10
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Janus-associated kinase (JAK) inhibitor for treatment of rheumatoid arthritis

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 5 & 10 mg tofacitinib (8 & (b) (4) tofacitinib citrate, respectively)/tablet; taken BID

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

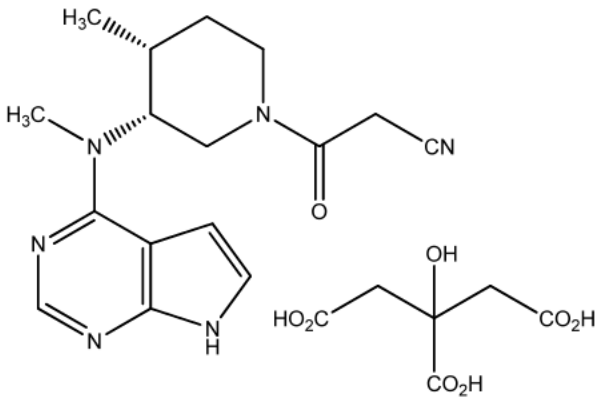
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

3-((3*R*,4*R*)-4-methyl-3-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile, 2-hydroxypropane-1,2,3-tricarboxylic acid

Molecular Formula: $C_{16}H_{20}N_6O \cdot C_6H_8O_7$ (citrate salt)
Molecular Weight: 504.50 g/mol (312.37 g/mole for free base)

Reference ID: 3151040

Chemistry Review Data Sheet



tofacitinib citrate

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	3		(b) (4)	4	Adequate	See NDA review	
	4			4	Adequate	See NDA review	
	3			4	Adequate	See NDA review	
	3			4	Adequate	See NDA review	
	3			4	Adequate	See NDA review	
	3			3	Adequate	June 16, 2011	Reviewed by Dr. George Lunn
	3			4	Adequate	See NDA review	
	3			4	Adequate	See NDA review	
	3						
	3			4	Adequate	See NDA review	

[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

Reference ID: 3151040

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:
N/A

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	70903	Pfizer Inc.	Tofacitinib (CP-690,550-10) for treatment of rheumatoid arthritis
(b) (4)			

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES		02-NOV-2011	Pending	
Pharm/Tox	Drug substance and degradant related impurities	22-NOV-2011	Final/L. Leshin, Ph.D.	See evaluation of 30-APR-2012, amendment, comment 11
LNC	N/A			
Methods Validation	Assessment of drug substance assay/ID/impurities method TM-0986A	20-JAN-2012	Final/Michael Trehy	The method was found to be suitable for regulatory purposes (b) (4)
OSE/DMEPA	N/A			
EA	Categorical exclusion		See NDA review	Acceptable
Microbiology	N/A			

The Chemistry Review for NDA 203214

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This drug product is recommended for approval from Chemistry, Manufacturing, and Control (CMC) perspective pending overall acceptable recommendation from the Office of Compliance.

The 24 month shelf life for the drug product when stored at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F), is proposed and granted.

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)

(1) Drug Substance

The drug substance tofacitinib citrate (CP-690,550-10) is a white to off-white crystalline (b) (4) that is (b) (4) and it is not hygroscopic. Tofacitinib citrate is highly soluble as per the Biopharmaceutics Classification System and the applicant indicates that it has low permeability (BCS class 3). The structure of tofacitinib citrate includes an arylamine function, which is a structural alert for mutagenicity. The drug substance is not photosensitive and the stability data provided supports both the proposed retest period of (b) (4), as well as the post-approval stability protocol proposed.

The applicant has also followed Quality by Design (QbD) principles in their development of the manufacturing process for the drug substance and the method that will be used for the determination of drug substance assay and impurities. These approaches included the use of risk-based assessment to identify drug substance quality attributes and process parameters that had potential to impact drug product safety and efficacy. Critical quality attributes (CQAs) of the drug substance were identified and process parameters were categorized as critical or non-critical (CPPs or NCPPs). The applicant performed multivariate experiments and modeled output data to establish links between synthesis

Reference ID: 3151040

process parameters and the quality attributes of intermediates and the final drug substance. In this way they defined the acceptance criteria for the material attributes of the synthesis materials (starting materials, reagents, etc.) and "operational boundaries" for process parameters, optimizing the process and providing greater assurance of the production of acceptable drug substance. In conjunction with these studies the applicant gained an understanding of the fate of and process parameters that affected the synthetic impurities in the drug substance. Overall, the applicant has presented additional information and data demonstrating enhanced process understanding of the drug substance synthesis process. (b) (4) (b) (4) (b) (4) The Agency is also still developing regulatory standards for using QbD approaches for analytical methods and is not taking any regulatory action with respect to the proposed (b) (4) which has been acknowledged by Pfizer.

The drug substance is manufactured in Pfizer Ireland Pharmaceuticals, Ringaskiddy, Ireland. The drug substance is packaged in (b) (4) and retest period of (b) (4) is supported.

(2) Drug Product

The drug product immediate release tofacitinib tablets are formulated as film-coated round tablet. Two strengths, 5 mg and 10 mg, are proposed for commercialization. The strengths of the drug products are based on the equivalent amount of tofacitinib. The 5 mg tablets are white to off-white, film-coated, round tablets debossed with "Pfizer" on one side and "JKI5" on the other side. (b) (4)

The tablets are manufactured with (b) (4) Risk assessment and quality by design (QbD) approaches have been utilized for formulation and manufacturing process development. Due to the (b) (4), tablet content uniformity is defined as a critical quality attribute (CQA) and drug substance particle size is defined as a critical quality attribute (CQA). The acceptance criteria for the drug substance particle size distribution have been discussed extensively during the review cycle. Comprehensive pharmaceutical development information is provided in the submission. Design space for the process parameters has been established through risk assessment, design of experiment, prior knowledge and modeling.

Reference ID: 3151040

Real time release tests of identification, assay and dosage content uniformity by NIR have been proposed for the drug product. This is a relatively novel approach and has been only used in a few recently approved products. Comprehensive model development and validation information (for the proposed analytical methods) have been submitted in the application which were reviewed in depth. The methods have been deemed adequate for its intended purpose. In conjunction with the NIR method, a large sample size and its associated acceptance criteria have been proposed for dose content uniformity test at release. The same acceptance criteria have been accepted for other drug products recently approved. The proposed acceptance criteria for dose content uniformity using the large sample size have been deemed acceptable at this point.

The drug product is packed in high-density polyethylene (HDPE) bottles with desiccant and closures with induction seal liners.

The Drug Product is manufactured and packaged in Frieburg, Germany and is also being packaged in Puerto Rico.

The submitted drug product stability data include 12 months at long term storage condition of 25°C/60%RH and 6 month accelerated storage condition of 40°C/75%RH for 3 batches of each strength. The stability data supports the proposed 24 month shelf life for the drug product when stored at the proposed 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F).

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

The drug product is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs.

The recommended starting dose of the drug is 5 mg two times a day taking orally and [redacted] (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The CMC part of the NDA is in a pilot program with parallel reviews between FDA and European Medicinal Agency (EMA). There have been extensive discussions between the two agencies on some of the CMC issues particularly in quality by design (QbD) areas. Some of the comments and approaches were harmonized between the two agencies. Due to the differences in regulations and precedents some of the comments and approaches have not been harmonized.

The original proposed acceptance criteria for each identified degradant and total impurities in the drug product were [redacted] (b) (4) the actual batch data (including clinical and stability data) supported. These acceptance criteria have been negotiated during the review cycle and have [redacted] (b) (4) to adequate ranges.

Reference ID: 3151040

The drug substance and drug product are very stable and the quality and purity are well controlled. The manufacturing processes were well developed and adequately controlled.

Based on the comprehensive information provided by the applicant in the NDA, ONDQA recommends approval pending an acceptable EES status.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D.
Bogdan Kurtyka, Ph.D.
Donghao (Robert) Lu, Ph.D.
Ying Wang, Ph.D.
Prasad Peri, Ph.D., Branch Chief
Eric Duffy, Ph.D., Division Director

C. CC Block

OND/DPARP/NNikilov
OCP/DCPII/LJain
OND/DPARP/LLeshin
OB/DBIII/YKim
OND/DPARP/PBowen
ONDQA/DHenry
OCP/DCPII/LJain
ONDQA/Biopharm/JDuan
ONDQA/DNDQA3/ASchroeder
ONDQA/DnDQA3/EDuffy

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/s/

DON L HENRY
06/26/2012

CRAIG M BERTHA
06/26/2012

DONGHAO R LU
06/26/2012

YING WANG
06/26/2012

BOGDAN KURTYKA
06/26/2012

PRASAD PERI
06/26/2012
I concur

ERIC P DUFFY
06/26/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
Telephone (314) 539-3815
FAX (314) 539-2113

Date: May 16, 2012

To: Craig M. Bertha, CMC Reviewer, ONDQA

Through: B.J.Westenberger, Deputy Director, Division of Pharmaceutical Analysis

From: Michael Trehy, Chemist, Division of Pharmaceutical Analysis

Subject: Method Validation for NDA 203-214
(b) (4) (tofacitinib) tablets, 5 & 10 mg
Pfizer Inc.

The following method was evaluated and is acceptable for quality control and regulatory purposes:

TM-01-0986A-01 approval date 30 Aug 2011 "Identity, assay, and purity evaluation of CP-690,550-10 drug substance by reversed-phase liquid chromatography"

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the method.

1. The method version evaluated for use for quality control and regulatory purposes was the current version TM-01-0986A-01 which is significantly changed from version TM-01-0986A originally submitted. The significant changes are removal of the instrumental ranges for which the method could be used and the procedure for calculating the assay value. Since the ranges were removed only the method as specified in the current method was evaluated for quality control and regulatory purposes.

2. Identification (LC) in method specifications has acceptance criteria of "Retention time conforms to that of the reference standard". Typically a range of acceptable relative retention times is given in the specification such as from 0.98 to 1.02 relative to the standard. Simply stating retention time conforms to that of the reference standard is ambiguous.

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/s/

MICHAEL L TREHY
05/21/2012

BENJAMIN J WESTENBERGER
05/22/2012

Date: March 29, 2012

To: Extended Tofacitinib (NDA 203214) Review Team

From: Ying Wang, Ph.D. (301-796-1479, ying.wang@fda.hhs.gov) and Bogdan Kurtyka, Ph.D. (301-796-1431, Bogdan.kurtyka@fda.hhs.gov)

Subject: CMC Considerations for upcoming Pre-Approval Inspection (PAI) at Drug Product Manufacturing Site of Pfizer Deutschland

Tofacitinib (CP-690,550-10) is formulated as an immediate-release tablet for oral administration at 5 and 10 mg strengths. The 5 mg and 10 mg tablets are packaged in high density polyethylene (HDPE) bottles containing desiccant, with induction seal, (b) (4)

The tablets are manufactured with (b) (4)

The formulation and process development of CP-690,550-10 has focused on the quality attributes, which are derived from the drug product profile.

Flow diagram of drug product manufacturing process for 5 mg tablets is listed below (b) (4):

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/s/

YING WANG
03/30/2012

BOGDAN KURTYKA
03/30/2012

PRASAD PERI
03/30/2012

ONDQA Review for
OND Division of Pulmonary Allergy and Rheumatology Products
Initial Quality Assessment
Date: December 14, 2011

NDA: 203214
Drug name: tofacitinib citrate
Applicant: Pfizer Inc.
Stamp Date: October 21, 2011
PDUFA Date: August 21, 2012
ONDQA 5 month date: March 21, 2012
Proposed Proprietary Name: (b) (4) Tablets
Established Name: tofacitinib citrate
Dosage form and strength: 10 mg tablets
Route of Administration: oral
Indications: CMC Lead: Alan C. Schroeder, Ph.D. /DNDQA III/ONDQA
Filability recommendation: fileable
Review team recommendation: Craig Bertha (drug substance) and Ying Wang (drug product)
Recommended briefing level: ONDQA
Time goals:

- Initial Quality Assessment in DFS: draft prior to filing meeting
- Filing/planning meeting: December 2, 2011
- Filing date: December 20, 2011
- Filing letter "Day 74": January 3, 2012
- **Chemistry Review (DR/IR) letter:** by January 21, 2011 (90 day target for the draft CMC review for this FDA/EMA pilot review)
- Mid-cycle meeting "Month 5": March 20, 2012
- Wrap Up meeting: June 18, 2012
- **Final Chemistry Review "Month 8" in DFS:** June 21, 2012
- PDUFA: August 21, 2012

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm	Dr. John Duan is the assigned reviewer for biopharmaceutics aspects of this NDA.
CDRH	N.A.
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on November 2, 2011.
DMETS	Labeling consult request will be sent as part of DPARP's request.
Methods Validation	Methods validation for non-compendial methods will be requested of FDA laboratories for at least one method since this is an NME and a QbD application
Microbiology	N.A.
Pharm/Tox	DS and DP impurities/degradants to be evaluated for safety.

Background:

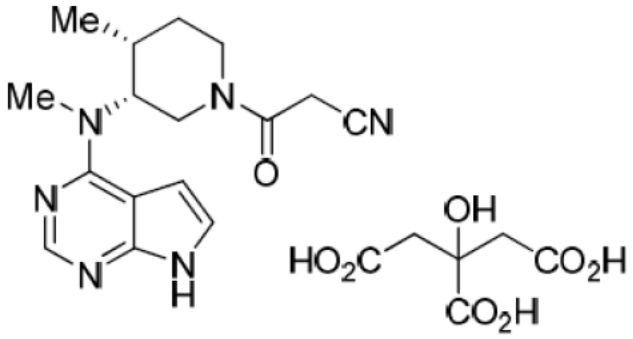
This is a NDA for a product which was developed using principles of Quality by Design. This includes both drug substance and drug product manufacturing process, and it includes the development of analytical methods. The development information is provided in sections 2.3.P.2 and 3.2.P.2 for the drug product, and 2.3.S.2 and 3.2.S.2.6 for the drug substance. The analytical method development approach is summarized in the QOS introduction and in QOS section 2.3.S.4.3.

Drug substance

The drug substance is a new molecular entity (NME).

Structure and related information (from Section 2.3.S.1):

Figure 2.3.S.1-1. CP-690,550-10 Structure



Molecular Formula: $C_{16}H_{20}N_6O \cdot C_6H_8O_7$ (citrate salt)

Molecular Weight: 504.49 Daltons (citrate salt)

"[redacted] (b) (4)

(b) (4)

[redacted]

Filing Review:

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?	these are review issues		Note that CMC does not seem to have been discussed at the pNDA meeting according to DPARP's minutes of that meeting. There was a separate EOP2 CMC meeting on March 7, 2011. Pfizer responded to the Agency's questions. They agreed to provide data to assure a consistent drug substance impurity profile despite potential differences in (b) (4) impurity profiles. They indicated that they would use a (b) (4) range in the NDA for NIR Real Time Release testing of the drug product. The Agency asked that Pfizer consider validation of the NIR method over the design space and provide justification of calibration parameters. The Agency asked for a brief description or clarification of Standard Operating Procedures, e.g. when HPLC is used to release a batch after NIR results are OOS. Content uniformity specifications were discussed using a two one-sided parameteric tolerance interval approach; the Agency requested that 98% coverage, and 90% confidence level two one-sided parametric tolerance interval. The proposed large sample size should be pre-specified. A disintegration method is proposed for the drug product: the Agency asked for adequate dissolution data in a full development report to support this approach. Adequate data should be provided to support the dissolution method used to obtain dissolution profiles. Data are to be provided in the NDA to demonstrate that dissolution is not affected by the critical manufacturing variables tests. Pfizer agreed to submit 12 months of stability data (including dissolution). Pfizer agrees to provide NDA data to demonstrate that disintegration is (b) (4) equivalent throughout the design space. Disintegration will be monitored under Pfizer's quality system to evaluate the effects of process or raw material changes. The Agency agreed with Pfizer's proposal to submit disintegration data from 25 batches of drug product.

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**

5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		See attachment to form FDA 356h
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.**			Not relevant.
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		Full street addresses are not provided, but CFN/FEI numbers correspond to data in the FDA EES. The reviewer may request e-mail information for the site contacts as it is not provided.

8.	Are drug product manufacturing sites are 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		Full street addresses are not provided, but CFN/FEI numbers correspond to data in the FDA EES. The reviewer may request e-mail information for the site contacts as it is not provided.
9.	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: • 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)			Not applicable
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		x	Not found. This may not be necessary as the facilities may be acceptable based on file review. One site already has an AC OC recommendation and the other two sites have AC district office recommendations

* 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		Section 1.12.14 provides a categorical exclusion claim and states that to their knowledge, no extraordinary circumstances exist.

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	In Section 3.2.S.2.4, the applicant states that based on their evaluation of "intermediate material attributes with the potential to affect drug substance quality…there are no critical steps or critical intermediate material attributes identified in the manufacture of CP-690,550-10 [drug substance]." **The reviewer should confirm this.** Critical starting material attributes are indicated to be discussed in Section 3.2.S.2.3.
14.	Does the section contain information regarding the characterization of the DS?	x		Yes. The structure was elucidated using IR spectroscopy, mass spectrometry, 1H and 13C NMR. Interpreted spectra are provided. The structure was confirmed with a single crystal x-ray structure determination which also determined the absolute stereochemistry. A UV spectrum is provided as is the optical rotation. Other characteristics were investigated (e.g., polymorphism, solubility, ionization constant, hygroscopicity, octanol/water partition coefficient, etc.)
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		A retest period of (b) (4) is proposed
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	This has not been found in the NDA.

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	"No critical steps or intermediates have been identified within the ranges studied during development." There are no analytical procedures for in-process tests. (3.2.P.3.4) This is a review issue.
21.	Is there a batch production record and a proposed master batch record?			Executed batch records are provided for the drug product, one for each strength, but master batch records are not listed in section 3.2.R. This is a review issue. The executed batch records appear to have at least a few pages without English translation but this may not be a significant issue.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		There are some differences between investigational drug product formulations used in the clinical studies, and the intended commercial tablet formulation. The applicant states that (b) (4) [redacted] Phase 3 tablets were film coated [5 mg tablet] and the commercial tablets will be film coated (b) (4) [redacted]
23.	Have any biowaivers been requested?	x		(b) (4) [redacted] 5 mg commercial film coated tablets.
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		A 24 month expiry period has been proposed based upon 12 months of stability data for 6 batches of 5 mg and 10 mg tablets packed in HDPE bottles with desiccant (b) (4) . Graphical and tabular summaries of the stability data are provided. It is claimed that there are no trends in assay, degradation products, or chiral purity values therefore no statistical analysis was performed. Likewise no trends are claimed in stability for dissolution. (b) (4), disintegration
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		NIR for identification, content uniformity and assay of tablet cores of 5 mg and 10 mg tablets. Real Time Release testing for content uniformity is proposed.

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		Section 3.2.R.2

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Not applicable

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?			Not applicable. There is no DMF for drug substance.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
See earlier in this review for this information. LOAs are provided.					

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.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}

Alan C. Schroeder, Ph.D.
CMC Lead
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

Date

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: ____x___Yes; _____No Review date:
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No__x____ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?
4) Is the nanomaterial a reformulation of a previously approved product? Yes No
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____ API_____; Other_____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble **(**e.g., gold nanoparticle**)** in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____(Complete 8); No_____ (go to 9).
8) What is the reported particle size? Mean particle size_____ ; Size range distribution_____; Other_____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial?_____ _____

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/s/

ALAN C SCHROEDER
12/15/2011

PRASAD PERI
12/15/2011
I concur