

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203491Orig1s000

CHEMISTRY REVIEW(S)

Addendum#1 to Memo in lieu of Product Quality Memo

The previously filed (DARRTS 10/11/12) Memo contained attachments that could not be opened after processing in DARRTS, therefore, this addendum is being filed in which the information in the attachments is added to this memo as Appendixes 1-4.

APPEARS THIS WAY ON ORIGINAL.

Memo in lieu of Product Quality Memo

NDA# 203491

Drug Name: Nepafenac Ophthalmic Suspension, 0.3%

Applicant: Alcon Research, Ltd.

Usually if an NDA contains information regarding Quality by Design (QBD), a Product Quality Memo (PQM) is prepared and then communicated to the Division of Manufacturing and Product Quality (OC). The inspection of the drug product manufacturing facility (Alcon, Forth Worth, TX) was scheduled much sooner than the usual because OC decided to combine the PAI of this NDA with other NDAs. Therefore, there was not enough time to prepare the PQM. Here is the e-mail communication regarding this issue:

From: Li, Zhong
Sent: Friday, March 09, 2012 1:16 PM
To: Kambhampati, Rao V
Cc: Gorski, Lori M
Subject: Knowledge Transfer for NDA-203491

Rao,

As we discussed, there is a pending pre-approval inspection at ALCON LABORATORIES INC (FEI: 1610287) in support of NDA-203491 during the week of March 19, 2012. We'd like to provide the investigator with any manufacturing and laboratory issues found during application review. Please send me any concerns you may have regarding this application that could be covered on the upcoming inspection by **COB March 14, 2012**.

We may issue a memo to the district or have a tele-con briefing with the investigator to communicate our findings prior to the start of the inspection.

Thank you for your help,
Zhong

From: Kambhampati, Rao V
Sent: Friday, March 09, 2012 1:55 PM
To: Madurawe, Rapti
Cc: Cruz, Celia; Cuff, Althea; Shanmugam, Balajee; Li, Zhong
Subject: FW: Knowledge Transfer for NDA-203491

Rapti,

Surprisingly the inspection of Alcon facility will be conducted in the week of 3/19/12. Since there is not adequate time for writing detailed memos, myself and Steve Donald (product microbiology reviewer) will be sending QBD comments to Li Zhong by 3/14/12. Li will convey all the comments to the investigator before 3/19/12.

Rao

On 3/13/12, the following comments related to QBD were conveyed to Zhong Li, Ph.D. (DMPQ, OC) and others by Celia Cruz, Ph.D. (DNDQA II QBD Liaison):

Dear all

Here are my thoughts regarding the considerations for inspection for NDA 203491. Luckily, the applicant has completed a FMEA on the control strategy for NDA 203491. In this FMEA, they rate impact, severity and detectability of failure modes of key or critical process parameters against current site controls. The determination of the parameters as critical and the proposed set ranges are part of the long QbD development process and are a review issue, which should not impact the imminent inspection. However, the adequacy of the proposed control strategy and the monitoring of certain operating ranges are worthwhile to communicate.

Please refer to the attached technical report in 3.2.P.3.3, document TDOC-0014813 titled "Summary of Key Process Variables and Control Strategy (QbD) for the Manufacture of Nepafenac Ophthalmic Suspension 0.3% (FID 115535). In particular, the FMEA tables are most useful for determining Product Quality Manufacturing Memo risks (pages 11 to 16, Table 4.2), though the entire document is a summary of the proposed control strategy (all raw materials, process, and equipment controls).

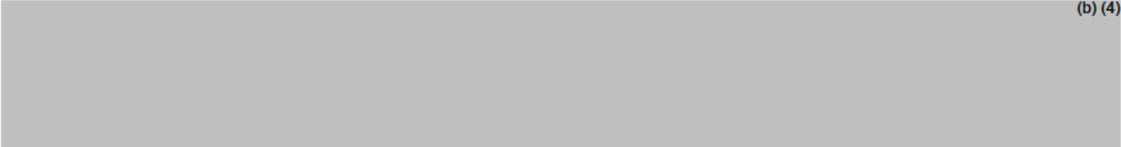


manuf-process-and
-controls-1.p...

(see Appendix 1 for this document)

- The parameters that are stated as fixed and refer back to a CoA, or the Master Batch Record (Table 4.1) are in general low risk for inspection, as long as there are adequate batch record controls at the site.

-  (b) (4)

-  (b) (4)

Therefore, based on this and on my reading of the development and manufacturing sections, I would suggest the following considerations for inspection:

 (b) (4)

Finally,

I will be sending a separate document on the review items for QbD, but I hope this email helps the inspection efforts on such short notice.

Thanks,
Celia

On 3/15/2012, the following QBD related comments and the Alcon Technical Document were communicated to Dr. Li and others by Rao Kambhampati, Ph.D. (DNDQA II):



(See Appendix 2 for this document)

203491 Rao
Comments regarding .



(See Appendix 3 for this document)

Attachment1 -
Alcon Technical ...

On 3/12/12, Steven Donald, Ph.D. (Product Quality Microbiologist, OPS) communicated the following document containing comments to Dr. Li and others:



(See Appendix 4 for this document)

N203491QbdMemo.
doc (41 KB)

On the basis of the above comments and information and after his own evaluation of the NDA, Dr. Li prepared a Knowledge Transfer Memo (KTM) and communicated to the DAL-DO.

Conclusion: Even though there was not adequate time for the preparation of PQM, the QBD information in the NDA was reviewed by Drs Kambhampati, Cruz, and Donaldson and the comments and recommendations were communicated to Dr. Li for the preparation of KTM.

61 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

RAO V KAMBHAMPATI
10/12/2012

NDA 203491**Nepafenac Ophthalmic Suspension, 0.3%****Applicant: Alcon Research, Ltd.****Addendum#2 to Chemistry Review #1****Rao V. Kambhampati, Ph.D.****For Division of Transplant and Ophthalmology Products
(DTOP)**

Addendum#2 to Chemistry Review#1

1. NDA# **203491**
2. REVIEW #: Addendum#2 to Chemistry Review#1
3. REVIEW DATE: 10/10/2012
4. REVIEWER: Rao V. Kambhampati, Ph.D.

6. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|----------------------------------|----------------------|
| Chemistry Review# 1 | 9/5/2012 |
| Addendum#1 to Chemistry Review#1 | 9/19/12 |

6. SUBMISSION(S) BEING REVIEWED:

| Submissions Reviewed | Document (Letter) Date |
|-----------------------------|-------------------------------|
| N203491 Original SN-0000 | 12/15/2011 |
| N203491 Amendment SN-008 | 7/17/2012 |
| N203491 Amendment SN-009 | 7/25/2012 |
| N203491 Amendment SN-010 | 7/27/2012 |
| N203491 Amendment SN-011 | 8/20/2012 |
| N203491 Amendment SN-012 | 8/30//2012 |
| N203491 Amendment SN-013 | 9/7/2012 |
| N203491 Amendment SN-014 | 9/10/2012 |
| N203491 Amendment SN-015 | 9/12/2012 |

M. NAME & ADDRESS OF APPLICANT:

Name: Alcon Research, Ltd.
Address: 6201 South Freeway
Fort Worth, TX 76134-2099
Representative: N/A
Telephone: 817-551-8568

Chemistry Review Data Sheet

NDA 203491

M. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
b) Non-Proprietary Name (USAN): Nepafenac ophthalmic suspension, 0.3%
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA (CDA, 21 CFR 314.50), 505 (b)(1)

10. PHARMACOL. CATEGORY: Topical ocular anti-inflammatory and analgesic

11. DOSAGE FORM: Ophthalmic suspension

12. STRENGTH/POTENCY: 0.3%

13. ROUTE OF ADMINISTRATION: Topical (ocular)

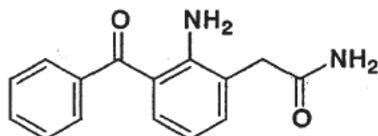
14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

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

2-Amino-3-benzoylbenzeneacetamide

or

2-(2-Amino-3-benzoylphenyl)acetamide

 $C_{15}H_{14}N_2O_2$
254.28

17. RELATED/SUPPORTING DOCUMENTS:

M. DMFs:

| DMF # | TYP E | HOLDER | ITEM REFEREN CED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETE D | COMMENTS |
|---------|-------|---------|------------------|-------------------|---------------------|------------------------------------|------------------------------------|
| (b) (4) | II | (b) (4) | (b) (4) | 1 | Adequate | 7/27/12 | Reviewed by Rao Kambhampati, Ph.D. |
| | II | | 1 | Adequate | 7/27/12 | Reviewed by Rao Kambhampati, Ph.D. | |
| | III | | 4 | | | | |
| | III | | 4 | | | | |
| | I | | 2 | | | | |
| | I | | 2 | | | | |

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:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|---|
| NDA | 21-862 | NEVANAC® (Nepafenac Ophthalmic Suspension, 0.1%), Approved 8/19/2005, Applicant: Alcon Pharmaceuticals Ltd. |

M. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|------------------------|------------------|------------------------|
| EES | Acceptable | 4/23/12 | M. Stock (HFD-324, OC) |
| Clinical Pharmacology Studies | Acceptable | 8/28/12 | Y. Zhang, Ph.D. (DCP4) |
| ONDQA Biopharm | Biowaiver not required | 9/14/12 (DARRTS) | Tapash Ghosh, Ph.D. |
| LNC (ONDQA) | Not applicable | 7/31/12 | Rao Kambhampati, Ph.D. |
| Methods Validation | Not applicable | 7/31/12 | Rao Kambhampati, Ph.D. |
| DMEPA (Labels and Labeling) | Pending | 9/5/12 | Jung E. Lee, R.Ph. |
| EA | Acceptable | 7/31/12 | Rao Kambhampati, PhD |
| Product Quality Microbiology | Acceptable | 5/25/12 | Steven Donald, MS |

19. ORDER OF REVIEW (OGD Only): N/A

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The proposed labeling and labels have adequate information as required. The tradename for the drug product is pending but DTOP decided to take action without a tradename. The applicant will submit revised labeling and labels with a tradename after the NDA action. The inspection of the manufacturing and testing facilities was complete and the Office of Compliance issued an Overall Acceptable Recommendation for this NDA. From the CMC perspective, this NDA is recommended for approval.

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

Not applicable.

II. Summary of Chemistry Assessments

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

Drug Substance:

The drug product contains nepafenac as the drug substance. Nepafenac was previously approved by the FDA for its use in NEVANAC[®] (nepafenac ophthalmic suspension, 0.1%) for the NDA# 21-862. The approved NEVANAC is also marketed by Alcon Research, Ltd., Fort Worth, TX. The applicant proposed the same drug substance manufacturers (b) (4) that are currently used for the manufacturing of NEVANAC and the CMC information for the drug substance was cross-referenced to the DMFs (b) (4) and (b) (4), respectively, which are currently adequate. In addition, some CMC information was also directly provided in the NDA.

Nepafenac drug substance is a yellow crystalline solid or powder with a melting point of 184°C to 184.9°C and it has a molecular formula of C₁₅H₁₄N₂O₂ and molecular weight of 254.28. It has a solubility of 0.014 mg/mL in water. It does not exhibit polymorphism. The manufacturing of the drug substance was cross-referenced to (b) (4) DMF# (b) (4) and (b) (4) DMF# (b) (4) and the applicant provided LOAs for the cross-reference of the information in those DMFs. Both the DMFs were previously reviewed by the ONDQA reviewers and were found to be adequate. Later, amendments and annual reports to those DMFs were submitted by the Holders, therefore, those DMFs were again reviewed by this reviewer and they are found to be adequate as of the date of this review.

Drug Product:

The drug product is nepafenac ophthalmic suspension, 0.3% and it is sterile, preserved, multi-dose aqueous suspension formulated for topical ophthalmic application. (b) (4)

Each 100 mL of the suspension contains 0.3 g (w/v) of nepafenac as the active ingredient and the following compendial grade (USP or NF) excipients: benzalkonium chloride (0.005 g; antimicrobial agent), carboxymethylcellulose sodium (b) (4), guar gum (b) (4), carbomer 974P (b) (4), boric acid (b) (4), edetate disodium (b) (4), propylene glycol (b) (4), sodium chloride (b) (4), sodium hydroxide and/or hydrochloric acid (QS for pH adjustment), and purified water (b) (4). The suspension is packaged in 4-mL size oval, LDPE Drop-Tainer[®] dispenser (bottle) with a LDPE dispensing plug and gray polypropylene cap filled with either 1.7 mL (for trade) or with 0.8 mL (for sample) of the suspension.

The drug product is manufactured by Alcon Laboratories Inc., Fort Worth, TX. The manufacturing process consists of (b) (4)

(b) (4) Key process variables and control strategy (QbD) were provided for the manufacture of the drug product. The specification for the drug product was finalized after negotiation with the reviewer and they are as follows: nepafenac identity (by TLC and HPLC), nepafenac assay (by HPLC: (b) (4)), impurities (b) (4), benzalkonium chloride identity, benzalkonium chloride assay (b) (4), edetate disodium identity, edetate disodium assay (b) (4), pH (b) (4), osmolality (b) (4), appearance of suspension (b) (4), redispersibility (b) (4), viscosity (b) (4), particle size distribution, endotoxin content (b) (4) and sterility (meets USP). Analytical method description was provided for all the methods and method validation was provided for non-compendial methods. Three production scale (b) (4) primary stability batches were produced in Alcon's ASPEX Manufacturing Facility using the above process. Adequate in-process controls are in place. After comment, 52 weeks (for trade size) and 39 weeks (for sample size) long-term stability data and statistical analysis of the data and 6 months accelerated stability data were provided. On the basis of this data, the applicant requested an expiration dating period of 18 months, which is acceptable. The post-approval stability commitment to place the commercial lots on stability is acceptable.

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

Nepafenac Ophthalmic Suspension, 0.3% is indicated for the treatment of pain and inflammation associated with cataract surgery. Each multi-dose trade bottle contains 1.8 mL of the suspension and each multi-dose sample bottle contains 0.8 mL of the suspension. One drop of Nepafenac Ophthalmic Suspension, 0.3% should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance is already in use in the lower strength (0.1%) formulation and it is manufactured and supplied by the same manufacturers for the proposed 0.3% formulation. Both the DMFs for the manufacturing of drug substance are adequate. The applicant provided adequate CMC information for the drug product manufacturing, controls, and testing. The manufacturing process is well controlled and demonstrated to produce a product that is consistent in quality and purity. All the facilities that are involved in the manufacturing and testing of the drug product are acceptable by the OC. The manufacturing process including sterilization process, which is found to be acceptable by the product quality microbiologist (OPS). The proposed packaging system (Drop-Tainer[®]) is already in the market and the gray cap color is consistent with AAO recommendation for NSAIDS. The established name is already in use, therefore, doesn't require a review. The tradename is pending and the clinical division decided to take action without a tradename. The package insert, commercial bottle and carton labels, and physician sample bottle, pouch, and carton labels contained all the required CMC related information. Per current ONDQA policy, analytical method validation by the FDA lab is not required. Adequate long-term and accelerated stability data and statistical analysis of the long-term data support the 18-month expiration dating period for the drug product when stored at 2°-25°C (36°F to 77°F) with protection from light. Per Tapash Ghosh's (ONDQA Biopharm Reviewer) review that was filed in DARRTS (9/14/12), a bio-waiver is not required for this drug product and he also agreed that an in-vitro drug release data are not necessary for this product.

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

Rao V. Kambhampati, Ph.D.

B. Endorsement Block

| | |
|--|----------|
| Primary Reviewer/Date: Rao V. Kambhampati, Ph.D. | 10/10/12 |
| Secondary Reviewer/Date: Rapti Madurawe, Ph.D. | 10/10/12 |

C. CC Block

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/s/

RAO V KAMBHAMPATI
10/11/2012

RAPTI D MADURawe
10/12/2012

NDA 203491
Chemistry Classification Code Correction

Drug Name: Tradename (nepafenac ophthalmic suspension), 0.3%

Related Document: Quality Review #1 of NDA 203491, filed in DARRTS on 9/13/2012

In the Quality Review #1 of the NDA 203491 which was filed in DARRTS on 9/13/12, it was inadvertently stated that the chemistry classification code for the drug as Type 3. According to the recently issued Drug Application MAPP 7500.3 dated 9/19/12, the actual chemistry classification code should be Type 5.

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/s/

RAO V KAMBHAMPATI
09/19/2012

RAPTI D MADURawe
09/19/2012

NDA 203491

Nepafenac Ophthalmic Suspension, 0.3%

Applicant: Alcon Research, Ltd.

Rao V. Kambhampati, Ph.D.

**For Division of Transplant and Ophthalmology Products
(DTOP)**

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Chemistry Review Data Sheet

1. NDA# **203491**
2. REVIEW #: 1
3. REVIEW DATE: 09-5-2012 (draft date 07-31-2012)
4. REVIEWER: Rao V. Kambhampati, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed

N203491 Original SN-0000

N203491 Amendment SN-001

N203491 Amendment SN-002

N203491 Amendment SN-003

N203491 Amendment SN-005

N203491 Amendment SN-006

N203491 Amendment SN-007

N203491 Amendment SN-008

N203491 Amendment SN-010

N203491 Amendment SN-010

N203491 Amendment SN-010

Document (Letter) Date

12/15/2011

2/10/2012

2/13/2012

3/15/2012

5/7/2012

6/6/2012

7/16/2012

7/17/2012

7/25/2012

7/27/2012

8/20/2012

M. NAME & ADDRESS OF APPLICANT:

Name: Alcon Research, Ltd.

Address: 6201 South Freeway
Fort Worth, TX 76134-2099

Chemistry Review Data Sheet

NDA 203491

Representative: N/A

Telephone: 817-551-8568

M. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Pending
b) Non-Proprietary Name (USAN): Nepafenac ophthalmic suspension, 0.3%
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA (CDA, 21 CFR 314.50), 505 (b)(1)

10. PHARMACOL. CATEGORY: Topical ocular anti-inflammatory and analgesic

11. DOSAGE FORM: Ophthalmic suspension

12. STRENGTH/POTENCY: 0.3%

13. ROUTE OF ADMINISTRATION: Topical (ocular)

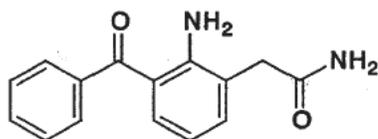
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

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

2-Amino-3-benzoylbenzeneacetamide

or

2-(2-Amino-3-benzoylphenyl)acetamide

C₁₅H₁₄N₂O₂
254.28

17. RELATED/SUPPORTING DOCUMENTS:

M. DMFs:

| DMF # | TYP E | HOLDER | ITEM REFEREN CED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETE D | COMMENTS |
|---------|-------|---------|------------------|-------------------|---------------------|------------------------------------|------------------------------------|
| (b) (4) | II | (b) (4) | (b) (4) | 1 | Adequate | 7/27/12 | Reviewed by Rao Kambhampati, Ph.D. |
| | II | | 1 | Adequate | 7/27/12 | Reviewed by Rao Kambhampati, Ph.D. | |
| | III | | 4 | | | | |
| | III | | 4 | | | | |
| | I | | 2 | | | | |
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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:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|---|
| NDA | 21-862 | NEVANAC [®] (Nepafenac Ophthalmic Suspension, 0.1%), Approved 8/19/2005, Applicant: Alcon Pharmaceuticals Ltd. |

M. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|------------------------|---------|------------------------|
| EES | Acceptable | 4/23/12 | M. Stock (HFD-324, OC) |
| Clinical Pharmacology Studies | Acceptable | 8/28/12 | Y. Zhang, Ph.D. (DCP4) |
| ONDQA Biopharm | Biowaiver not required | 9/5/12 | Tapash Ghosh, Ph.D. |
| LNC (ONDQA) | Not applicable | 7/31/12 | Rao Kambhampati, Ph.D. |
| Methods Validation | Not applicable | 7/31/12 | Rao Kambhampati, Ph.D. |
| DMEPA (Labels and Labeling) | Pending | 9/5/12 | Jung E. Lee, R.Ph. |
| EA | Acceptable | 7/31/12 | Rao Kambhampati, PhD |
| Product Quality Microbiology | Acceptable | 5/25/12 | Steven Donald, MS |

19. ORDER OF REVIEW (OGD Only): N/A

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 203491

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate information as required. The tradename for the drug product is pending. The inspection of the manufacturing and testing facilities was complete and the Office of Compliance issued an Overall Acceptable Recommendation for this NDA. From the CMC perspective, this NDA is recommended for approval.

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

Not applicable.

II. Summary of Chemistry Assessments

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

Drug Substance:

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Drug Product:

The drug product is nepafenac ophthalmic suspension, 0.3% and it is sterile, preserved, multi-dose aqueous suspension formulated for topical ophthalmic application. (b) (4)

Each 100 mL of the suspension contains 0.3 g (w/v) of nepafenac as the active ingredient and the following compendial grade (USP or NF) excipients: benzalkonium chloride (0.005 g; antimicrobial agent), carboxymethylcellulose sodium (b) (4), guar gum (b) (4), carbomer 974P (b) (4), boric acid (b) (4), edetate disodium (b) (4), propylene glycol (b) (4), sodium chloride (b) (4), sodium hydroxide and/or hydrochloric acid (QS for pH adjustment), and purified water (b) (4). The suspension is packaged in 4-mL size oval, LDPE Drop-Tainer[®] dispenser (bottle) with a LDPE dispensing plug and gray polypropylene cap filled with either 1.7 mL (for trade) or with 0.8 mL (for sample) of the suspension.

The drug product is manufactured by Alcon Laboratories Inc., Fort Worth, TX. The manufacturing process consists of (b) (4)

Key process variables and control strategy (QbD) were provided for the manufacture of the drug product. The specification for the drug product was finalized after negotiation with the reviewer and they are as follows: nepafenac identity (by TLC and HPLC), nepafenac assay (by HPLC: (b) (4)), impurities (b) (4), benzalkonium chloride identity, benzalkonium chloride assay (b) (4), pH (b) (4), edetate disodium identity, edetate disodium assay (b) (4), osmolality (b) (4), appearance of suspension (b) (4), redispersibility (b) (4), viscosity (b) (4), particle size distribution, endotoxin content (b) (4), and sterility (meets USP). Analytical method description was provided for all the methods and method validation was provided for non-compendial methods. Three production scale (b) (4) primary stability batches were produced in Alcon's ASPEX Manufacturing Facility using the above process. Adequate in-process controls are in place. After comment, 52 weeks (for trade size) and 39 weeks (for sample size) long-term stability data and statistical analysis of the data and 6 months accelerated stability data were provided. On the basis of this data, the applicant requested an expiration dating period of 18 months, which is acceptable. The post-approval stability commitment to place the commercial lots on stability is acceptable.

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

Nepafenac Ophthalmic Suspension, 0.3% is indicated for the treatment of pain and inflammation associated with cataract surgery. Each multi-dose trade bottle contains 1.8 mL of the suspension and each multi-dose sample bottle contains 0.8 mL of the suspension. One drop of Nepafenac Ophthalmic Suspension, 0.3% should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance is already in use in the lower strength (0.1%) formulation and it is manufactured and supplied by the same manufacturers for the proposed 0.3% formulation. Both the DMFs for the manufacturing of drug substance are adequate. The applicant provided adequate CMC information for the drug product manufacturing, controls, and testing. The manufacturing process is well controlled and demonstrated to produce a product that is consistent in quality and purity. All the facilities that are involved in the manufacturing and testing of the drug product are acceptable by the OC. The manufacturing process including sterilization process, which is found to be acceptable by the product quality microbiologist (OPS). The proposed packaging system (Drop-Tainer[®]) is already in the market and the gray cap color is consistent with AAO recommendation for NSAIDS. The established name is already in use, therefore, doesn't require a review. The tradename is pending and expected to be decided before the NDA action date. The package insert and the bottle and carton labels contained all the required CMC related information. Per current ONDQA policy, analytical method validation by the FDA lab is not required. Adequate long-term and accelerated stability data and statistical analysis of the long-term data support the 18-month expiration dating period for the drug product when stored at 2°-25°C (36°F to 77°F) with protection from light.

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

Rao V. Kambhampati, Ph.D.

B. Endorsement Block

| | |
|--|---------|
| Primary Reviewer/Date: Rao V. Kambhampati, Ph.D. | 8/31/12 |
| Secondary Reviewer/Date: Rapti Madurawe, Ph.D. | 8/31/12 |

C. CC Block

150 Pages have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

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

/s/

RAO V KAMBHAMPATI
09/12/2012

RAPTI D MADURawe
09/13/2012

Initial Quality Assessment Branch V Pre-Marketing Assessment Division II

OND Division: Division of Transplant and Ophthalmology Products
NDA: 203491

Applicant: Alcon Research, Ltd.

Stamp Date : 16 December, 2011

Proposed Trademark: Not identified at the time of this review

Established Name: Nepafenac ophthalmic suspension 0.3%

Dosage Form: Ophthalmic suspension

Route of Administration: Topical (ocular)

Strength: 0.3%

Indication: Treatment of pain and inflammation associated with
cataract surgery

Reviewer : Rao Kambhampati

CMC Lead : Bala Shanmugam

Prdt Quality Microbiologist: Denise Miller

QBD Liaison: Celia Cruz

| | YES | NO |
|-----------------------------|-------------------------------------|--------------------------|
| Acceptable for filing: | <input checked="" type="checkbox"/> | <input type="checkbox"/> |
| Comments for 74-Day Letter: | <input checked="" type="checkbox"/> | <input type="checkbox"/> |

Summary and Critical Issues

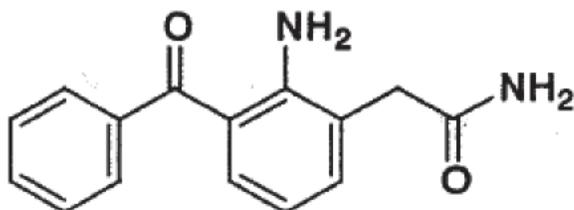
Summary

Nepafenac a non-steroidal anti-inflammatory pro-drug to amfenac was approved in 2005 by the FDA as a 0.1% ophthalmic suspension (NEVANAC®, NDA 21-862) for the same indication (as mentioned above) for this NDA. The NDA under review provides for an increased concentration (0.3%) of nepafenac. Nepafenac 0.3% dosed once a day is reported to be as efficacious as NEVANAC® 0.1% dosed 3 times a day. The submission, including methods validation is all electronic and located in the EDR. The drug product is formulated as a sterile, preserved ophthalmic suspension for topical administration. The proposed commercial package is 1.7 mL in 4 mL LDPE bottle. Additionally, a physician sample size of 0.8 mL in 4 mL LDPE bottle is also being proposed. The current formulation is slightly different from the previously approved formulation in that it has an increased level of nepafenac (0.3%), and among other changes to excipients, it includes (b) (4) guar gum and boric acid. QBD approach was implemented to establish the key process variables and evaluate attributes of the material used in the manufacture of the drug product. The company is requesting a shelf-life of 78-weeks for the 1.7 mL fill size (intended commercial size) and 52-weeks for the 0.8 mL fill size (sample) when stored at 2-25°C.

All manufacturing and testing facilities have been entered in EES. Please note that a pre-NDA meeting was held. The minutes of the Pre-NDA meeting is attached to this IQA for quick reference to the reviewer.

This NDA will be reviewed on a Standard time line. The PDUFA goal date is October 16, 2012.

Drug Substance



All drug substance information related to manufacturing and controls is referenced to DMF (b)(4) (which was also referenced for the approved NDA 21-862) (manufactured by (b)(4)) and DMF (b)(4) (manufactured by (b)(4)). The table below provides status of the above mentioned DMF's at the time of writing this IQA. Letters of authorization from the respective DMF holder's has been provided.

| Drug Substance | DMF # | LOA provided (Yes/No) | Status | Comments |
|----------------|--------|-----------------------|--|---|
| Nepafenac | (b)(4) | Y | The last review is by Linda Ng, dated August 11, 2005. | There are several Quality submissions and Annual Reports which requires to be reviewed. |
| Nepafenac | (b)(4) | Y | Adequate per last review by Libaniel Rodriguez, dated July 31, 2009. | There is one Annual Report which needs review. |

- As mentioned above the API, from both DMF holders have been used in the manufacture of the lower strength nepafenc.
- The specification provided in the NDA appears to match the previously approved specification.

Drug Product

The product is formulated as a sterile, preserved ophthalmic suspension containing 0.3% nepafenac.

- All excipients used in the formulation are compendial
- While guar gum has been used in other dosage forms it is considered novel for an ophthalmic application *and it will be important to notify pharm/tox review team of this* (please see attached EOP 2 meeting minutes). The company has provided

COA and several study reports which details the tests and specifications for the excipient. *The adequacy of data provided to support quality of the excipient should be evaluated. The company mentions that alternate suppliers may be used if appropriately qualified (footnote to Table 3.2.P.4.1-2). As it is derived from natural sources, differences in quality can be expected. Since guar gum has among other compounds, (b) (4) (which is controlled at NMT (b) (4) etc. and also because this will be the first instance of the excipient being used in an ophthalmic preparation, it may be worth to reiterate to the company about the need to adequately qualify the vendor, should there be a change. It should be verified if the excipient at the levels proposed has been qualified in pre-clinical studies and also consult Pharm/tox on any potential safety concerns. Also, during review it should be determined if any class of impurities of concern from the excipient should be controlled in the drug product specification to ensure that these impurities are adequately controlled.*

- The formulation has other changes to the previously approved version and one such change is the addition of boric acid which is reported to function as a (b) (4)
- Benzalkonium chloride is used as a preservative at the same level as the approved formulation.
- (b) (4)
- The drug product composition is attached to this review
- Manufacturing process is defined by (b) (4)
- (b) (4)
- The company has adopted a QBD approach to identifying and establishing the key process variables and acceptable ranges by employing FMEA analysis. *Note this study also includes evaluating (b) (4) The need to consult with the QBD liaison and/or Product Quality Microbiologist can be determined by the reviewer. The document providing details of the study is: TDOC-0014813. In evaluating the safety of the excipient, it may be pertinent to note that the drug product should be applied (one drop) beginning day1 prior to cataract surgery, continued on the day of surgery and through the first 2-weeks of the post-operative period.*
- The DP specification is attached to serve as a quick reference for the reviewer. The specification compares to the approved specification of Nevanac™ except that there are some differences in the acceptance criteria for a few quality attributes. For example, the acceptance criterion for BAK is set at (b) (4) as compared to (b) (4) in the approved product. Similarly, the acceptance criterion for redispersibility is specified at NMT (b) (4) in the NDA under review while the

same attribute is controlled at NMT (b) (4) The acceptance criterion for viscosity is specified at (b) (4) *These acceptance criteria proposed for the aforementioned quality attributes should be evaluated and tightened if needed as based on batch and stability data.*

- Particle size, sterility and viscosity are the key quality attributes of this drug product formulation.
- *The downward trend in quality attributes on stability, specifically assay and viscosity should be evaluated in considering the proposed shelf-life of (b) (4) and how it affects, if any the shelf-life attributes of the drug product.*
- The DROP-TAINER® package system used in this NDA was approved for the suspension product. The company has provided LOA for the DMF's for the (b) (4) used in the container, dispensing plug and closure. *However, no DMF's have been referenced for the container closure (manufactured by (b) (4) and (b) (4) (b) (4)). The NDA does provide information on the container closure which maybe adequate to evaluate its suitability. It can be determined upon review, if a request for referencing DMF's should be requested from the company.*
- The oval bottles and the dispensing plugs are (b) (4) *Whether residual levels of (b) (4) are controlled should be verified and that the levels are acceptable.*
- Draft container and carton label has been provided *but mock label should be requested.*

Early action needed:

- 1) Reviewer should evaluate items identified (*in italics*) in this IQA.

Comments for 74-day letter

None at this time.

Comments and Recommendation:

Based on the perusal of this NDA, it is determined to be complete and therefore filable from CMC perspective. Dr. Rao Kambhampati is assigned to review this NDA. Dr. Celia Cruz is the QBD liaison assigned for QBD consultation.

Balajee Shanmugam
CMC Lead

See DARRTS
Date

Rapti Madurawe, Ph.D.
Branch Chief

See DARRTS
Date

Meetings

Meetings Conducted over the Course of Product Development

An End-of-Phase II meeting was held in October 2009. Provided below is the summary of comments from this meeting.

1.6.3. Correspondence Regarding Meetings

An End-of-Phase 2 meeting was held with the U.S. Food and Drug Administration on October 5, 2009, at which Alcon presented a development plan for Nepafenac (AL-6515) Ophthalmic Suspension, 0.3% in order to obtain advice from the Agency before proceeding with clinical development. An FDA clarification meeting was held on January 10, 2011 in order to obtain advice from the Agency on the Agency's expectation for adequate evidence to support product benefit for the increased drug concentration.

The following comments were received during the meetings:

- A single Phase 3 clinical trial with Nepafenac Ophthalmic Suspension, 0.3% dosed once daily is sufficient to establish the safety and efficacy of the product as long as a clinical advantage of the new 0.3% formula is demonstrated over the existing NEVANAC formula.
- Clinical trials including patients under the age of 18 years of age need not be undertaken and a waiver should be submitted.
- Aqueous cells and flare can be used as endpoints to established safety and efficacy for the treatment of postoperative pain and inflammation associated with cataract surgery.
- Guar gum is to be considered a novel excipient and degradation products are to be reported according to ICH Q3B(R).
- A single 1-month topical ocular toxicology study will be sufficient to support the application.
- A single Phase 1 study is sufficient to evaluate systemic exposure of nepafenac and amfenac resulting from topical ocular administration of Nepafenac Ophthalmic Suspension, 0.3% in humans.

In summary, the concerns and comments from the consulted regulatory authorities have been addressed in the relevant sections of this application.

Drug Product Composition

| Component | Percent w/v | Function | Compendial Status |
|--|--------------------|---------------------|-----------------------------|
| Nepafenac (AL-6515) | 0.3 | Active Ingredient | Non-compendial ^a |
| Benzalkonium Chloride | 0.005 ^b | Antimicrobial Agent | NF |
| Carboxymethylcellulose Sodium ^{(b) (4)} | | | USP |
| Guar Gum | | | NF |
| Carbomer 974P | | | NF ^c |
| Boric Acid | | | NF |
| Edetate Disodium | | | USP |
| Propylene Glycol | | | USP |
| Sodium Chloride | | | USP |
| Sodium Hydroxide and/or Hydrochloric Acid | | | QS for pH adjustment |
| Purified Water | | | NF |
| | | | USP |

Note: FID = Formulation Identification Number

^aMeets in-house monograph

(b) (4)



Drug Product Specification

| Test | Specification | |
|--|---------------|---|
| Nepafenac (AL-6515) Identity (TLC) ^a | (b) (4) | |
| Nepafenac (AL-6515) Identity (HPLC) ^a | | |
| Nepafenac (AL-6515) Assay | | |
| Impurities: | | |
| (b) (4) | | |
| | | Benzalkonium Chloride Identity ^a |
| | | Benzalkonium Chloride Assay |
| | | Edetate Disodium Identity ^a |
| | | Edetate Disodium Assay |
| pH | | |
| Osmolality | | |
| Appearance Suspension: | | |
| Color | | |
| Uniformity | | |
| Redispersibility | | |
| Viscosity @ 12 rpm, CP-52 LVT | | |
| Particle Size, Suspension (b) (4) | | |
| Endotoxin ^a | | |
| Sterility | | |

^a Release test only

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

/s/

BALAJEE SHANMUGAM
01/24/2012
N203491IQA

RAPTI D MADURawe
01/24/2012

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 203-491

Supplement Number and Type:

Established/Proper Name:

Nepafenac ophthalmic
Suspension, 0.3%

Applicant: Alcon
Research Ltd.

Letter Date: 15-Dec-2011

Stamp Date: 16-Dec-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? | ✓ | | |
| 2. | Is the CMC section indexed and paginated (including all PDF files) adequately? | ✓ | | |
| 3. | Are all the pages in the CMC section legible? | ✓ | | |
| 4. | Has all information requested during the IND phase, and at the pre-NDA meetings been included? | ✓ | | An EOP2 meeting was held on Oct 5, 2009. Section 1.6.3 of the NDA provides a summary. |

| B. FACILITIES* | | | | |
|----------------|---|-----|----|--|
| | Parameter | Yes | No | Comment |
| 5. | Is a single, comprehensive list of all involved facilities available in one location in the application? | | ✓ | The facilities have been identified with contact information in section 1.4.4 of the NDA. The facilities have been entered into EES. |
| 6. | For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API. | | | NA |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| | | | | |
|----|--|---|--|--|
| 7. | <p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered 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) | ✓ | | <p>The Drug substance is referenced to DMF (b) (4) and DMF (b) (4) LOA's have been provided.</p> |
| 8. | <p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) | ✓ | | |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| | | | | |
|-----|--|---|--|---|
| 9. | <p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) | ✓ | | |
| 10. | <p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p> | ✓ | | <p>Yes, statement provided in Section 1.4.4 of the NDA.</p> |

* 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. | <p>Has an environmental assessment report or categorical exclusion been provided?</p> | ✓ | | |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API) | | | | |
|--|---|------------|-----------|---|
| | Parameter | Yes | No | Comment |
| 12. | Does the section contain a description of the DS manufacturing process? | | | The drug substance is referenced to DMF (b) (4) (last reviewed in 2005) and DMF (b) (4) (last reviewed in 2009). LOA's have been provided in the NDA. |
| 13. | Does the section contain identification and controls of critical steps and intermediates of the DS? | | | Referenced to DMF |
| 14. | Does the section contain information regarding the characterization of the DS? | | | Referenced to DMF |
| 15. | Does the section contain controls for the DS? | | | Referenced to DMF |
| 16. | Has stability data and analysis been provided for the drug substance? | ✓ | | |
| 17. | Does the application contain Quality by Design (QbD) information regarding the DS? | | ✓ | |
| 18. | Does the application contain Process Analytical Technology (PAT) information regarding the DS? | | ✓ | |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| 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? | ✓ | | |
| 20. | Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable? | ✓ | | |
| 21. | Is there a batch production record and a proposed master batch record? | ✓ | | |
| 22. | Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product? | ✓ | | |
| 23. | Have any biowaivers been requested? | ✓ | | |
| 24. | Does the section contain description of to-be-marketed container/closure system and presentations)? | ✓ | | <p>The NDA references the following DMF's for the (b) (4) used in the container closure:</p> <p>a) DMF (b) (4)</p> <p>b) DMF (b) (4)</p> <p>In addition, the following DMF's have been referenced for (b) (4)</p> <p>a) DMF (b) (4)</p> <p>b) DMF (b) (4)</p> <p>LOA's have been provided in the NDA.</p> |
| 25. | Does the section contain controls of the final drug product? | ✓ | | |
| 26. | Has stability data and analysis been provided to support the requested expiration date? | ✓ | | |
| 27. | Does the application contain Quality by Design (QbD) information regarding the DP? | ✓ | | The NDA provides elements of QBD which will be evaluated by the reviewer in consultation with the QBD liaison. |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| | | | | |
|-----|--|--|---|----|
| 28. | Does the application contain Process Analytical Technology (PAT) information regarding the DP? | | ✓ | NA |
|-----|--|--|---|----|

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

| G. MICROBIOLOGY | | | | |
|-----------------|--|-----|----|---------|
| | Parameter | Yes | No | Comment |
| 30. | If appropriate, is a separate microbiological section included assuring sterility of the drug product? | ✓ | | |

| 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? | ✓ | | |

| DMF # | TYPE | HOLDER | ITEM REFERENCED | LOA DATE | COMMENTS |
|---------|------|---------|-----------------|------------|----------|
| (b) (4) | II | (b) (4) | Nepafenac | 14-Oct-11 | |
| | II | | Nepafenac | 12-July-11 | |
| | III | | (b) (4) | 11-May-09 | |
| | III | | | 7-Oct-10 | |
| | V | | | 12-Apr-10 | |
| | V | | | 04-Aug-11 | |

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

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| J. FILING CONCLUSION | | | | |
|----------------------|--|-----|----|---------|
| | Parameter | Yes | No | Comment |
| 34. | IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? | ✓ | | |
| 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. | | | NA |
| 36. | Are there any potential review issues to be forwarded to the Applicant for the 74-day letter? | | ✓ | |

{See appended electronic signature page}

Balajee Shanmugam
CMC Lead
Division of Pre-Marketing Assessment
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Rapti Madurawe Ph.D.
Branch Chief
Branch V
Division of Pre-Marketing Assessment
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

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

/s/

BALAJEE SHANMUGAM
01/24/2012
N203491CMCFilingReview

RAPTI D MADURawe
01/24/2012