CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205677Orig1s000

CHEMISTRY REVIEW(S)

Hetlioz (tasimelteon) Capsules

NDA 205677

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

Applicant: Vanda Pharmaceuticals
2200 Pennsylvania Avenue NW
Suite 300E
Washington, D.C. 20037

Indication: For the treatment of non 24-hour disorder in totally blind subjects.

Presentation: The product will be available as a single 20 mg strength capsules. The capsules are size 1, dark blue, hard gelatin capsules printed with "VANDA 20 mg" in white. The capsules are packaged in 60cc HDPE bottles with each bottle containing 30 capsules, (b) (4)

EER Status: Overall recommendation is "Acceptable" as of 11-Dec-2013.

Consults: ONDQA Biopharmaceutics – Acceptable (Dr. Kareen Riviere's review dated 10/30/2013).

Microbiology- Acceptable (Bryan S. Riley, 6-Jun-2013)

Methods Validation – Requested on 16-Dec-13. The NDA may be approved prior to completion of methods validation by DPA.

EA – Categorical exclusion granted.

Post-Approval Agreements: None

Drug Substance:

The drug substance, tasimelteon, is a new molecular entity. The drug substance is a white to off-white crystalline (b) (4) with molecular weight of 245.32. The molecule has two chiral centers and 1R,2R-isomer is being developed for this NDA. The drug substance is non-hygroscopic. The drug substance can potentially exist in (b) (4) The drug substance is manufactured by (b) (4) The synthesis involves (b) (4)

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

Drug product:

Hetlioz (tasimelteon) capsules are an immediate release product to be marketed in single 20-mg strength. The drug product formulation uses standard compendial excipients, e.g., lactose, microcrystalline cellulose, colloidal silicon dioxide, crosscarmellose sodium, and magnesium stearate. The manufacturing process includes (b) (4) The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through end product testing. The end product specification includes testing for appearance, identification (by UV and HPLC), assay, content uniformity, related substances, dissolution, disintegration, (b) (4) and microbial limits tests. All analytical procedures for the drug product are adequately described and validated. The provided stability data support the proposed 30-month expiration period for this product. The product is labeled to be protected from exposure to light and moisture.

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

Conclusion: Adequate from CMC perspective.

Additional Items:

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

Overall Conclusion: The application is recommended for **"Approval"** from CMC perspective.

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

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/s/

RAMESH K SOOD
12/19/2013

NDA 205677
Review #1 Addendum

Hetlioz™ (tasimelteon) Capsules, 20 mg

Applicant: Vanda Pharmaceuticals Inc.

Wendy I. Wilson-Lee, Ph.D.
ONDQA/DNDQA I/Branch I

Quality (CMC) Review
For Division of Neurology Products (DNP)

Chemistry Review Data Sheet

1. NDA# **205677**

2. REVIEW #: 1 Addendum

3. REVIEW DATE: 12-4-2013

4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N205677 Initial NDA	05/31/13
N205677 Amendment 0001 (2)	06/18/13
N205677 Amendment 0002 (3)	07/1/13
N205677 Amendment 0003 (4)	07/3/13
N205677 Amendment 0007 (11)	08/20/13
N205677 Amendment 0019 (22)	10/9/13
N205677 Amendment 0020 (23)	10/10/13
N205677 Amendment 0023 (26)	10/25/13
N205677 Amendment 0024 (27)	10/28/13
N205677 Amendment 0027 (30)	10/30/13
N205677 Amendment 0029 (32)	11/12/13
Product Quality Review #1 (R. Kambhampati)	11/12/13

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed (Global Submit)	Global Submit Date
N205677 Amendment 0030 (33)	11/22/13

7. NAME & ADDRESS OF APPLICANT:

Name:	Vanda Pharmaceuticals Inc.
Address:	2200 Pennsylvania Ave NW Suite 300E Washington, D.C. 20037
Representative:	N/A
Telephone:	202-734-3400

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Hetlioz™ Capsules
b) Non-Proprietary Name (USAN and INN): Tasimelteon Capsules
c) Code Name/# (company): VEC-162 (Vanda); BMS-214778 (BMS); (b) (4); (b) (4); and (b) (4)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Circadian regulator

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 20 mg of tasimelteon/capsule

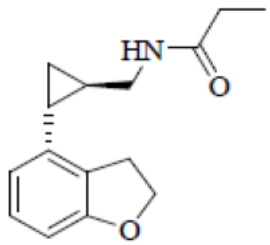
13. ROUTE OF ADMINISTRATION: Oral

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:
(1R, 2R)-N-[2-(2,3-Dihydrobenzofuran-4-yl)-cyclopropylmethyl]propanamide



$C_{15}H_{19}NO_2$
245.32

17. RELATED/SUPPORTING DOCUMENTS:

M. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	Adequate	9/10/12	
	III			3	Adequate	10/25/12	
	III			3	Adequate	12/20/10	
	III			3	Adequate	4/17/12	

[1] Action codes for DMF Table:
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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
IND	54776	Tasimelteon capsules (Vanda Pharmaceuticals Inc.)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	**Pending**	**12/03/13**	**OMPQ, OC**
ONDQA Biopharm	Dissolution method acceptable.	10/30/13	Kareen Riviere, Ph.D.
LNC (ONDQA) for Established Name	Not applicable. USAN name available.	10/31/13	Rao Kambhampati, Ph.D.
Methods Validation	Pending	10/31/13	DPA, St. Louis
DMEPA (Labels and Labeling)	Pending	10/31/13	Julie V. Neshiewat (DMEPA)
Proprietary name	Hetlioz™ acceptable	09/16/13	Carol A. Holquist, RPh (DMEPA)
EA	Acceptable	10/31/13	Rao Kambhampati, PhD
Product Quality Microbiology	Recommended for approval	6/6/13	Bryan S. Riley, Ph.D. (NDMS, OPS)

The Chemistry Review for NDA 205677

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing, and Controls (CMC) review stand point, the NDA# 205677 for Hetlioz™ (tasimelteon), 20 mg, capsules is recommended for approval provided all the manufacturing and testing facilities are acceptable to the Office of Compliance (OC) with an Overall Acceptable Recommendation is issued by the OC and pending final labeling.

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:

Tasimelteon is the established name for the drug substance. It has a molecular formula of $C_{15}H_{19}NO_2$ and molecular weight of 245.32. It has two chiral centers and the applicant chose to develop the trans-1*R*,2*R*-isomer. It is a non-hygroscopic, white to off-white crystalline powder and has a melting range of 73°-77°C. It can exist as (b) (4) It is slightly soluble in water (b) (4) and 0.1N-HCl (b) (4) and freely soluble in isopropanol, PEG 300, and propylene glycol. It exhibits a pH of 8.5 (b) (4) at (b) (4). It has a partition coefficient (Po/w) of 2.43 (log P). It is manufactured by (b) (4) The synthesis of drug substance is (b) (4) All the intermediates were clearly identified and specifications and batch analysis information were provided for the isolated ones. Some of the acceptance criteria for the intermediates were tightened upon comment. Similarly, the specifications were provide for the (b) (4) drug substance and some of their acceptance criteria were tightened upon comment. Critical process parameters for Intermediates (b) (4) (b) (4) were provided. The proof-of structure of the drug substance is based on a combination of the spectroscopic data, physic-chemical characteristics, and (b) (4) analysis. All the potential impurities arising from residual materials and intermediates were identified. In-process control test methods, release methods, and validation reports were provided. All the potential by-products and degradation products were identified. The specification for (b) (4) drug substance included appearance, identification (FTIR, specific rotation, chiral HPLC), mp, residue on ignition, heavy metals, elemental impurities, (b) (4) assay, purity, chiral

purity, related substances which were divided into known impurities [redacted], unspecified impurities [redacted], Total impurities, [redacted] residual solvents, [redacted] DMF, [redacted] and [redacted] and other tests included [redacted] particle size, and microbial limits. On the basis of the batch release and stability data, some of the acceptance criteria for the [redacted] drug substance were tightened upon comment. All the non-compendial methods were described and method validation reports were provided. Batch analysis information were provided for the batches manufactured at the proposed [redacted] facility as well as the previously used [redacted] and BMS facilities. The drug substance is stored in [redacted] Stability data were provided for six [redacted] and four [redacted] drug substance lots that were stored in [redacted] commercial containers. For four [redacted] lots, the stability data included up to 9 months storage under long-term and refrigerated storage conditions and 6 months storage under accelerated conditions. For the six [redacted] lots, the data included up to 18 months storage under long-term conditions and 6 months under accelerated conditions. It was demonstrated that the drug substance was stable under these conditions. The requested shelf-life [redacted] for the [redacted] drug substance [redacted] is acceptable.

Drug Product:

The proposed commercial drug product formulation for tasimelteon is Size 1, dark blue opaque, hard gelatin capsules printed with "VANDA 20 mg" in white, containing 20 mg of tasimelteon per capsule. The components and composition of the each capsule [redacted] include tasimelteon drug substance as the active pharmaceutical ingredient (20 mg) and the following excipients: lactose [redacted] microcrystalline cellulose [redacted] colloidal silicon dioxide [redacted] croscarmellose sodium [redacted] magnesium stearate [redacted] The [redacted] capsule wt is approximately [redacted] Thirty capsules are packaged in 60-cc white HDPE bottles [redacted] and then sealed [redacted] and closed with a [redacted] closure. All excipients of the capsule [redacted] are of compendial grade. A detailed formulation development report was provided. The drug product is manufactured and packaged by [redacted] A batch formula for [redacted] capsules was provided. The manufacturing process involves [redacted] The final blend is [redacted] size 1, dark blue opaque, hard gelatin capsules printed with "VANDA 20 mg" in white. The [redacted] capsules are packaged into 60-cc high density polyethylene (HDPE) bottles (30-count) [redacted] caps containing induction seals. Each bottle also contains a [redacted] It was demonstrated that the drug product capsules can be manufactured with consistent quality and purity. Adequate in-process controls are in place. The specification for drug product capsules included appearance, identification (by UV and HPLC), assay, content uniformity, related substances [redacted], dissolution, disintegration, [redacted] and microbial limits tests. On the basis of lot release and stability data, upon comment, the applicant tightened some of the acceptance criteria. All non-compendial test methods were described and their method validation reports were provided. Batch analysis results were provided for three NDA registration batches, which demonstrated consistent quality and purity.

The stability data included for three registration batches and three supportive batches. 18 Months of long-term and 6 months of accelerated data were provided for primary batches and 30 months of long-term and 6 months of accelerated data were provided for supportive batches. On the basis of the real time data and statistical analysis, the requested expiration dating period of 30 months when stored at controlled room temperature, 25°C (77°F) is acceptable.

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

Hetlioz is a circadian regulator of the master body clock indicated for the treatment of Non-24-Hour Disorder in the totally blind subjects. The recommended dose of Hetlioz is 20 mg per day taken one hour prior to bedtime, preferably at the same time every night. Each bottle of Hetlioz™ (tasimelteon) contains 30 capsules. Therefore, a 30 count bottle will provide a month supply to the patient. Hetlioz 20 mg capsules are available as size 1, dark blue opaque, hard gelatin capsules printed with "VANDA 20 mg" in white, containing 20 mg of tasimelteon per capsule, in the following quantities:

NDC 43068-220-01 Bottles of 30

The recommended storage conditions are: Store Hetlioz 20 mg capsules at controlled room temperature, 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature]. Protect Hetlioz 20 mg capsules from exposure to light and moisture.

D. Basis for Approvability or Not-Approval Recommendation

The applicant provided adequate chemistry, manufacturing, and controls (CMC) information for the drug substance and drug product. The applicant satisfactorily addressed all the deficiencies that were communicated during the review. The established name, tasimelteon, is USAN name and it is acceptable. The tradename, Hetlioz™ is acceptable to DMEPA. The manufacturing process is acceptable from product microbiology reviewer stand point and a review was filed in DARRTS. The chemistry related portion of the package insert and medication guide and the proposed container and carton labels contain all the required CMC information. All the facilities (b) (4) are acceptable, therefore, the NDA is recommended for approval provided all the facilities are found to be acceptable by the Office of Compliance and pending final labeling.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

Wendy I. Wilson-Lee, Ph.D.

B. Endorsement Block

Primary Reviewer/Date: Wendy I. Wilson-Lee, Ph.D. 12/3/2013
Senior Chemist/ONDQA/DNDQA I/Branch I

Secondary Reviewer/Date: Olen Stephens, Ph.D. 12/3/2013
Acting Branch Chief/ONDQA/DNDQA I/Branch I

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/s/

WENDY I WILSON-LEE
12/04/2013

OLEN M STEPHENS
12/04/2013
Recommendation is pending OC evaluation of manufacturing facilities.

NDA 205677

Hetlioz™ (tasimelteon) Capsules, 20 mg

Applicant: Vanda Pharmaceuticals Inc.

Rao V. Kambhampati, Ph.D.
ONDQA/DNDQA I/Branch I

Quality (CMC) Review
For Division of Neurology Products (DNP)

Chemistry Review Data Sheet

1. NDA# **205677**

2. REVIEW #: 1

3. REVIEW DATE: 11-12-2013

4. REVIEWER: Rao V. Kambhampati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed (Global Submit)	Global Submit Date
N205677 Initial NDA	05/31/13
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N205677 Amendment 0002 (3)	07/1/13
N205677 Amendment 0003 (4)	07/3/13
N205677 Amendment 0007 (11)	08/20/13
N205677 Amendment 0019 (22)	10/9/13
N205677 Amendment 0020 (23)	10/10/13
N205677 Amendment 0023 (26)	10/25/13
N205677 Amendment 0024 (27)	10/28/13
N205677 Amendment 0027 (30)	10/30/13
N205677 Amendment 0029 (32)	11/12/13

7. NAME & ADDRESS OF APPLICANT:

Name:	Vanda Pharmaceuticals Inc.
Address:	2200 Pennsylvania Ave NW Suite 300E Washington, D.C. 20037
Representative:	N/A
Telephone:	202-734-3400

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Hetlioz™ Capsules
b) Non-Proprietary Name (USAN and INN): Tasimelteon Capsules
c) Code Name/# (company): VEC-162 (Vanda); BMS-214778 (BMS); [redacted] (b) (4) and [redacted] (b) (4)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Circadian regulator

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 20 mg of tasimelteon/capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

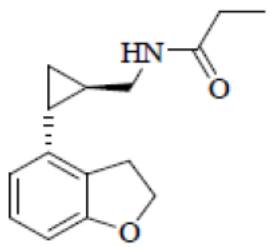
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

(1R, 2R)-N-[2-(2,3-Dihydrobenzofuran-4-yl)-cyclopropylmethyl]propanamide



$C_{15}H_{19}NO_2$
245.32

17. RELATED/SUPPORTING DOCUMENTS:

M. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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	III			3	Adequate	4/17/12	

[1] Action codes for DMF Table:
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5 – Authority to reference not granted
6 – DMF not available
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[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
IND	54776	Tasimelteon capsules (Vanda Pharmaceuticals Inc.)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	10/31/13	OMPQ, OC

ONDQA Biopharm	Dissolution method acceptable.	10/30/13	Kareen Riviere, Ph.D.
LNC (ONDQA) for Established Name	Not applicable. USAN name available.	10/31/13	Rao Kambhampati, Ph.D.
Methods Validation	Pending	10/31/13	DPA, St. Louis
DMEPA (Labels and Labeling)	Pending	10/31/13	Julie V. Neshiewat (DMEPA)
Proprietary name	Hetlioz™ acceptable	09/16/13	Carol A. Holquist, RPh (DMEPA)
EA	Acceptable	10/31/13	Rao Kambhampati, PhD
Product Quality Microbiology	Recommended for approval	6/6/13	Bryan S. Riley, Ph.D. (NDMS, OPS)

The Chemistry Review for NDA 205677

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing, and Controls (CMC) review stand point, the NDA# 205677 for Hetlioz™ (tasimelteon), 20 mg, capsules is recommended for approval provided all the manufacturing and testing facilities are acceptable to the Office of Compliance (OC) and an Overall Acceptable Recommendation is issued by the OC.

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:

Tasimelteon is the established name (USAN) for the drug substance and it is a New Molecular Entity (NME). It has a molecular formula of $C_{15}H_{19}NO_2$ and molecular weight of 245.32. It has two chiral centers and the applicant chose to develop the trans-1*R*,2*R*-isomer. It is a non-hygroscopic, white to off-white crystalline powder and has a melting range of 73°-77°C. It can exist as (b) (4) It is slightly soluble in water (b) (4) and 0.1N-HCl (b) (4) and freely soluble in isopropanol, PEG 300, and propylene glycol. It exhibits a pH of 8.5 (b) (4) at (b) (4) It has a partition coefficient (Po/w) of 2.43 (log P). It is manufactured by (b) (4). The synthesis of drug substance is a (b) (4) (b) (4) All the intermediates were clearly identified and specifications and batch analysis information were provided for the isolated ones. Some of the acceptance criteria for the intermediates were tightened upon comment. Similarly, the specifications were provided for the (b) (4) drug substance and some of their acceptance criteria were tightened upon comment. Critical process parameters for Intermediates (b) (4) (b) (4) were provided. The proof-of structure of the drug substance is based on a combination of the spectroscopic data, physic-chemical

characteristics, and [(b) (4)] analysis. All the potential impurities arising from residual materials and intermediates were identified. In-process control test methods, release methods, and validation reports were provided. All the potential by-products and degradation products were identified. The specification for [(b) (4)] drug substance included appearance, identification (FTIR, specific rotation, chiral HPLC), mp, residue on ignition, heavy metals, elemental impurities, [(b) (4)] assay, purity, chiral purity, related substances which were divided into known impurities [(b) (4)] unspecified impurities [(b) (4)] Total impurities, [(b) (4)] residual solvents, [(b) (4)] DMF, [(b) (4)] and other tests included [(b) (4)], particle size, and microbial limits. On the basis of the batch release and stability data, some of the acceptance criteria for the [(b) (4)] drug substance were tightened upon comment. All the non-compendial methods were described and method validation reports were provided. Batch analysis information were provided for the batches manufactured at the proposed [(b) (4)] facility as well as the previously used [(b) (4)] and BMS facilities. The drug substance is stored in [(b) (4)] Stability data were provided for six [(b) (4)] and four [(b) (4)] drug substance lots that were stored in [(b) (4)] commercial containers. For four [(b) (4)] lots, the stability data included up to 9 months storage under long-term and refrigerated storage conditions and 6 months storage under accelerated conditions. For the six [(b) (4)] lots, the data included up to 18 months storage under long-term conditions and 6 months under accelerated conditions. It was demonstrated that the drug substance was stable under these conditions. The applicant requested for a shelf-life of [(b) (4)] for the [(b) (4)] drug substance lots which is acceptable.

Drug Product:

The proposed commercial drug product formulation for tasimelteon is Size 1, dark blue opaque, hard gelatin capsules printed with "VANDA 20 mg" in white, containing 20 mg of tasimelteon per capsule. The components and composition of the each capsule [(b) (4)] include tasimelteon drug substance as the active pharmaceutical ingredient (20 mg) and the following excipients: lactose [(b) (4)] microcrystalline cellulose [(b) (4)] colloidal silicon dioxide [(b) (4)] croscarmellose sodium [(b) (4)] magnesium stearate [(b) (4)] The [(b) (4)] capsule wt is approximately [(b) (4)] Thirty capsules are packaged in 60-cc white HDPE bottles [(b) (4)] and then sealed [(b) (4)] and closed with a [(b) (4)] closure. All excipients of the capsule [(b) (4)] are of compendial grade. A detailed formulation development report was provided. The drug product is manufactured and packaged by [(b) (4)] A batch formula for [(b) (4)] capsules was provided. The manufacturing process involves [(b) (4)] The final [(b) (4)] is [(b) (4)] size 1, dark blue opaque, hard gelatin capsules printed with "VANDA 20 mg" in white. The [(b) (4)] capsules are packaged into 60-cc high density polyethylene

(HDPE) bottles (30-count) with [redacted] caps containing induction seals. Each bottle also contains a [redacted]
It was demonstrated that the drug product capsules can be manufactured with consistent quality and purity. Adequate in-process controls are in place. The specification for drug product capsules included appearance, identification (by UV and HPLC), assay, content uniformity, related substances [redacted] dissolution, disintegration, [redacted] and microbial limits tests. On the basis of lot release and stability data, upon comment, the applicant tightened some of the acceptance criteria. All non-compendial test methods were described and their method validation reports were provided. Batch analysis results were provided for three NDA registration batches, which demonstrated consistent quality and purity. The stability data included for three registration batches and three supportive batches. 18 Months of long-term and 6 months of accelerated data were provided for primary batches and 30 months of long-term and 6 months of accelerated data were provided for supportive batches. On the basis of the real time data and statistical analysis, the applicant requested for an expiration dating period of 30 months when stored at controlled room temperature, 25°C (77°F), which is acceptable.

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

Hetlioz is a circadian regulator of the master body clock indicated for the treatment of Non-24-Hour Disorder in the totally blind subjects. The recommended dose of Hetlioz is 20 mg per day taken one hour prior to bedtime, preferably at the same time every night. Each bottle of Hetlioz™ (tasimelteon) contains 30 capsules. Therefore, a 30 count bottle will provide a month supply to the patient. Hetlioz 20 mg capsules are available as size 1, dark blue opaque, hard gelatin capsules printed with "VANDA 20 mg" in white, containing 20 mg of tasimelteon per capsule, in the following quantities:

NDC 43068-220-01 Bottles of 30

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D. Basis for Approvability or Not-Approval Recommendation

The applicant provided adequate chemistry, manufacturing, and controls (CMC) information for the drug substance and drug product. The applicant satisfactorily addressed all the deficiencies that were communicated during the review. The established name, tasimelteon, is USAN name and it is acceptable. The tradename, Hetlioz™ is acceptable to DMEPA. The manufacturing process is acceptable from product microbiology reviewer stand point and a review was filed in DARRTS. The chemistry related portion of the package insert and medication guide and the proposed container and carton labels contain all the required CMC information. All the facilities [redacted] are acceptable, therefore,

the NDA is recommended for approval provided all the facilities are found to be acceptable by the Office of Compliance.

III. Administrative

A. Reviewer's Signature

Rao V. Kambhampati, Ph.D.

B. Endorsement Block

Primary Reviewer/Date: Rao V. Kambhampati, Ph.D. 11/12/13
Senior Chemist/ONDQA/DNDQA I/Branch I

Secondary Reviewer/Date: Olen Stephens, Ph.D. 11/12/13
Acting Branch Chief/ONDQA/DNDQA I/Branch I

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/s/

RAO V KAMBHAMPATI
11/12/2013

OLEN M STEPHENS
11/12/2013

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet

1. OMPQ Reviewer: Christina Capacci-Daniel

2. NDA/BLA Number: NDA 205677
   Submission Date: 31-May-2013
   21st C. Review Goal Date: 30-Nov-2013
   PDUFA Goal Date: 31-Jan-2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Hetlioz
Established or Non-Proprietary Name (USAN) and strength:	Tasimelteon, 20mg
Dosage Form:	Hard gelatin capsule

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY (orphan indication)
Applicant Name:	Vanda Pharmaceuticals, Inc.
Responsible Organization (OND Division):	DNP – Sedatives and Hypnotics

II. Application Detail

1. INDICATION: Treatment of Non-24-hour disorder in the totally blind.
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 20mg
4. Rx/OTC DISPENSED: ☒Rx ☐OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	☑			
2.	Breakthrough Therapy Designation		☑		
3.	Orphan Drug Designation	☑			Priority review
4.	Unapproved New Drug		☑		NCE
5.	Medically Necessary Determination			☑	
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		☑		
7.	Rolling Submission		☑		
8.	Drug/device combination product with consult		☑		
9.	Complex manufacturing	☑			
10.	Other (e.g., expedited for an unlisted reason)		☑		
11.	At this time, is a KTM warranted for any PAI?	☑			DP manufacturer; OMPQ reviewer to accompany DP PAI

*If a priority consideration is indicated, please forward immediately to NDMAB BC and TL and do not process associated EERs.

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
12.	Is a single comprehensive list of all involved facilities available in one location in the application?	☑		
13.	Is all site information complete (e.g., contact information, responsibilities, address)?	☑		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	☑		-stability testing not explicitly stated
15.	Do all sites indicate they are ready to be inspected (on 356h)?	☑		
16.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?		☑	- (b) (4) (CTL) has no inspectional history -Remaining 4 EER facilities have good inspection history -EES comment & communication with ORA to participate in DP manufacturing site PAI

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQ. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
17.	Is the drug substance process or analytics considerably complex? (If so, comment)	☑		(See Part IV)
C. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
18.	Is the DP production (formulation, processing, finishing, filling, labeling and packaging, etc) or analytics considerably complex?	☑		(See Part IV)
19.	Have any Comparability Protocols been requested?		☑	

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
20.	Does this application fit one of the EES Product Specific Categories?	☑		NME, First FDA Evaluation for one establishment
21.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	☑		
22.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	☑		All sites listed as ready for inspection.

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	☑		(b) (4)

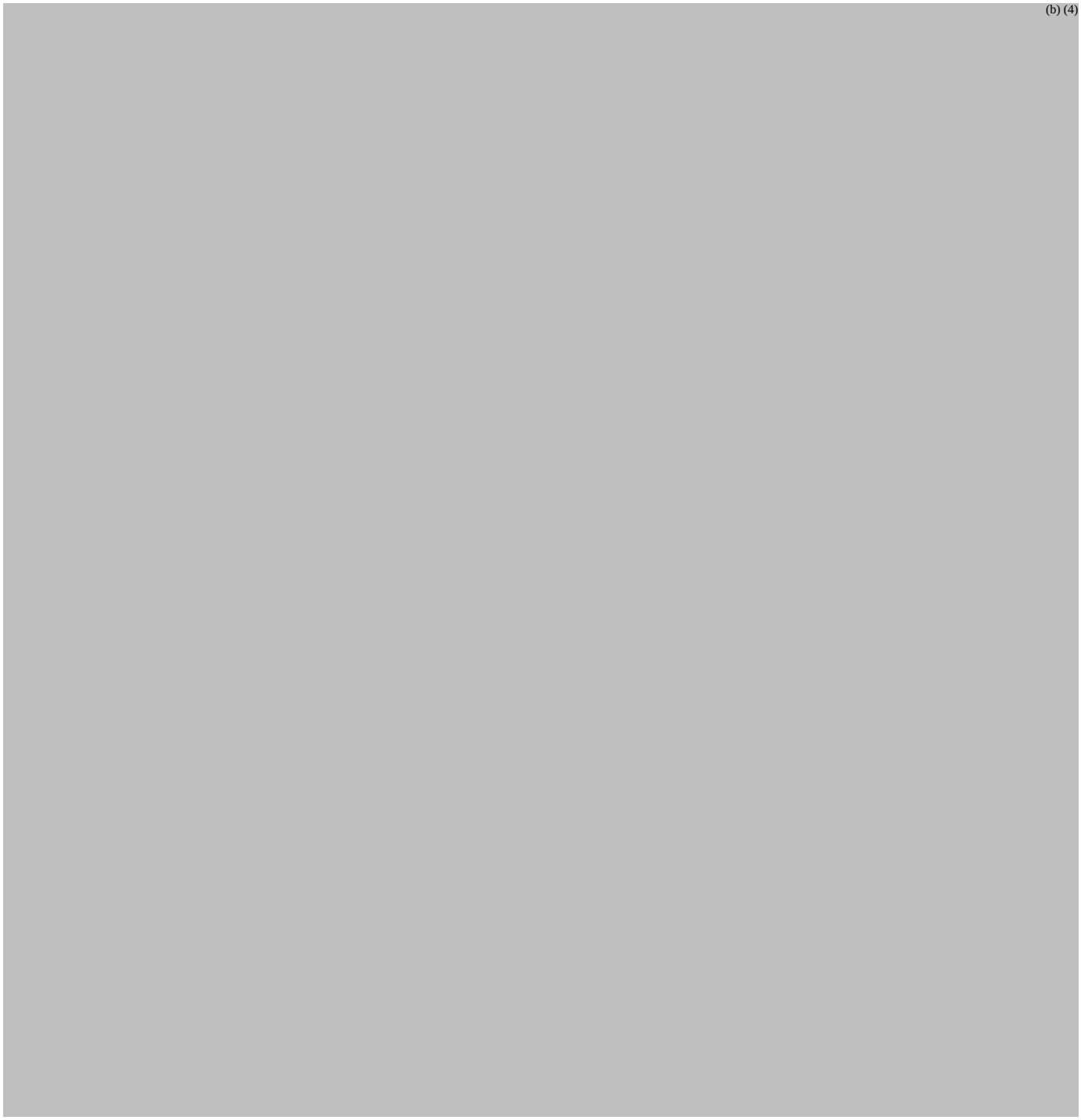
2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	☑		(b) (4) -Content uniformity sampling plan -**Unique capsule quality sample plan and reject limits**

3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.)

None

(b) (4)




(b) (4)

V. Overall Conclusions and Recommendations

Is the application filable? (yes/no)	**YES**
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no)	**NO**
Comments for 74 Day Letter	
1.	
2.	
3.	

REVIEW AND APPROVAL

Mahesh Ramanadham 6/26/2013
Don Henry 7/10/2013
Christina Capacci-Daniel 7/11/2013

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/s/

CHRISTINA A CAPACCI-DANIEL
07/15/2013
Corrected version

DON L HENRY
07/15/2013

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

OND Division:	Division of Neurology Products
NDA:	205677
Applicant:	Vanda Pharmaceuticals, Inc
Stamp Date:	31-May-2013
PDUFA Date:	31-Jan-2014
Trademark:	Hetlioz is proposed
Established Name:	Tasimelteon
Dosage Form:	Capsules
Route of Administration:	Oral
Indication:	Treatment of non-24 hour disorder (circadian rhythm sleep disorder) in the totally blind
CMC Lead:	Martha R. Heimann, Ph.D.
	Yes No
ONDQA Fileability:	☒ ☐
Comments for 74-Day Letter:	☒ ☐
Note:	NME, in Program, orphan indication

Summary and Critical Issues:

Summary

Tasimelteon (VEC-162) is an orally acting dual melatonin receptor agonist with selective agonist with selective agonist activity at the MT_1 and MT_2 receptors. It was originally developed by Bristol-Myers-Squibb, under IND 54776, as BMS-214778. The original indication at the time the IND was submitted was for treatment of primary insomnia. Vanda Pharmaceuticals (Vanda) subsequently acquired the rights to the compound and has investigated its use for a number of circadian rhythm related sleep disorders.

This NDA provides for an immediate release capsule formulation containing 20 mg of tasimelteon. The product is intended to be used for the treatment of non-24-hour disorder in the totally blind. The recommended dose is 20 mg per day taken one hour prior to bedtime, preferably at the same time every night.

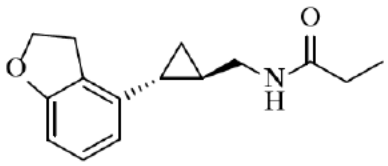
During development, Vanda sought CMC input via an end of Phase 2 CMC-meeting scheduled for October 11, 2007. The firm cancelled the meeting after receiving preliminary comments. Note that FDA did not agree with the firm's proposals. However, the issues raised are no longer relevant due to subsequent manufacturing changes.

A CMC-only pre-NDA meeting was held on October 23, 2012. Key CMC issues were designation of drug substance starting materials (agreed), issues related to agglomeration of the

(b) (4) drug substance on storage, and limited stability data for (b) (4) drug substance batches. The firm has extensive data for (b) (4) tasimelteon but limited data for (b) (4) batches. FDA and the firm agreed that limited data for the (b) (4) batches would not be a filing issue; retest period will be determined based on review of the provided data.

Drug Substance

The active ingredient, tasimelteon [chemical name: *N*-[[(1*R*,2*R*)-2-(2,3-dihydro-4-benzofuranyl)-cyclopropyl]methyl]propanamide] is a neutral small molecule with molecular formula $C_{15}H_{19}NO_2$ and molecular weight 245.32. The chemical structure of tasimelteon is:

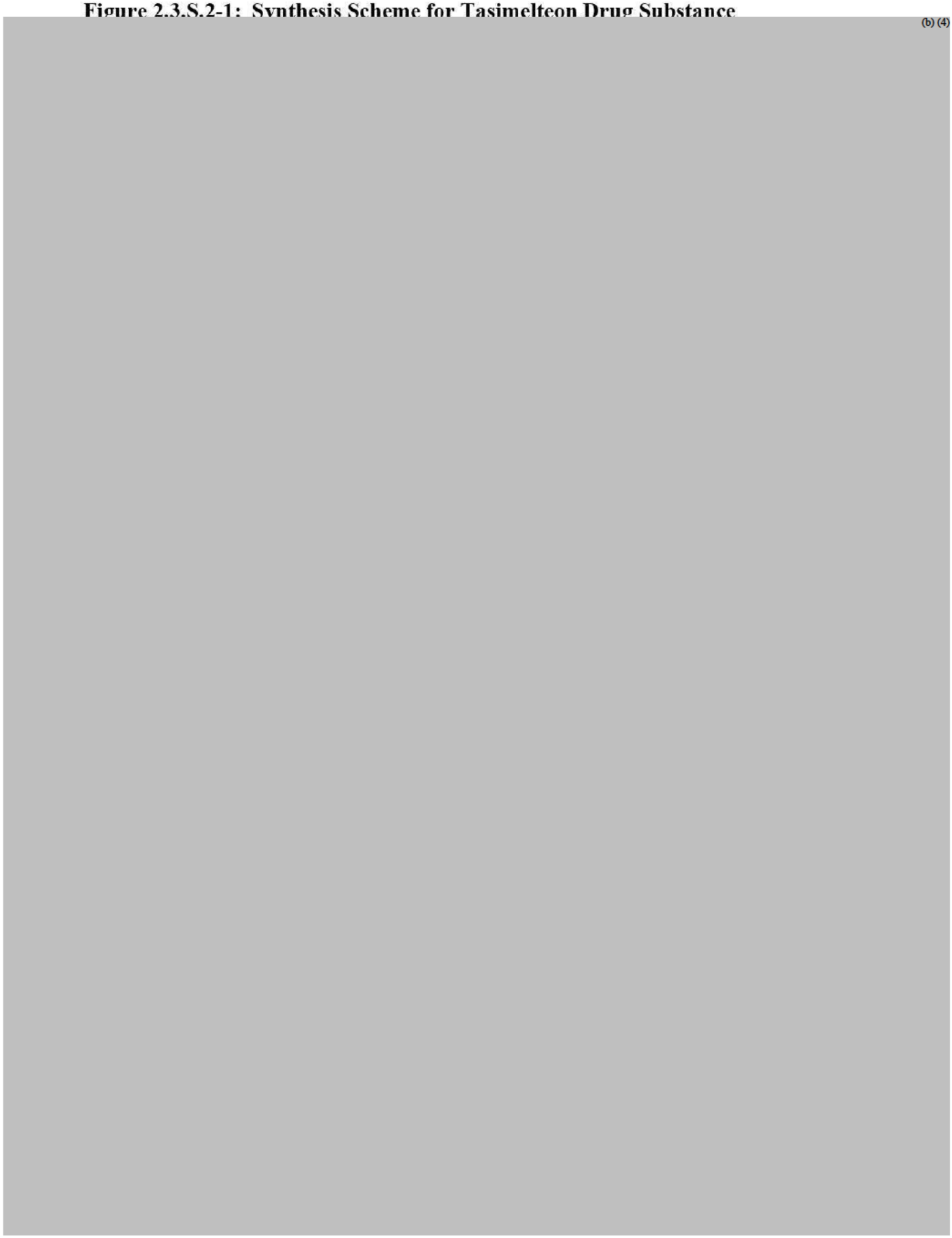


Tasimelteon is slightly soluble in water (b) (4) (b) (4) The melting point is relatively low (73°C - 77°C), (b) (4) (b) (4) (b) (4)

The drug substance is manufactured by (b) (4) As outlined in the applicant's Figure 3.2.S.2.6-1 on the following page, the manufacturing process involves (b) (4) The proposed commercial batch scale is intended to produce approximately (b) (4) tasimelteon. The (b) (4) material will be stored and (b) (4)

Figure 2.3.S.2-1: Synthesis Scheme for Tasimelteon Drug Substance

(b) (4)



The following points are noted with regard to drug substance manufacture:

- During development, the manufacturing process has undergone several iterations since the original IND process. This includes changes to the manufacturer and manufacturing site (b) (4) Thus, the linkage between pivotal nonclinical and clinical batches and the proposed commercial material should be evaluated carefully.

- The commercial tasimelteon manufacturing process involves (b) (4) (b) (4)

- (b) (4) has limited experience with the manufacturing process. The applicant indicates that to date, five batches (b) (4) of (b) (4) tasimelteon drug substance meeting all specifications have been manufactured at (b) (4) [Module 3.2.S.2., p 1] However, two of the five batches, (b) (4) required (b) (4) respectively. [Module 3.2.S.2., p. 51]

The proposed drug substance specification is included in Attachment 1. The specification includes appropriate tests (identity, potency, chiral purity, inorganic impurities, organic impurities, residual solvents, (b) (4) particle size, etc) and the analytical procedures appear straightforward. The following concerns are noted:

- The applicant proposes that a number of tests only be performed on (b) (4) tasimelteon. The acceptability of this approach for parameters such as residual solvents is considered a matter for review. The applicant should be asked to acknowledge that the drug substance (b) (4) should, if tested, comply with all requirements.

- (b) (4) The applicant proposes that this impurity be controlled as (b) (4). Given the potential for genotoxicity, reliance on an indirect control strategy may not be appropriate.

The drug substance primary stability package includes long-term (25°C/60% R. H.) and accelerated (40°C/75% R. H.) data through six months for three drug substance batches manufactured (b) (4) according to the proposed commercial

process. Available data for a fourth batches are limited to 3 months long-term and accelerated data. Batch scales for the primary stability batches range from (b) (4) Additional supportive data (up to 36 or 48 months long-term) are provided for batches manufactured by BMS and (b) (4) As communicated to the firm during the CMC pre-NDA meeting, data for (b) (4) tasimelteon batches manufactured by (b) (4) are also considered as supportive only.

The applicant proposes a (b) (4) retest date for both (b) (4) tasimelteon and for the (b) (4) drug substance. The retest date for (b) (4) tasimelteon is supported by real time data. The adequacy of the data to support a (b) (4) retest date for the (b) (4) drug substance is a review issue.

Drug Product

The proposed dosage form is an immediate release capsule containing 20 mg of tasimelteon and commonly used excipients. The unit composition is given in the applicant's Table 3.2.P.1-1 below. Tasimelteon Capsules will be marketed in 30-count HDPE bottles. The applicant doe not propose distribution of physician samples.

Table 3.2.P.1-1: Unit Formula for Tasimelteon 20-mg Capsules

Component	Function	Quantitative composition weight per capsule (mg)
Tasimelteon drug substance	Active ingredient	20.00[1]
Lactose anhydrous	(b) (4)	(b) (4)
Microcrystalline cellulose (b) (4)		
Colloidal silicon dioxide		
Croscarmellose sodium		
Magnesium stearate (b) (4)		
(b) (4)		
Size 1, dark blue opaque, hard gelatin capsules printed with "VANDA 20 mg" in white[2]	Gelatin capsule[3]	(b) (4)
Total capsule weight for size 1	NA	376.00

[1] Weight is adjusted for % assay of drug substance.
[2] Capsules used for stability and clinical batches were printed with (b) (4) but validation and commercial batches will have "VANDA 20 mg" printed in white.
[3] Gelatin capsule consists of gelatin, titanium dioxide, FD&C Blue #1, FD&C Red #3, and FD&C Yellow #6 (COA)
(b) (4)

Tasimelteon Capsules will be manufactured by a contract manufacturer. (b) (4) The manufacturing process involves (b) (4) which are then packaged in 30-HDPE bottles with (b) (4) -caps containing induction seals, (b) (4) Reasonably detailed process narratives and flow diagram are provided. The proposed commercial scale is (b) (4)

The proposed master batch record is not provided; this (or additional process details) may be requested if the reviewer determines that the information provided is insufficient. Executed batch records are provided for the registration stability/clinical batches.

The application includes limited information on pharmaceutical development. Capsule strengths ranging from 1 mg to 100 mg were used in clinical studies performed by BMS (1 mg, 10 mg and 50 mg) and Vanda (5 667 mg, 10 mg, 20 mg, 50 mg 100 mg). With the exception of the 5.667 mg capsule, both companies manufactured clinical capsules (b) (4) . The (b) (4) composition for the 20 mg Vanda clinical/commercial capsule is (b) (4) to that of the 10 mg clinical capsule originally developed by BMS. A very brief summary of the original BMS clinical formulation and manufacturing process is included, supporting data are not provided. Formulation development performed by Vanda and (b) (4) appears limited to adjustment of clinical capsule formulations (b) (4) Similarly, the only significant changes from the original BMS manufacturing process to the proposed commercial process are (b) (4) .

(b) (4) It is not clear that (b) (4) would be consistent with the requirement that *"The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient."* [211.101(a)] It is recommended that this be determined during the review in consultation with the Office of Compliance.

The proposed specification for Tasimelteon Tablets is included in Attachment 2. Test parameters and analytical procedures are straightforward and typical for a solid oral dosage form. The HPLC method for assay and impurities appears to be essentially the same as for the drug substance. Specified known and unspecified impurities are controlled at the ICH qualification and identification thresholds, respectively, based on the proposed 20 mg daily dose.

The NDA primary stability package includes long-term data (25°C/60% R. H.) through 12 months and accelerated data (40°C/75% R. H.) through 6 months for three batches of Tasimelteon Tablets 20 mg. The primary stability batches were manufactured by (b) (4) at commercial scale using commercial process drug substance batches manufactured by (b) (4) The post-approval commitment provides for placement of the first three commercial batches, and subsequent annual batches, on long-term stability. A (b) (4) expiration dating period is proposed based on the applicant's statistical analyses (assay, impurities, disintegration, dissolution and (b) (4) Based on a preliminary assessment of the provided statistical output for assay and impurities, extrapolation from 12 to 24 months may not be allowable.

Critical issues for review

Drug Substance

As noted above, the commercial manufacturer has limited experience with the manufacturing process. (b) (4) has only manufactured five batches (b) (4) of (b) (4) tasimelteon, with two of these requiring (b) (4) to conform to specification.

The tendency of the (b) (4) drug substance to (b) (4) The applicant's attributes the lack of (b) (4) in stability samples to the (b) (4). If so, results from studies performed (b) (4) may not provide sufficient assurance of quality.

Drug Product

The most critical issue regarding the drug product is whether the manufacturing process is robust enough (b) (4) of the active ingredient without compromising the quality of the resulting

Additional issues

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

Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing of tasimelteon and Tasimelteon Tablets is provided in the submission. All facilities have been submitted in EES.

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

Methods Validation: The drug substance is a new molecular entity; therefore, methods validation studies by the DPA St. Louis laboratory will be requested Given the number of possible impurities resulting from the synthesis process, it is recommended that the drug substance assay and related substances methods be validated.

Comments for 74-Day Letter

The following comments are suggested for inclusion in the 74-Day Letter, pending any additions or revisions by the reviewer.

With respect to the drug substance:

Based on our initial evaluation of the information provided in the application, it is unclear whether you have adequate understanding and control of the manufacturing process. We note that two of the five batches of (b) (4) tasimelteon manufactured by (b) (4) to

date have required (b) (4) in order to conform to specification. Of these, batch (b) (4) was (b) (4) Clarify whether this batch was tested for residual metals per the specification for (b) (4) tasimelteon (Table 3.2.S.2.4-5) prior to release for (b) (4)

You indicate that (b) (4) tasimelteon is observed after long-term storage in (b) (4), but not in formal stability studies. Thus, we are concerned that results from studies performed using (b) (4), would not indicative of the effects of the storage and shipping conditions on drug substance (b) (4). Provide any available data obtained from drug substance stored or shipped (b) (4)

With respect to the drug product:

The proposed manufacturing process for Tasimelteon Capsules provides for (b) (4) (b) (4)

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective.

The drug substance is a well-characterized small molecule and the drug product is a simple immediate release capsule. The application does not present QbD approaches or use of in-process analytical technologies. Assignment of a CMC reviewer and a Biopharmaceutics reviewer is recommended. The submission has been evaluated by the New Drug Microbiology Staff. Per the Micro Filing Review (Brian Riley, 06-Jun-2013) the microbiological controls are acceptable and further is not required. A Division-level regulatory briefing is appropriate for a new molecular entity and standard solid oral dosage form.

{See appended electronic signature page}

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

{See appended electronic signature page}

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

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CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number:	**Supplement Number and Type:**	**Established/Proper Name:**
205677	N/A	Tasimelteon Capsules
Applicant:	**Letter Date:**	**Stamp Date:**
Vanda Pharmaceuticals	30-May-2013	31-May-2013

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?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		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.**			N/A
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

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

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

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

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

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?			Executed batch records are provided. The proposed master batch record is not provided.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			N/A

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	11-Mar-2013	
	III			19-Mar-2013	
	III			04-Mar-2013	
	III			11-Mar-2013	

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

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**Is the product quality section of the application fileable?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		Refer to comments in Initial Quality Assessment above.

{See appended electronic signature page}

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

{See appended electronic signature page}

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

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/s/

MARTHA R HEIMANN
06/28/2013

RAMESH K SOOD
07/01/2013

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205677/000	**Sponsor:**	VANDA PHARMS INC
Org. Code:	120		2200 PENNSYLVANIA AVE NORTHWEST STE 3
':	1		WASHINGTON, DC 20037
S...p Date:	31-MAY-2013	**Brand Name:**	TASIMELTEON
PDUFA Date:	31-JAN-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	TASIMELTEON
District Goal:	30-SEP-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; CAPSULE; TASIMELTEON; 20MG

FDA Contacts:	R. KAMBHAMPATI	Prod Qual Reviewer	(HFD-830)	3017961382
	T. BOUIE	Product Quality PM		3017961649
	C. MICHALOSKI	Regulatory Project Mgr	(HFD-120)	3017961123
	M. HEIMANN	Team Leader		3017961678

Overall Recommendation:	ACCEPTABLE	on 11-DEC-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 15-NOV-2013	by EES_PROD		
	PENDING	on 18-OCT-2013	by EES_PROD		
	PENDING	on 25-JUN-2013	by EES_PROD		
	PENDING	on 21-JUN-2013	by EES_PROD		

Establishment:	**CFN:**	**FEI:**	(b) (4)
			(b) (4)
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-JUN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-DEC-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-DEC-2013

Decision: ACCEPTABLE

: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-AUG-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION
