CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-991

CHEMISTRY REVIEW(S)

NDA 21-991

REVIEW # 2

ZOLINZA® (Vorinostat)
100 mg Capsules

JOSEPHINE M. JEE
CMC REVIEWER

DIVISION OF DRUG ONCOLOGY PRODUCTS

Pre-Marketing Assessment Division III

CMC Review of Original NDA

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Chemistry Review Data Sheet

1. NDA 21-991

2. REVIEW: # 2

3. ASSIGNED DATE: 03-OCT-2006

4. REVIEW DATE: 03-OCT -2006

5. REVIEWER: Josephine M. Jee

6. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Suberoylanilide Hydroxamice Acid	IND 58,915, 21-MAY-2001
CMC EOP 2 Meeting	IND 58,915, 09-SEP-2003
Pre-NDA (proposed to file eCTD)	IND 58,915, 04-NOV-2005
CMC Pre-NDA meeting (responses to Pre-NDA background package)	IND 58,915, 30-NOV-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-991 - (Rolling Submission - CMC)	06-DEC-2005
NDA 21-991 - Module 3- Quality, QOS, & LOAs)	22-FEB-2006
NDA 21-991 – (CTD intro., EA, and Labeling)	05-APR-2006
NDA 21-991 – (Merck Response to Rev. # 1 Comments) (Email)	02-OCT-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck & Co., Inc.
Address:	One Merck Drive P.O. Box 100 Whitehouse Station, New Jersey 08889-0100
Representative:	Randi Albin, Ph.D., Director, Regulatory Affairs
Telephone:	732-594-4240

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ZOLINZA™

b) Non-Proprietary Name (USAN): Vorinostat

c) Code Name/# (ONDC only): MK-0683

d) CAS Registry Number: 149647-78-9

e) Chemical Name (IUPAC): *N*-hydroxy-*N'*-phenyloctanediamide

Other Names: suberoylanilide hydroxamic acid (SAHA)

Alternative names: *N*-hydroxy-*N'*-phenyl-octane-1,8-dioic acid diamide (original name)

f) Chem. Type/Submission Priority (ONDC only):

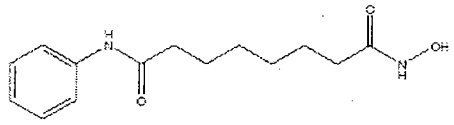
- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NDA is submitted under 505 (b)
10. PHARMACOL. CATEGORY: Oral Treatment of Cutaneous T Cell Lymphoma
11. DOSAGE FORM: Capsules
12. STRENGTH/POTENCY: 100 mg
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

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



Molecular Formula: $C_{14}H_{20}N_2O_3$

Molecular Mass: 264.32

Chemical Name: *N*-hydroxy-*N*-phenyloctanediamide

CAS Registry Number: 149647-78-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
	II			1	A*	23-JUN-2006	Acceptable
	IV			3	A*	30-DEC-2002	Acceptable
	III			1	A*	22-JUN-2006	Acceptable
	III			1	A*	22-JUN-2006	Acceptable
	III			1	A*	23-JUN-2006	Acceptable
	III			1	A*	23-JUN-2006	Acceptable
	III			1	A*	23-JUN-2006	Acceptable
	III			1	A*	23-JUN-2006	Acceptable
	III			1	A*	01-AUG-2006	Acceptable
	IV			3	A*	11-JUN-2003	Acceptable

*A=Adequate

[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)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,915	Suberoylanilide Hydroxamic Acid (SAHA)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	No consult required. There was no significant change in any of the quality attributes on stability.	------	--------
EES	Overall Acceptable.	11-MAY-2006	Shirnette Ferguson, Consumer Safety Officer, Office of Compliance
Pham/Tox	Impurities are adequately qualified.	03-AUG-2006	Leigh Verbois, Ph.D., Reviewer Pharmacologist
LNC	NA. Appropriate USAN and common dosage form.	12-JUL-2006	J.Jee
Methods Validation	N/A. Methods do not qualify for any of the seven criteria outlined in ONDQA policy on methods validation		J.Jee
ODS/DMETS	Tradename "Zolinza" acceptable by DMETS and DDMAC	9/22/2006	Diane Smith
EA	Exemption adequately justified.	28-JUL-2006	J.Jee
Microbiology	N/A. The DP does not promote microbial growth.	28-JUL-2006	J.Jee

The Chemistry Review for NDA 21-991

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the standpoint of Product quality CMC, NDA 21-991 is recommended for approval. An expiration period of 24 months may be granted based on the assessment of , real time stability data.

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

There are no Phase 4 CMC commitments.

II. Summary of Chemistry Assessments

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

Drug Product:
ZOLINZA™ (vorinostat) is intended to treat advanced, refractory cutaneous T-cell lymphoma (CTCL), which is a rare type of malignant non-Hodgkin's lymphoma. ZOLINZA is available in 100 mg white opaque hard gelatin capsules that are imprinted with "568" over "100 mg" within radial bar in black ink on the capsule body. This drug product is packaged in bottles (containing 120 capsules) with closures. The drug product is an immediate-release formulation containing pharmaceutical excipients that are conventional in nature and consist of microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The capsule shell excipients are titanium dioxide, gelatin and contain sodium lauryl sulfate.

Drug Substance:
Vorinostat is a member of a new class of anti-neoplastic agents called histone deacetylase (HDAC) inhibitors. HDACs catalyze the removal of acetyl groups from the lysine residues of proteins, including histones. Vorinostat is also known as suberoylanilide hydroxamic acid (SAHA), MK-0683, and L-001079038. The chemical name of the drug substance is *N*-hydroxy-*N'*-phenyloctanediamide. The USAN Council adopted name is vorinostat. Vorinostat is a hydroxamic acid made by .
Vorinostat is a white to light orange powder with a molecular weight of 264.3 and molecular formula of $C_{14}H_{20}N_2O_3$. The differential scanning calorimetry (DSC) ranged from 161.7 (endotherm) to 163.9°C. The endotherms is associated with the melting of the sample. The pH of saturated water solutions of vorinostat drug substance was 6.6. This drug substance is very slightly soluble in water and physiological pH and sparingly soluble in solvents with pH > 8.5 and it is slightly soluble in ethanol.

. Vorinostat is photostable and non-reactive in the solid state.

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

ZOLINZA is indicated for

The recommended dose is 400 mg orally once daily with food. If patients are intolerant to therapy, subsequent doses may be reduced to 300 mg orally once daily with food. The dose schedule may be further reduced to 300 mg once daily with food for 5 consecutive days each week, as necessary. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

The marketed drug product would be packaged in bottles of 120 capsules with child-resistant closure, NDC 0006-0568-40. The recommended storage condition is at 20 - 25°C (68 - 77°F).
The recommended handling statement "Direct contact of the powder in ZOLINZA capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly. ZOLINZA capsules should not be opened or crushed *[see Nonclinical Toxicology(13.1)]."*

C. Basis for Approvability or Not-Approval Recommendation

During process development of the API synthesis, to form vorinostat and several processes were explored before they chose the final synthetic route. The key issues in the manufacturing of vornostat drug substance were

Vorinostat is stable under 25°C/60% RH and 40°C/75% RH storage conditions and to moisture and light. The retest date for vorinostat is supported by extensive real-time stability data on clinical and primary stability batches and on the drug substance batches manufactured from four manufacturing processes described in the application. Most test results (either accelerated or long-term study) did not show significant change during the course of the stability study. Most impurities identified were below with exception of

CMC deficiencies pertaining to the API were communicated to the DMF Holder on 04-AUG-2006 and their responses were reviewed and were deemed adequate to support the NDA.

Manufacturing process of the drug product consists of including microcrystalline cellulose (MCC), croscarmellose sodium, and magnesium stearate. These excipients were chosen to Preliminary

stability studies demonstrated that the above excipients were compatible with vorinostat drug substance. MCC was selected Croscarmellose sodium was chosen . Magnesium stearate was included . All inactive ingredients are compendial excipients with the exception of the hard gelatin capsule and the black inks , which are accepted on suppliers' certificates of analysis.

Based on the Biopharmaceutics Classification System (BCS), vorinostat has low solubility and low permeability (Class IV compound). is the primary factor controlling in vitro capsule dissolution.

The proposed two-time point dissolution specification at 15 and 60 minutes provides control over the dissolution rate while the dissolution window at 15 minutes ensures that the dissolution kinetics are neither too fast nor too slow in comparison to the dissolution profile of the biobatch. The sponsor used the biobatch (Lot No. 0683DFC004A001) using the similarity factor f2 to guide formulation development and was selected for capsule formulation.

The dissolution tests were conducted using USP Apparatus II (paddles, 100 rpm). Initially, the dissolution tests involved a as the dissolution medium. Because of variable dissolution results, which were attributed to the dissolution medium, the dissolution method was modified to include 2.0% Tween 80 and an HPLC method was developed. Appropriate sampling time points were added to the method to characterize the dissolution profile of the drug product.

The proposed dissolution acceptance criteria of 15 min: ≥ and ≤ 60 min: ≥ are based on clinical, FSS, and biobatch batches and are acceptable.

The stability data of Vorinostat Capsules generated from the three FSS drug product batches for up to are included in this application. Additionally, up to 13 weeks of stability data are included for a fourth FSS batch (bridging batch) that bridged the changes made to the formulation and the manufacturing process subsequent to the manufacture of the biobatch.

The FSS have been conducted in accordance with the ICH Guidelines for stability testing of new drug products. The FSS data show satisfactory stability of the drug product, conforming to the specifications, when packaged in the market container closure system. No significant changes were observed at any of the storage conditions. Based on stability data available to date, Merck & Co., Inc. proposes an initial shelf life of 24 months for Vorinostat Capsules when stored at 20-25°C (68-77°F).

Evaluation of the stability data submitted on a Biobatch and three FSS batches of the drug product indicated that vorinostat drug product shows no significant variability in the assay, impurities, dissolution, moisture, and appearance. One identified impurity, , is found at level, no unidentified impurities were reported at the intermittent (30°C/65% RH) and accelerated (40°C/75% RH) storage conditions. However, Merck did not submit any statistical analysis, as per ICH QIE Evaluation of Stability Data, to support the requested 24-month expiration dating period. However, since there are no trends on stability for any of the stability-indicating attributes and since the stability data meets the ICH Q1E requirements for an extrapolation of 12 months beyond the real time stability data an expiration dating period of 24 months is granted for this product.

Issues pertaining to vorinostat drug substance have been addressed in DMF and the deficiencies were communicated to the DMF Holder on 04-AUG-2006. Subsequently, the responses were reviewed and were deemed satisfactory.

Comments on carton labels were communicated to Merck on 29-SEP-2006 and Merck's revision dated 02-OCT-2006 were reviewed and were deemed adequate. Similarly, the labeling (PI and PPI) was revised to include adequate information in the description and how-supplied sections.

All manufacturing facilities were found to be acceptable by the Office of Compliance on 11-MAY-2006.

In conclusion, from the standpoint of Product quality CMC, NDA 21-991 is recommended for approval. An expiration period of 24 months may be granted based on the assessment of 52 weeks real time stability data.

APPEARS THIS WAY
ON ORIGINAL

III. Administrative

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

See DFS

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✓ § 552(b)(4) Trade Secret / Confidential

__ § 552(b)(5) Deliberative Process

__ § 552(b)(4) Draft Labeling

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

/s/

Josephine Jee
10/3/2006 05:51:14 PM
CHEMIST

Ravi Harapanhalli
10/3/2006 06:02:00 PM
CHEMIST

NDA 21-991

REVIEW # 1

ZOLINZA® (Vorinostat)
100 mg Capsules

JOSEPHINE M. JEE
CMC REVIEWER

DIVISION OF DRUG ONCOLOGY PRODUCTS

Pre-Marketing Assessment Division III

CMC Review of Original NDA

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C. CC Block 10

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Chemistry Review Data Sheet

1. NDA 21-991

2. REVIEW: # 1

3. ASSIGNED DATE: 20-APR-2006

4. REVIEW DATE: 04-AUG -2006/ 28-SEP-2006

5. REVIEWER: Josephine M. Jee

6. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Suberoylanilide Hydroxamice Acid	IND 58,915, 21-MAY-2001
CMC EOP 2 Meeting	IND 58,915, 09-SEP-2003
Pre-NDA (proposed to file eCTD)	IND 58,915, 04-NOV-2005
CMC Pre-NDA meeting (responses to Pre-NDA background package)	IND 58,915, 30-NOV-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-991 - (Rolling Submission - CMC)	06-DEC-2005
NDA 21-991 - Module 3- Quality, QOS, & LOAs)	22-FEB-2006
NDA 21-991 – (CTD intro., EA, and Labeling)	05-APR-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck & Co., Inc.
Address:	One Merck Drive P.O. Box 100 Whitehouse Station, New Jersey 08889-0100
Representative:	Randi Albin, Ph.D., Director, Regulatory Affairs
Telephone:	732-594-4240

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ZOLINZA™

b) Non-Proprietary Name (USAN): Vorinostat

c) Code Name/# (ONDC only): MK-0683

d) CAS Registry Number: 149647-78-9

e) Chemical Name (IUPAC): *N*-hydroxy-*N'*-phenyloctanediamide

Other Names: suberoylanilide hydroxamic acid (SAHA)

Alternative names: *N*-hydroxy-*N'*-phenyl-octane-1,8-dioic acid diamide (original name)

f) Chem. Type/Submission Priority (ONDC only):

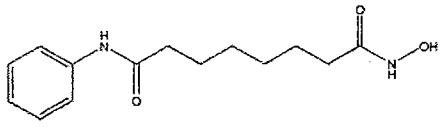
- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NDA is submitted under 505 (b)
10. PHARMACOL. CATEGORY: Oral Treatment of Cutaneous T Cell Lymphoma
11. DOSAGE FORM: Capsules
12. STRENGTH/POTENCY: 100 mg
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

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

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



Molecular Formula: $C_{14}H_{20}N_2O_3$

Molecular Mass: 264.32

Chemical Name: *N*-hydroxy-*N*-phenyloctanediamide

CAS Registry Number: 149647-78-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
	II			1	A*	23-JUN-2006	Acceptable
	IV			3	A*	30-DEC-2002	Acceptable
	III			1	A*	22-JUN-2006	Acceptable
	III			1	A*	22-JUN-2006	Acceptable
	III			1	A*	23-JUN-2006	Acceptable
	III			1	A*	23-JUN-2006	Acceptable
	III			1	A*	23-JUN-2006	Acceptable
	III			1	A*	23-JUN-2006	Acceptable
	III			1	A*	01-AUG-2006	Acceptable
	IV			3	A*	11-JUN-2003	Acceptable

*A=Adequate

[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)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,915	Suberoylanilide Hydroxamic Acid (SAHA)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	No consult required. There was no significant change in any of the quality attributes on stability.	------	--------
EES	Overall Acceptable.	11-MAY-2006	Shirnette Ferguson, Consumer Safety Officer, Office of Compliance
Pham/Tox	Impurities are adequately qualified.	03-AUG-2006	Leigh Verbois, Ph.D., Reviewer Pharmacologist
LNC	NA. Appropriate USAN and common dosage form.	12-JUL-2006	J.Jee
Methods Validation	N/A. Methods do not qualify for any of the seven criteria outlined in ONDQA policy on methods validation		J.Jee
ODS/DMETS	Tradename "Zolinza" acceptable by DMETS and DDMAC	9/22/2006	Diane Smith
EA	Exemption adequately justified.	28-JUL-2006	J.Jee
Microbiology	N/A. The DP does not promote microbial growth.	28-JUL-2006	J.Jee

The Chemistry Review for NDA 21-991

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the standpoint of Product quality CMC, NDA 21-991 is recommended for approval. An expiration period of 24 months may be granted based on the assessment of — real time stability data. Comments on carton labels, listed at the end of the review should be communicated to the firm and should be included in the final printed labels.

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

There are no Phase 4 CMC commitments.

CMC Agreement: Provide justification and summary data for the selection of 2% Tween 80 and 100 rpm in the regulatory method for dissolution testing and comment on its discriminatory power. To this end, provide supporting data using lower concentrations of Tween 80 and lower paddle speeds.

II. Summary of Chemistry Assessments

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

Drug Product:

ZOLINZA™ (vorinostat) is intended to treat advanced, refractory cutaneous T-cell lymphoma (CTCL), which is a rare type of malignant non-Hodgkin's lymphoma. ZOLINZA is available in 100 mg white opaque hard gelatin capsules that are imprinted with "568" over "100 mg" within radial bar in black ink on the capsule body. This drug product is packaged in — (containing 120 capsules) with — closures. The drug product is an immediate-release formulation containing pharmaceutical excipients that are conventional in nature and consist of microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The capsule shell excipients are titanium dioxide, gelatin and contain sodium lauryl sulfate.

Drug Substance:

Vorinostat is a member of a new class of anti-neoplastic agents called histone deacetylase (HDAC) inhibitors. HDACs catalyze the removal of acetyl groups from the lysine residues of proteins, including histones. Vorinostat is also known as suberoylanilide hydroxamic acid (SAHA), MK-0683, and L-001079038. The chemical name of the drug substance is *N*-hydroxy-*N*'-phenyloctanediamide. The USAN Council adopted name is vorinostat. Vorinostat is a hydroxamic acid made by —

Vorinostat is a white to light orange powder with a molecular weight of 264.3 and molecular formula of $C_{14}H_{20}N_2O_3$. The differential scanning calorimetry (DSC) ranged from 161.7 (endotherm) to 163.9°C. The endotherms is associated with the melting of the sample. The pH of saturated water solutions of vorinostat drug substance was 6.6. This drug substance is very slightly soluble in water and physiological pH and sparingly soluble in solvents with pH > 8.5 and it is slightly soluble in ethanol. —

Vorinostat is photostable and non-reactive in the solid state. —

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

ZOLINZA is indicated —

The recommended dose is 400 mg orally once daily with food. If patients are intolerant to therapy, subsequent doses may be reduced to 300 mg orally once daily with food. The dose schedule may be further reduced to 300 mg once daily with food for 5 consecutive days each week, as necessary. Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

The marketed drug product would be packaged in bottles of 120 capsules with child-resistant closure, NDC 0006-0568-40. The recommended storage condition is at 20 - 25°C (68 - 77°F).
The recommended handling statement "Direct contact of the powder in ZOLINZA capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly. ZOLINZA capsules should not be opened or crushed *[see Nonclinical Toxicology(13.1)]*."

C. Basis for Approvability or Not-Approval Recommendation

During process development of the API synthesis, —) form vorinostat and several processes were explored before they chose the final synthetic route. The key issues in the manufacturing of vornostat drug substance were —

Vorinostat is stable under 25°C/60% RH and 40°C/75% RH storage conditions and to moisture and light. The retest date for vorinostat is — supported by extensive real-time stability data on clinical and primary stability batches and on the drug substance batches manufactured from four manufacturing processes described in the application. Most test results (either accelerated or long-term study) did not show significant change during the course of the stability study. Most impurities identified were below — with exception of —

CMC deficiencies pertaining to the API were communicated to the DMF Holder — on 04-AUG-2006 and their responses were reviewed and were deemed adequate to support the NDA.

Manufacturing process of the drug product consists of [redacted] including microcrystalline cellulose (MCC), croscarmellose sodium, and magnesium stearate. These excipients were chosen [redacted] Preliminary stability studies demonstrated that the above excipients were compatible with vorinostat drug substance. MCC was selected [redacted] . Croscarmellose sodium was chosen [redacted] Magnesium stearate was included [redacted] . All inactive ingredients are compendial excipients with the exception of the hard gelatin capsule and the [redacted] black inks [redacted] , which are accepted on suppliers' certificates of analysis.

Based on the Biopharmaceutics Classification System (BCS), vorinostat has low solubility and low permeability (Class IV compound). [redacted] ne primary factor controlling in vitro capsule dissolution. [redacted]

The proposed two-time point dissolution specification at 15 and 60 minutes provides control over the dissolution rate [redacted] while the dissolution window at 15 minutes ensures that the dissolution kinetics are neither too fast nor too slow in comparison to the dissolution profile of the biobatch. The sponsor used the biobatch (Lot No. 0683DFC004A001) using the similarity factor f2 to guide formulation development [redacted]

The dissolution tests were conducted using USP Apparatus II (paddles, 100 rpm). Initially, the dissolution tests involved a [redacted] as the dissolution medium. Because of variable dissolution results, which were attributed to the dissolution medium, the dissolution method was modified to include 2.0% Tween 80 and an HPLC method was developed. Appropriate sampling time points were added to the method to characterize the dissolution profile of the drug product.

The proposed dissolution acceptance criteria of 15 min: [redacted] but [redacted] , 60 min: [redacted] are based on clinical, FSS, and biobatch batches and are acceptable.

The stability data of Vorinostat Capsules generated from the three FSS drug product batches for up to [redacted] are included in this application. Additionally, up to [redacted] of stability data are included for a fourth FSS batch (bridging batch) that bridged the changes made to the formulation and the manufacturing process subsequent to the manufacture of the biobatch.

The FSS have been conducted in accordance with the ICH Guidelines for stability testing of new drug products. The FSS data show satisfactory stability of the drug product, conforming to the specifications, when packaged in the market container closure system. No significant changes were observed at any of the storage conditions. Based on stability data available to date, Merck & Co., Inc. proposes an initial shelf life of 24 months for Vorinostat Capsules when stored at 20-25°C (68-77°F).

Evaluation of the stability data submitted on a Biobatch and three FSS batches of the drug product indicated that vorinostat drug product shows no significant variability in the assay, impurities, dissolution, moisture, and appearance. One identified impurity, [redacted] is found at [redacted] evel, no unidentified impurities were reported at the intermittent (30°C/65% RH) and accelerated (40°C/75% RH) storage conditions. However, Merck did not submit any statistical analysis, as per ICH QIE Evaluation of Stability Data, to support the requested 24-month expiration dating period. However, since there are no trends on stability for any of the stability-indicating attributes and since the stability data meets the ICH Q1E requirements for an extrapolation of 12 months beyond the real time stability data an expiration dating period of 24 months is granted for this product.

Issues pertaining to vorinostat drug substance have been addressed in DMF [redacted] and the deficiencies were communicated to the DMF Holder on 04-AUG-2006. Subsequently, the responses were reviewed and were deemed satisfactory.

All manufacturing facilities were found to be acceptable by the Office of Compliance on 11-MAY-2006.

In conclusion, from the standpoint of Product quality CMC, NDA 21-991 is recommended for approval. An expiration period of 24 months may be granted based on the assessment of ~ real time stability data. Comments on carton labels, listed at the end of the review should be communicated to the firm and should be included in the final printed labels.

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III. Administrative

A. Reviewer's Signature

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B. Endorsement Block

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__ § 552(b)(5) Deliberative Process

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/s/

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9/29/2006 01:09:06 PM
CHEMIST

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9/29/2006 04:29:50 PM
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