CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
202736Orig1s000

<u>CHEMISTRY REVIEW(S)</u>

Memorandum DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **February 3, 2012**

From: **Caroline Strasinger, Ph.D.**
New Drug Quality Assessment Division II
ONDQA

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch IV
New Drug Quality Assessment Division II
ONDQA

To: **CMC Review #1 of NDA 202-736**

Subject: **Final Recommendation**

The CMC review #1 has noted the following two pending issues:

1. Final "Acceptable" recommendation from the Office of Compliance was not issued.
2. Label/labeling issues were not resolved.

And because of these deficiencies, in the CMC Review #1, this NDA was not recommended for approval from the ONDQA perspective.

On February 3, 2012, the Office of Compliance issued the "Acceptable" recommendation for the facilities involved in the NDA (see the Attachment I).

On February 2, 2012, the final label and labeling were submitted by the Applicant via email and they are revised satisfactorily from the ONDQA perspective (see the Attachment II).

Recommendation:

This NDA is **now** recommended for approval from the ONDQA perspective.

Reviewer Erratum:
On page 7 of CMC review #1 NDA 202-736 is incorrectly referred to as NDA 22-560. The title of page 7 should read ***"The Chemistry Review for NDA 202-736."***

Attachment:

1. EES report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 202736/000	**Action Goal:**	
Stamp Date:	07-APR-2011	**District Goal:**	08-AUG-2011
Regulatory:	07-FEB-2012		
Applicant:	TOPAZ INC 100 WILMER RD STE 280 HORSHAM, PA 19044	**Brand Name:** **Estab. Name:** **Generic Name:**	Sklice (Ivermectin) IVERMECTIN
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	540	001; CREAM, AUGMENTED; IVERMECTIN; .5%	

Application Comment:

FDA Contacts:	J. DAVID	Project Manager		301-796-4247
	C. STRASINGER	Review Chemist	(HFD-800)	
	S. DING	Team Leader		301-796-1349

Overall Recommendation:	ACCEPTABLE	on 03-FEB-2012	by M. STOCK	(HFD-320)	301-796-4753
	PENDING	on 09-JUN-2011	by EES_PROD		
	PENDING	on 31-MAY-2011	by EES_PROD		
	ACCEPTABLE	on 02-MAY-2011	by A. INYARD	()	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: 1628114 FEI: 1000117684

DPT LABORATORIES INC

200/307 E JOSEPHINE STREET
SAN ANTONIO, TX 78215

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: WE HAVE CONCERNS REGARDING THE APPLICANT'S USE OF DPT LABORATORIES INC. AT 307 E. JOSEPHINE ST, SAN ANTONIO, TX (FEI# 1000117684).

ONE OF THE REGISTRATION DRUG PRODUCT LOTS (LOT #BEF) FAILED MICROBIAL LIMITS TESTING (MOLD GROWTH) ON REPEATED TESTS (6 MO, 9 MO, 12 MO). THE APPLICANT HAS STATED THAT AFTER INVESTIGATION THEY DON'T KNOW THE ROOT CAUSE.

WOULD IT BE FEASIBLE TO RECONSIDER THIS SITE FOR INSPECTION? WE ARE HOPING AN INVESTIGATOR CAN GO TO THIS SITE AND CHECK TO SEE WHAT CAUSED THE MICROBIAL FAILURE. (on 31-MAY-2011 by J. DAVID () 301-796-4247)

SITE FOR DRUG PRODUCT MANUFACTURE, PACKAGING, RELEASE TESTING, STABILITY STORAGE AND TESTING. (on 20-APR-2011 by J. DAVID () 301-796-4247)

Profile: OINTMENT,NONSTERILE (INCLUDES CREAM, JELLY, PASTE) **OAI Status:** NONE

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	22-APR-2011				DAVIDJE
SUBMITTED TO DO	22-APR-2011	10-Day Letter			SMITHDE
DO RECOMMENDATION	02-MAY-2011			ACCEPTABLE	JMARTIN1
PREVIOUSLY INSPECTED NOV 2010.				BASED ON FILE REVIEW	
OC RECOMMENDATION	02-MAY-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	31-MAY-2011				DAVIDJE
SUBMITTED TO DO	01-JUN-2011	Product Specific			STOCKM
REQUESTING PAI DUE TO ISSUES IDENTIFIED BY REVIEW TEAM.					
DO RECOMMENDATION	14-JUL-2011			ACCEPTABLE	JMARTIN1
				BASED ON FILE REVIEW	
OC RECOMMENDATION	18-JUL-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: FEI: 3005023061

DPT LABORATORIES INC

3300 RESEARCH PLAZA BROOKS CITY BASE
SAN ANTONIO, TX 78235

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: SITE FOR TESTING, RELEASE, AND DISPENSING OF CHEMICAL COMPONENTS, TESTING AND RELEASE OF PACKAGING MATERIALS, INSPECTION AND RELEASE OF LABELING. (on 20-APR-2011 by J. DAVID () 301-796-4247)

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

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	22-APR-2011				DAVIDJE
OC RECOMMENDATION	22-APR-2011			ACCEPTABLE	SMITHDE
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: 9611402 FEI: 3002807210

HOVIONE MACAU SOCIEDADE QUIMICA LDA

ESTRADA CORONEL MESQUITA BOX 89
TAIPA, , MACAU

DMF No: 21395 **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: [redacted] (b) (4)

Profile: [redacted] (b) (4) **OAI Status:** NONE

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	22-APR-2011				DAVIDJE
SUBMITTED TO DO	22-APR-2011	10-Day Letter			SMITHDE
NEW PROFILE? IVERMECTIN IS IN FACTS SUMMARY FOR LAST EI, BUT IT IS A FERMENATION PRODUCT. CSN COVERED CLASS ON EI NOT CFN?					
DO RECOMMENDATION	27-APR-2011			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	29-APR-2011			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: FEI: [redacted] (b) (4)

[redacted] (b) (4)

DMF No: **AADA:**

Responsibilities: [redacted] (b) (4)

Establishment Comment: [redacted] (b) (4)

Profile: [redacted] (b) (4) **OAI Status:** NONE

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	09-JUN-2011				DAVIDJE
SUBMITTED TO DO	09-JUN-2011	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	16-JUN-2011	Product Specific			PHILPYE
INSPECTION SCHEDULED	30-SEP-2011		18-NOV-2011		IRIVERA
DO RECOMMENDATION AS PER F. GODWIN, EMAIL 2/3/2012	03-FEB-2012			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	03-FEB-2012			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

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/s/

CAROLINE STRASINGER
02/03/2012

MOO JHONG RHEE
02/03/2012
Chief, Branch IV

NDA 202-736

Sklice (ivermectin) Lotion
0.5%

Topaz Pharmaceuticals Inc.

Caroline Strasinger, Ph.D.
Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

CMC Review of NDA 202-736
For the Division of Dermatological and Dental Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-736
2. REVIEW #: #1
3. REVIEW DATE: 8-NOV-2011
4. REVIEWER: Caroline Strasinger, Ph.D.
5. PREVIOUS DOCUMENTS:

   Previous Documents

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA 202-736	07-APR-2011
Amendment 0003	23-MAY-2011
Amendment 0005	01-JUL-2011
Amendment 0010	06-SEP-2011
Amendment 0012	16-SEP-2011
Amendment 0014	11-OCT-2011
Amendment 0015	14-OCT-2011
Amendment 0016	04-NOV-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Topaz Pharmaceuticals, Inc.

Address: 100 Witmer Rd.
Suite 280
Horsham, PA 19044

Representative:	Lisa Deluca, VP Regulatory Affairs
Telephone:	267-960-3325

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Sklice
b) Non-Proprietary Name (USAN):	Ivermectin Lotion
c) Code Name/# (ONDQA only):	TPZ-0434
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	3
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2), Stromectol, Oral, Merck, NDA 50-742

10. PHARMACOL. CATEGORY: Antiparasitic

11. DOSAGE FORM: Lotion

12. STRENGTH/POTENCY: 0.5% w/w

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

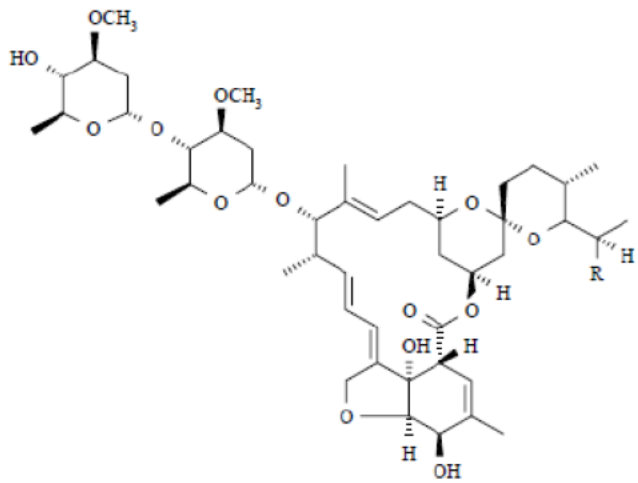
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Ivermectin:

A mixture of H_2B_{1a} and H_2B_{1b}; containing not less than 95.0% H_2B_{1a} (calculated as H_2B_{1a}/(H_2B_{1a} + H_2B_{1b}).



Component H_2B_{1a}: R = CH_2CH_3 Component H_2B_{1b}: R = CH_3

Molecular Formula

Component H_2B_{1a}: $C_{48}H_{74}O_{14}$

Component H_2B_{1b}: $C_{47}H_{72}O_{14}$

Molecular Weight

Component H_2B_{1a}: 875.1

Component H_2B_{1b}: 861.1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4) [redacted]	N/A	(b) (4) [redacted]	(b) (4) [redacted]	1	Adequate	10/24/2011	Reviewed by Dr. B Shanmugam
	IV	(b) (4) [redacted]	Shea (b) (4) [redacted]	1	Adequate	8/23/2011	Reviewed by Dr. C. Strasinger
	III	(b) (4) [redacted]	(b) (4) [redacted]	7	N/A	N/A	Removed from commercial use (7/1/11)
21395	II	Hovione	Ivermectin	1	Adequate	11/01/2011	Reviewed by Dr. C. Strasinger

[redacted] (b) (4)	IV	[redacted] (b) (4)	1	Adequate	10/3/2011	Reviewed by Dr. C. Strasinger
	IV		1	Adequate	9/1/2011	Reviewed by Dr. C. Strasinger
	III		4	N/A	N/A	

[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
IND	73,134	TPZ-0434
NDA	50-742	STROMECTOL

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
EES	PENDING		
Biopharm	N/A		
Methods Validation	N/A		
EA	Categorical Exclusion Granted	8/24/11	Dr. C. Strasinger
Microbiology	Approval	9/15/2011	Dr. J. McVey

The Chemistry Review for NDA 22-560

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.

However, the Office of Compliance has issued a "***Pending***" overall recommendation on all the manufacturing facilities.

The labels/labeling also do not currently have adequate information.

Therefore, from the ONDQA perspective, this NDA is ***not*** recommended for approval per 314.125(b)(6),(13).

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

II. Summary of Chemistry Assessments

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

(1) Drug Product

The drug product is an off-white to tan topical lotion containing 0.5% (w/w) ivermectin to be marketed under the name Sklice®. The lotion is packaged in a single use tube and is intended to be applied once to the head for the treatment of head lice [redacted] (b) (4) There are three novel excipients used in the formulation and an adequate toxicological assessment has been provided by the Applicant in support of their use, which was further assessed by toxicologist and deemed satisfactory. Additional excipients are either USP or NF grade and controlled according to the compendial requirements.

The Sklice lotion is manufactured [redacted] (b) (4)

The release specification of the finished product includes description, pH, viscosity, identification, assay, degredation products, methylparaben and propylparaben assay, microbial limits, and fill weight. Viscosity is (b) (4) (b) (4) to be consistent with the dosage form of a lotion, the viscosity should be below 40,000 cPs.

The drug product is labeled for storage at controlled room temperature and packaged as a single use product. The drug product will be marketed in a white laminate tube with a (b) (4) (b) (4). It will be a blind end tube, and the cap will not be in contact with the drug product. The fill weight is 4 oz (b) (4) Based on stability data from four batches, an expiration dating period of 24 months, when stored at room temperature, is granted.

Environmental assessment was done and no significant impact is expected.

(2) Drug Substance

The drug substance, ivermectin, is manufactured by Hovione. The CMC information provided in DMF 21395 was reviewed on 01-NOV-2011 and found to be adequate. The DMF also references VMF (b) (4) for the source of the starting material, (b) (4) VMF (b) (4) was reviewed on 24-OCT-2011 and found to be adequate. The applicant has provided an LOA to reference the DMF and VMF for all CMC information.

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

Sklice (Ivermectin) Lotion, 0.5% is an (b) (4) indicated for the topical treatment of head lice (b) (4) in patients 6 months of age and older. Sklice is applied to dry hair in an amount sufficient (up to 1 tube) to thoroughly coat the hair and scalp, and rinsed off with water after 10 minutes. Sklice is supplied in a single use, four ounce laminate tube and can be stored at room temperature.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(6)

Labels/labeling are not adequate at this time. Label/labeling discussions between the Agency and the Applicant are to commence on 15-NOV-2011.

21 CFR 314.125(b)(13)

The Office of Compliance has issued a "Pending" overall recommendation for all facilities involved. The (b) (4) facility, the only pending facility, is scheduled for inspection on (b) (4).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Caroline Strasinger, PhD/08-NOV-2011
ChemistryTeamLeaderName/Date: Shulin Ding, PhD/08-NOV-2011

ProjectManagerName/Date: Jeannie David/25-NOV-2011

C. CC Block

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/s/

CAROLINE STRASINGER
11/17/2011

MOO JHONG RHEE
11/17/2011
Chief, Branch IV

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division:	Division of Dermatology and Dental Products
NDA:	202-736
Applicant:	Topaz Pharmaceuticals, Inc.
Stamp Date:	April 8, 2011
PDUFA Date	Feb. 8, 2012
Trademark:	Sklice
Established Name:	Ivermectin
Dosage Form:	Cream
Route of Administration:	Topical
Indication:	Head lice (b) (4) [redacted] in patients 6 months of age and older
CMC Lead:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

Topaz Pharmaceuticals is submitting a 505(b)(1) New Drug Application (NDA) for the prescription use of Sklice (ivermectin) cream, 0.05% in the treatment of head lice (b) (4) [redacted] in patients 6 months of age and older. In addition to its own clinical/preclinical studies, Topaz will also refer to preclinical and safety data submitted within Merck's NDA 50-742 Stromectol (ivermectin) tablet, for which Topaz has obtained a right of reference.

The proposed drug substance, ivermectin USP, is a semi-synthetic, antiparasitic agent derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of *Streptomyces avermitilis*. The applicant references all CMC information of the drug substance to DMF 21395 held by Hovione PharmaScience Limited located in Taipa, Macau S.A.R except drug substance specification, batch analysis, and an impurity profile comparison with Stromectol. To-date DMF 21395 has not been reviewed in support of any submissions.

The proposed drug product, Sklice (ivermectin) cream, 0.5% is off-white to tan in color, and packaged in 4 ounce, white, laminate tubes with (b) (4) [redacted] screw caps. Each tube is intended for a single use. (b) (4) [redacted]

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches. The formulation contains the following excipients: oliver oil, NF;

oleyl alcohol, NF; lanolin alcohol, NF; cyclomethicone, NF, methylparaben, NF; propylparaben, NF; citric acid, USP; purified water, USP; and Crodalan AWS, shea butter, and sorbitan tristearate. The last three ingredients are novel excipients. Additionally, lanolin alcohol and some componenets of Crodalan AWS [redacted] (b) (4) [redacted] are [redacted] (b) (4).

The proposed commercial manufacturing scale is [redacted] (b) (4) The proposed commercial drug product manufacturing site, DPT Laboratories in Texas, is also the manufacturing site of Phase 3 supplies and registration stability batches. The commercial drug product manufacturing process consists of the following steps: [redacted] (b) (4) (b) (4)

Stability data provided in the initial submission to support an expiration dating period of 24 months at a controlled room temperature of 68°-77°F (20°-25°C), excursions permitted to 15°-30°C, include long term (25°C/60% RH) data of 6-18 months, intermediate temperature (30°C/65% RH) data of 6 months and accelerated temperature (40°C/75% RH) data of 6 months from [redacted] (b) (4) full scale batches [redacted] (b) (4) Results of bulk stability, photostability, and freeze/thaw studies are also provided to support storage/handling of the product.

[redacted] (b) (4)

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(b) (4) [redacted]

C. Comments for 74-Day Letter:

- Provide drug product samples (2 units) with a lower viscosity for dosage form evaluation. The viscosity of the samples is preferred to be near the lower limit of the proposed viscosity acceptance criterion. The samples should be accompanied with their certificates of analysis.

- Confirm that the tube system supplied by (b) (4) [redacted] Provide drug product samples, container/carton labels, and three months of stability data from at least two more batches at a scale (b) (4) [redacted] of the production scale for the product packaged in the to-be-marketed tube system supplied by (b) (4) [redacted]

- Provide a clear rationale to support the method changes from Method 73.6416 to improved Method 73.6416, and then to the proposed regulatory method 73.6860. Provide a comparison among the three methods regarding procedures, chromatographic conditions, method precision, accuracy, specificity, quantitation limit, detection limit, etc. for the assay of the active ingredient and quantitation of impurities/degradants.

D. Comments/Recommendation:

The application is acceptable for filing from CMC perspective. The major CMC review issues with this NDA are drug substance manufacturing, method validation, method equivalence, impurity profile, and stability data.

Drug substance manufacturing sites are located in Macau and China. Drug product manufacturing site is located in U.S. GMP inspection requests are being processed.

The CMC review of this NDA is recommended for a team review. Dr. Balajee Shanmugam will be responsible for the review of the manufacture of [redacted] (b) (4) and Dr. Caroline Strasinger for the rest of CMC review, which includes the manufacture of ivermectin [redacted] (b) (4) drug product, appendices, regional information, and label/labeling.

Shulin Ding, Ph.D.
CMC Lead

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV

Appears This Way On Original

NDA Number: 202-736

Supplement Number and Type:

Established/Proper Name: Ivermectin/Sklice

Applicant: Topaz

Letter Date: April 7, 2011

Stamp Date: April 8, 2011

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

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	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		Information for the fermentation facility that produces [redacted] (b) (4) is included in the establishment list appended to Form 356h in the amendment dated May 23, 2011.
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.**	x		Information for the fermentation facility that produces [redacted] (b) (4) is provided in the amendment dated May 23, 2011.

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 are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		The statement of readiness for inspection for all facilities involved in this NDA is provided in the amendment dated May 23, 2011

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

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Categorically exclusion is 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	Referenced to DMF 21395 and VMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Also referenced to DMF 21395 and VMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	x		Also referenced to DMF 21395.
15.	Does the section contain controls for the DS?	x		Also referenced to DMF 21395.
16.	Has stability data and analysis been provided for the drug substance?	x		Also referenced to DMF 21395.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	n/a
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	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

	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?		x	This is not a sterile 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?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
21395	II	Hovione PharmaScience, Limited	Drug substance, ivermectin USP	3/30/2011	The DMF further references to Type II VMF (b) (4) [redacted] for the manufacture of (b) (4) [redacted]
(b) (4) [redacted]	III	(b) (4) [redacted]		11/1/2010	(b) (4) [redacted]
	III			12/20/2010	
	III			11/3/2010	
	III			1/04/2011	
	III			6/18/2009	

	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		The labels for the tubes supplied by (b) (4) [redacted] (b) (4) [redacted] are not provided.

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		See page 4

{See appended electronic signature page}

Shulin Ding, Ph.D.
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
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/

SHULIN DING
05/26/2011

MOO JHONG RHEE
05/26/2011
Chief, Branch IV