

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202428Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: May 4, 2012

FROM: Raymond P. Frankewich, Ph.D., Review Chemist, Branch IV, DNDQA II/ONDQA

THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, DNDQA II/ONDQA

TO: CMC Review #1 for NDA 202-428

SUBJECT: **Final Recommendation**

The previous CMC Review #1, dated 3-19-2012, made a recommendation of not approval of this NDA because of the following unresolved issues:

1. There has been no “Acceptable” recommendation from the Office of Compliance.
2. Label/labeling issues were not considered acceptable from the CMC perspective.

On May 3, 2012, the Office of Compliance has issued an overall “Acceptable” recommendation (see **Attachment 1**).

In addition, the label/labeling issues have been satisfactorily resolved (see **Attachment 2**). As of the date of this addendum, there is one outstanding issue involving labeling, which was noted in the review of this NDA dated May 4, 2012 by DMEPA (CDER / OSE / Office of Medication Error Prevention and Risk Management):

Revise the presentation of the proprietary name, FABIOR, from UPPERCASE to Title Case “Fabior” to improve readability of the name. Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.

This concern does not affect the CMC status of this NDA.

Therefore, from the ONDQA perspective, this NDA is now recommended for approval.

Attachment-1

EES report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 202428/000	Sponsor:	STIEFEL LABS INC
Org. Code:	540		20 TW ALEXANDER DR
Priority:	3		RESEARCH TRIANGLE PARK, NC 27709
Stamp Date:	29-JUL-2011	Brand Name:	Tazarotene, 0.1%
PDUFA Date:	29-MAY-2012	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	30-MAR-2012	Product Number; Dosage Form; Ingredient; Strengths	
		001: (b) (4)	AEROSOL FOAM; TAZAROTENE; .1%
FDA Contacts:	J. DAVID	Project Manager	3017964247
	R. FRANKWICH	Review Chemist	3017961354
	M. RHEE	Team Leader	3017961440

Overall Recommendation:	ACCEPTABLE	on 03-MAY-2012	by D. SMITH	(HFD-323)	3017969643
	PENDING	on 12-AUG-2011	by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:		OAI Status:	NONE
Profile:			
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-AUG-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 1628114 FEI: 1000117684
DPT LABORATORIES INC

DMF No: SAN ANTONIO, , UNITED STATES 78215
Responsibilities: (b) (4)
FINISHED DOSAGE MANUFACTURER
(b) (4)

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 17-AUG-2011
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 1644099 FEI: 1000117684
DPT LABORATORIES INC

DMF No: SAN ANTONIO, , UNITED STATES 78218
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 17-AUG-2011
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3005023061
DPT LABORATORIES INC

DMF No: SAN ANTONIO, , UNITED STATES 78235
Responsibilities: (b) (4)
Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 12-AUG-2011
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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

DMF No: AADA:
Responsibilities:

Profile: OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 03-MAY-2012
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

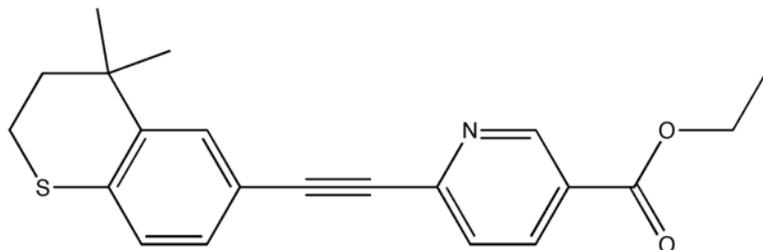
Attachment-2

1) Final Labeling (Description and How Supplied sections)

11 DESCRIPTION

Fabior (tazarotene) Foam, 0.1% contains the compound tazarotene, a member of the acetylenic class of retinoids. It is for topical use only.

Chemically, tazarotene is ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate. The structural formula is represented below:



Molecular Formula: $C_{21}H_{21}NO_2S$ Molecular Weight: 351.46

Tazarotene is a pale yellow to yellow substance. Fabior Foam contains tazarotene, 1 mg/g in aqueous-based white to off-white foam vehicle consisting of butylated hydroxytoluene, cetareth-12, citric acid anhydrous, diisopropyl adipate, light mineral oil, potassium citrate monohydrate, potassium sorbate, purified water, and sorbic acid. Fabior Foam is dispensed from an aluminum can pressurized with a hydrocarbon (propane/n-butane/isobutane) propellant.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Fabior Foam, 0.1% (1 mg/g) is a white to off-white foam, supplied as follows:

50 g aluminum can NDC 0145-0020-03
100 g aluminum can NDC 0145-0020-02

Storage and Handling

- Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). See USP-controlled room temperature.
- Store upright.
- Protect from freezing.
- Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 120°F (49°C).
- Shake can before use. Hold can at an upright angle and press firmly to dispense.

NOTE: the statements “Avoid contact with the eyes” and “Keep out of the reach of children” are included in section 17 (Patent Counseling Information) of the package insert.

3 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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

/s/

RAYMOND P FRANKEWICH
05/04/2012

MOO JHONG RHEE
05/04/2012
Chief, Branch IV

NDA 202428

**Tradename (tazarotene) foam
0.1%**

Stiefel Laboratories, Inc.

Raymond P. Frankewich, Ph.D.

Review Chemist

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

**CMC REVIEW
For the Division of Division of Dermatology and Dental Products
(CDER/ODEIII/DDDP, HFD-540)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202428
2. REVIEW #: 1
3. REVIEW DATE: March 16, 2012
4. REVIEWER: Raymond P. Frankewich, Ph.D.
5. PREVIOUS DOCUMENTS: IND 105564
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	July 29, 2011
Correspondence (C)	
Amendment (BC)	August 29, 2011
Amendment (BC)	November 15, 2011
Amendment (BC)	November 23, 2011
Amendment	January 20, 2012
Amendment	February 21, 2012

7. NAME & ADDRESS OF APPLICANT:

Name: Stiefel Laboratories, Inc.
Address: 20 T. W. Alexander Drive
Research Triangle Park, NC 27709
Representative: Salisa Hauptmann, MPH, VP Regulatory Affairs
Telephone: 919-315-7058

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Fabior (proposed)
b) Non-Proprietary Name: tazerotene
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):
 • Chem. Type: 3

CMC Review Data Sheet

• Submission Priority: S

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

10. PHARMACOL. CATEGORY: Keratolytic

11. DOSAGE FORM: Aerosol, foam

12. STRENGTH/POTENCY: 0.1% w/w

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

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

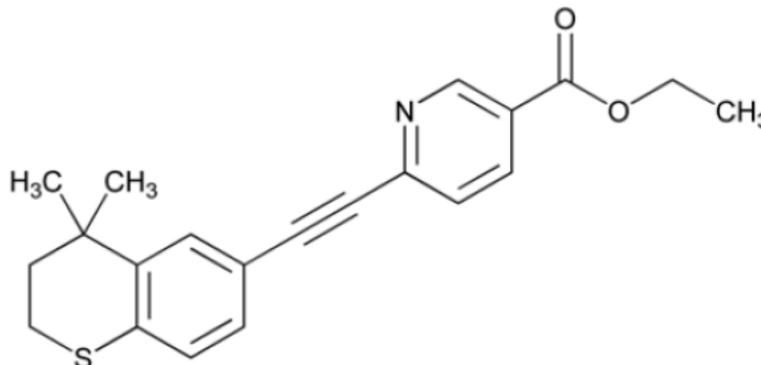
SPOTS product – Form Completed

Not a SPOTS product

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

Chemical name: ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate

Structural formula:



Molecular formula: C₂₁H₂₁NO₂S

Molecular weight: 351.46

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	Macrogol Cetostearyl Ether 12 (Cetareth 12)	1	Adequate	March 13, 2012	
	IV		Diisopropyl Adipate (b) (4)	1	Adequate	March 13, 2012	
	III		Aerosol aluminum containers	3	Adequate	November 7, 2002	

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		
	20-600	Tazorac [®] (tazarotene 0.05%, 0.1%) Gel
NDA	21-184	Tazorac [®] (tazarotene 0.05%, 0.1%) Cream Avage [®] (tazarotene 0.1%) Cream

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	
EES	Pending	-	Marissa Stock (Compliance Coordinator)
Pharm/Tox	N/A	-	-
Biopharm	NA	-	-
LNC	NA	-	-
Methods Validation	N/A, according to the current ONDQA policy	-	-
DMETS	N/A	-	-
EA	Categorical exclusion is granted (see the Review)	-	-
Microbiology	NA	-	-

Executive Summary Section

The CMC Review for NDA 202428

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has *not* issued an overall “Acceptable” recommendation for the facilities involved in this application.

Also, issues on labels/labeling are *not* satisfactorily resolved yet.

Therefore, from the ONDQA perspective, this NDA is not recommended for approval per 21 CFR314.125(b)(6) and (13) in its present form until the above issues are satisfactorily resolved.

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

Not applicable.

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance is tazarotene. Tazarotene is known as a keratolytic agent. It is described as a retinoid in the proposed labeling for this drug product (see discussion and definition of terms in the evaluation of labeling in this review). Keratolysis is defined as softening and dissolution or peeling of the horny layer of the epidermis. A retinoid is described as retinal, retinol, or any structurally similar natural derivative or synthetic compound (the latter need not have any vitamin A activity).

The indication of this drug product is treatment of ^{(b)(4)} acne vulgaris in patients 12 years of age or older. The effects of tazarotene in this drug product, according to the proposed labeling, may be due to its anti-hyperproliferative, normalizing-of-differentiation and anti-inflammatory effects.

Tazarotene is the active ingredient in three currently marketed drug products; Tazaorac[®] (tazarotene) Gel, 0.05% and 0.1%; Tazaorac[®] (tazarotene) Cream, 0.05% and 0.1%; and Avage[®] (tazarotene) Cream, 0.1%. The gel formulations

Executive Summary Section

were submitted in NDA 20-600, which was approved in June 1997. The cream formulations were submitted in NDA 21-184, which was approved in Sept. 2000 (Avage[®] was approved in Sept. 2002).

For most sections of this NDA which pertains to the drug substance, the applicant references NDA 20-600 and NDA 21-184. A Letter of Authorization (LOA) from the manufacturer of tazarotene and holder of NDAs 20-600 and 21-184 (Allergan Inc.), dated June 24, 2011, is provided by the applicant to allow the Agency to access to those two NDAs. The only departure from these NDAs is that the applicant has developed a single analytical procedure in this NDA for the assay and determination of impurities in the tazarotene drug substance. This new analytical procedure is evaluated in this review.

(2) Drug Product

The proposed drug product is a foam which contains tazarotene at a concentration of 0.1%. The bulk drug product is an (b) (4) which is packaged in an aluminum can fitted with a valve, actuator, and a cover cap (cap does not contact the drug product). The can is pressurized with a propellant which is a mixture of propane, n-butane, and isobutane. Three can sizes are intended: 10 g, 50 g, and 100 g (size refers to the amount of drug product inside the can). The 10 g can is a physician sample package; the 50 and 100 g cans are market packages.

The bulk drug product is referred to in the application as a (b) (4) (b) (4) but in this review it will simply be referred to as an (b) (4). One of the in-process tests used during manufacture of the bulk drug product is (b) (4). Acceptance criteria for this test is (b) (4).

The manufacturing process for the bulk foam includes (b) (4) (b) (4)

Drug product specification includes tests for Appearance, Identification, Assay, and Impurities of the drug substance. Also included are compendial microbial tests (USP <61> and <62>), and compendial tests for Minimum Fill (<755>), Dispensing Rate, Delivered Amount, and Leakage Rate (all <601>). Tests for Dispensing Rate,

Executive Summary Section

Delivered Amount, microbial contamination, along with a test for Weight Loss are performed as part of the stability specification.

Stability data through 18 month storage is provided for samples of two commercial batches of drug product, and data through 12 months storage is provided for samples of a third batch. Data are provided for storage at both the ICH Controlled Room Temperature conditions (CRT) (25 °C / 60% RH) and ICH Accelerated conditions (40 °C / 75% RH). Statistical analysis was performed for the CRT storage condition for each parameter evaluated in the stability specification. Data support an expiration dating period of 18 months for the 10 g physician sample package, and 24 months for the 50 g and 100 g commercial packages.

The original proposed tradename, ^{(b) (4)} was rejected (see DMEPA reviews). Another tradename, Fabior[®], is under evaluation as of the date of this review. In this review, where the tradename is referenced, the term “Tradename” or “TRADENAME” will be used.

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

According to the Dosage and Administration section of the proposed label for the drug product, the foam should be applied to affected areas of the skin once daily in the evening after washing with a mild cleanser and completely drying. The foam should be applied to the affected area in amounts such that the entire area is only lightly covered with a thin layer. The foam should then be gently massaged into the skin until it disappears.

The amount of tazarotene foam applied per day under conditions of maximal use was calculated to be 3.74 g in clinical study W0260-105 (this study is discussed in sec. 3.2.P.5.5 of this review (Characterization of Impurities). For the purposes of this review, the nominal daily dose is regarded to be 4 g.

C. Basis for Approvability or Not-Approval Recommendation

21 CFR 314.125(b)(13)

- Facility intended to manufacture tazarotene drug substance has not yet been declared “Acceptable” by the Office of Compliance.

21 CFR 314.125(b)(6)

- The size of font for the established name in the labels does not comply with the regulatory requirement. It should be at least 50% of that of the trade name. Also expiration date and lot number are missing from the labels.
- The “Description” and “How Supplied” sections of PI need to be revised

(see the List of Deficiencies, p. 103).

Executive Summary Section

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

(See appended electronic signature page)

B. Endorsement Block:

Raymond P. Frankewich, Ph.D.

(See appended electronic signature page)

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

C. CC Block: entered electronically in DFS

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

/s/

RAYMOND P FRANKEWICH
03/16/2012

MOO JHONG RHEE
03/19/2012
Chief, Branch IV

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

OND Division: Division of Dermatology and Dental Products
NDA: 202-428
Applicant: Stiefel Laboratories, Inc.
Stamp Date: July 29, 2011
PDUFA Date: May 29, 2012
Trademark: To be proposed
Established Name: Tazarotene
Dosage Form: Foam
Route of Administration: Topical
Indication: Acne vulgaris

CMC Lead: Shulin Ding

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues:

A. Summary

Stiefel has submitted a 505(b)(1) New Drug Application (NDA) for the prescription use of Tradename™ (tazarotene) foam, 0.1% for the topical treatment of (b)(4) acne vulgaris in patients 12 years of age or older.

The applicant references to the approved NDA 20-600 Tazorac gel and NDA 21-184 Tazorac cream held by Allergan for the CMC information of the proposed drug substance, tazarotene, with the exception of the analytical method for assay and related substances. A letter of authorization from Allergan is provided. The proposed drug substance manufacturer is (b)(4) (b)(4) with a reference to DMF (b)(4) (b)(4) is also Allergan's current source of tazarotene. DMF (b)(4) is a Type I DMF (not Type II), and has been closed by the holder. Its letter of authorization is not provided.

The proposed drug product is a (b)(4) packaged in an aluminum aerosol can under pressure at fill sizes of 10 g (physician sample), 50 g and 100 g. In addition to the active ingredient and a propellant, the formulation also contains the following excipients: light mineral oil, NF; potassium sorbate, NF; sorbic acid, NF; potassium citrate monohydrate, USP; butylated hydroxytoluene, NF; citric acid anhydrous, USP; purified water, USP; diisopropyl adipate, and macrogol cetostearyl ether 12. The non-compendial excipients present in the formulation are diisopropyl adipate, macrogol cetostearyl ether 12 (also known as cetareth-12), and components of the propellant (propane, n-butane and isobutane). There are no novel excipients present in the formulation.

The aluminum aerosol container is lined with a (b) (4) which is fitted with an inverted valve, an actuator, and a non-product contacting cap. The container, the subject of DMF (b) (4) has been reviewed previously and found adequate. The components of the can/valve assembly are currently used in approved foam products such as Olux-E, Verdeso, and Sorilux.

(b) (4)

The to-be-marketed formulation is the same formulation used in all clinical trials and registration stability batches. Stability data provided in the initial submission to support an expiration dating period of (b) (4) months at 25°C (excursions permitted to 15-30°C) include long term (25°C/60% RH) data of 12-18 months, and accelerated temperature (40°C/75% RH) data of 6 months for each fill size from three full scale batches (b) (4). Both upright and inverted orientations were studied but only the upright position is the proposed storage orientation for commercial batches.

Special stability studies such as in-use stability study, freeze/thaw and temperature cycling between refrigerated and elevated temperatures are also provided to support storage/handling of the drug product. The product does not withstand freeze/thaw cycling. Therefore, a precautionary statement "Do Not Freeze" is recommended for the product label/labeling.

B. Critical issues for review

- Drug Substance Method for Assay and Related Substances

A new method covers both assay and related substances has been developed and validated to support this NDA. This new method is different from the method approved under NDAs 20-600 and 21-184. The performance of this new method should be at least comparable to that of the drug substance method approved under NDAs 20-600 and 21-184 because the proposed drug substance specification and batch release/stability data were all referenced to NDAs 20-600 and 21-184.

- Drug Product Manufacturing Process and In-Process Controls

The manufacture of the bulk (b) (4)
The manufacturing process, its robustness, and in-process control need a critical review to ensure the correct product can be consistently achieved.

- Physical characteristics of the formulation in the aerosol can

The physical properties of the proposed product were characterized only up to the bulk (b) (4). No physical information is provided for the formulation after the filling operation. It is uncertain whether the formulation remains as a stable (b) (4).

(b) (4) in the aerosol can in the presence of propellants and under pressure throughout the proposed shelf-life.

- Extractables in Drug Product
Extractables are detected in the registration stability samples at low levels. Some form adducts with the active ingredient. The applicant includes the adducts in drug product specification under related substances, but proposes to (b) (4)
The proposal needs to be critically reviewed, and consultation be sought from Pharm/Tox regarding “safety.

C. Comments for 74-Day Letter:

None

D. Comments/Recommendation:

The application is acceptable for filing from CMC perspective. The major CMC review issues with this NDA are drug substance methods, drug product manufacturing, and extractables in drug product.

Drug substance manufacturing site are located in (b) (4) Drug product manufacturing site is located in U.S. GMP inspection requests are being processed.

Shulin Ding, Ph.D.
CMC Lead

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

NDA Number:

202-428

Supplement Number and Type:

Applicant: Stiefel

Letter Date: July 29, 2011

Established/Proper Name:

Tazarotene foam, 0.1%

Stamp Date: July 29, 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		
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		

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered 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.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered 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.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	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 Aug. 29, 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 NDAs 20-600 and 21-184.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to NDAs 20-600 and 21-184.
14.	Does the section contain information regarding the characterization of the DS?		x	Referenced to NDAs 20-600 and 21-184.
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?		x	Referenced to NDAs 20-600 and 21-184.
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		LoA for DS DMF (b)(4) is not provided but this is not critical because DMF (b)(4) is a Type I DMF which has been closed. The Agency normally does not review Type I DMFs.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b)(4)	IV	(b)(4)	(b)(4)	Aug. 11, 2011	
	IV		(b)(4) (diisopropyl adipate)	Sep. 3, 2010	
	III		Packaging material: Aerosol	Aug. 3, 2010	

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	

{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

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/s/

SHULIN DING
09/16/2011

MOO JHONG RHEE
09/16/2011
Chief, Branch IV

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/s/

MARY GRACE LUBAO
05/18/2012