

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205352Orig1s000

CHEMISTRY REVIEW(S)

**CMC Memo to File**

To:	NDA 205-352
Date	13 JUL 2014
Applicant	Bayer
Drug:	ALEVE® PM (naproxen sodium and diphenhydramine HCl) tablets
Subject	Approval recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall “acceptable” recommendation given on 13-JAN-2013 of the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 205-352 be approved. There are no pending CMC deficiencies.

HFD-/Division File

Olen Stephens, Ph.D.
Chemistry Reviewer

Danae Christodoulou, Ph.D.
Acting Branch Chief, ONDQA

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

Application:	NDA 205352/000	Sponsor:	BAYER HLTHCARE
Org. Code:	560		36 COLUMBIA RD
Priority:	4		MORRISTOWN, NJ 07962
Stamp Date:	20-MAR-2013	Brand Name:	NAPROXEN SODIUM, DIPHENHYDRAMINE HCl
PDUFA Date:	20-JAN-2014	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	21-NOV-2013	Product Number; Dosage Form; Ingredient; Strengths	

001; TABLET; DIPHENHYDRAMINE HYDROCHLORIDE; 25MG
001; TABLET; NAPROXEN SODIUM; 220MG

FDA Contacts:	O. STEPHENS	Prod Qual Reviewer	(HFD-510)	3017963901
	L. RIVERA	Product Quality PM		3017964013
	J. BUCHANAN	Regulatory Project Mgr	(HFD-560)	3017961007
	S. DE	Team Leader		3017961664

Overall Recommendation:	ACCEPTABLE	on 13-JAN-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 05-SEP-2013	by EES_PROD		
	PENDING	on 19-APR-2013	by EES_PROD		
	PENDING	on 19-APR-2013	by EES_PROD		

Establishment:	CFN:	FEI:	3003882513
	BAYER BITTERFELD GMBH SALEGASTER CHAUSSEE 1 GREPPIN, , GERMANY 06803		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	TABLETS, PROMPT RELEASE	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	13-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

Establishment: CFN: 2510692 FEI: 2510692
BAYER HEALTHCARE LLC CONSUMER CARE DIVISION

DMF No: MYERSTOWN, , UNITED STATES 170671418 **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-OCT-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-APR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-APR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:  (b) (4)

DMF No:  AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-APR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-APR-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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/s/

OLEN M STEPHENS

01/13/2014

CMC Recommendation: approval

DANAE D CHRISTODOULOU

01/13/2014

NDA 205-352

Aleve PM

Bayer healthcare, LLC

**Olen M. Stephens
ONDQA, Branch VI
Review for Office of Nonprescription Clinical
Evaluation**

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Chemistry Review Data Sheet

1. NDA 205-352
2. REVIEW #: 1
3. REVIEW DATE: 7-Nov-13
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Original submission (0000)

20-Mar-13

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Submission (0000)

20-Mar-13

General Correspondence (0002)¹

18-Apr-13

Labeling Amendment (0005)²

15-Jul-13

CMC Amendment (0008)

1-Oct-13

¹ By this memo, Bayer confirms that Section 3.2.P documents found in Module 3 were provided in duplicate in the two subsections (naproxen and diphenylhydramine).

² New labeling for the 20-, 40-, and 80-count bottles.

7. NAME & ADDRESS OF APPLICANT:

Name: Bayer Healthcare, LLC-Consumer Care
Address: 36 Columbia Road
PO Box 1910
Morristown, NJ 07962

Chemistry Review Data Sheet

Representative: Leonard Baum
Leonard.baum@bayer.com
Telephone: 973-254-4672

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aleve PM
- b) Non-Proprietary Name (USAN): naproxen sodium, diphenylhydramine HCl

9. LEGAL BASIS FOR SUBMISSION: We deem this application to be filed under 505(b)(2) even though the applicant filed this NDA as a 505(b)(1). The clinical PM is following up with this issue and the final determination will be captured in a close out memo for all pending items.

10. PHARMACOL. CATEGORY: Analgesia; Indicated for relief of occasional sleeplessness when associated with minor aches and pains.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 220 mg Naproxen sodium and 25 mg Diphenylhydramine HCl

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx ______OTC

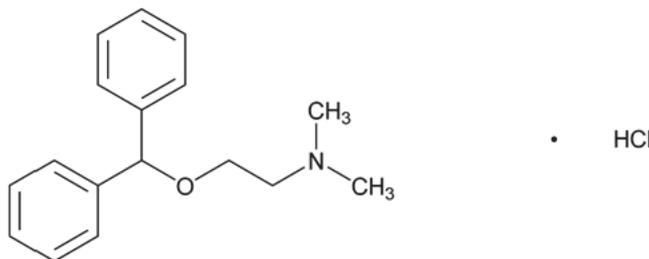
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

___ SPOTS product – Form Completed

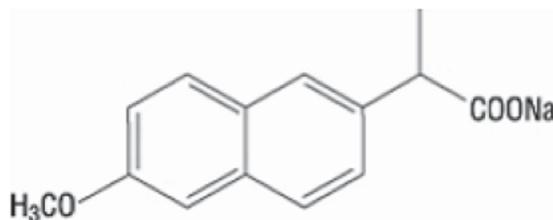
______ Not a SPOTS product

Chemistry Review Data Sheet

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



2-(Diphenylmethoxy)-*N,N*-dimethylethylamine hydrochloride
 $C_{17}H_{21}NO \cdot HCl$
 MW = 291.82 g/mol



(-)-Sodium (*S*)-6-methoxy- α -methyl-2-naphthaleneacetate
 $C_{14}H_{13}NaO_3$
 MW = 252.24 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11-Oct-13	
	II			1	Adequate	24-Sep-13	

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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	NDA 20-204	Naproxen Sodium 220 mg
	IND 103,407	For naproxen sodium and diphenylhydramine HCl
	NDA 200-364	Naproxen sodium extended release, 660 mg

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Biopharm	Pending		Minerva Hughes
EA	FONSI	2-May-2013	Raanan A. Bloom

The Chemistry Review for NDA 205-352

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval, pending an Acceptable recommendation from ONDQA Biopharm and the Office of Compliance.

The following recommendations are pending but will not have an impact on the specific findings discussed in this CMC review:

1. Office of Compliance – GMP status of the commercial manufacturing and testing facilities listed in the NDA.
2. ONDQA Biopharm Staff – dissolution method and specifications

The expiration dating period grantable for the Aleve PM® XR (naproxen sodium/diphenhydramine hydrochloride) tablets in all container closure configurations is 24 months with storage conditions of [REDACTED] (b) (4) [see USP Controlled Room Temperature].

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

None.

II. Summary of Chemistry Assessments

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

NDA 205-352 is submitted by Bayer for Aleve® PM (naproxen sodium/diphenhydramine HCl) tablets for oral administration, containing 220 mg/25 mg of naproxen sodium/diphenhydramine HCl. Both drug substances are active ingredients of previously approved drug products. Naproxen sodium is the active ingredient in Aleve® (naproxen sodium) Tablets (NDA 20-204), and diphenhydramine HCl is the active ingredient in several products including several combination products. The proposed indication is for relief of occasional sleeplessness when associated with minor aches and pains. The applicant is including all naproxen sodium drug substance information by reference to DMF [REDACTED] (b) (4)

The diphenhydramine HCl active ingredient is controlled by DMF [REDACTED] The film coat composition is contained within the application. All

Executive Summary Section

other components are compendial and controlled as per their respective monographs.

Aleve® PM (naproxen sodium/diphenhydramine HCl) tablets will be packaged in 20-, 40-, and 80-count HDPE bottles and a 2-count foil laminate pouch. The 2-count foil laminate pouch physician samples will not have a (b) (4) closures; the 20-, 40-, and 80-count configurations will have (b) (4) closures. The label should note the sodium content (20 mg/tablet).

The manufacturing process (b) (4)

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

Aleve® PM tablets will be available over the counter for relief of occasional sleeplessness when associated with minor aches and pains. The recommended dose is two tablets at bedtime with a full glass of water. The dose should not exceed 2 tablets per 24 hours. The drug product should be stored at (b) (4) [see USP Controlled Room Temperature]. A 2-count physician sample configuration will also be available.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry, Manufacturing and Controls deficiencies for the drug product were communicated to the applicant (26-MAR-2013; email) and have been sufficiently addressed through amendment 0008 (1-OCT-2013).

The following recommendations are pending but will not have an impact on the specific findings discussed in this CMC review:

1. Office of Compliance – GMP status of the commercial manufacturing and testing facilities listed in the NDA.
2. ONDQA Biopharm Staff – Dissolution method and specifications

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Olen M. Stephens, Reviewer
Danae Christodoulou, Active Branch Chief
Rebecca McKnight, Project Manager

C. CC Block

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/s/

OLEN M STEPHENS

11/07/2013

CMC Recommendation is for approval pending OC recommendation on facilities and biopharm recommendation.

DANAE D CHRISTODOULOU

11/08/2013

I concur with the reviewer's conclusion and recommendation

Division of Nonprescription Clinical Evaluation

NDA: 205-352
Applicant: Bayer HealthCare LLC, Consumer Care
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07960-1910
Stamp Date: 20-Mar-2013
PDUFA Date: 20-Jan-2014
Proposed Proprietary Name: Aleve® PM
Established Name: Naproxen Sodium, Diphenhydramine HCl
Dosage form and strength: Tablets, Naproxen Sodium 220 mg & Diphenhydramine HCl 25 mg
Route of Administration: Oral
Indications: For relief of occasional sleeplessness when associated with minor aches and pains and helps you fall asleep and stay asleep.

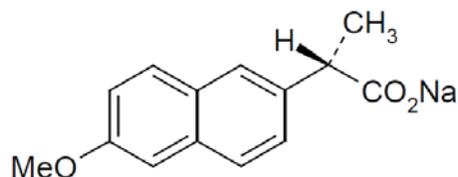
CMC Lead: Swapan K De

ONDQA Fileability: Fileable

Name: Naproxen Sodium (S)-2-Naphthalene acetic acid, -6- methoxy- α -methyl sodium salt

Molecular formula: C₁₄H₁₃O₃Na

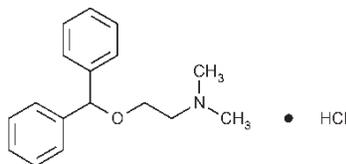
Molecular Weight: 252.2^(b)₍₄₎



Name: 2-(Diphenylmethoxy)-*N,N*-dimethylethylamine hydrochloride

Molecular formula: C₁₇H₂₁NO·HCl

Molecular Weight: 291.82



Has all information requested during the IND phases, and at the pre-NDA meetings been included?

Yes

Summary:

This is a CTD formatted NDA application for Naproxen Sodium 220 mg + Diphenhydramine Hydrochloride (DPH), two-tablet oral dose submitted as a 505(b)(2) NDA under the proposed trade name Aleve® PM. Naproxen sodium is a non-steroidal anti-inflammatory drug (NSAID). It inhibits prostaglandin synthesis by decreasing the activity of the enzyme cyclooxygenase, which in turn reduces the formation of prostaglandin chemical precursors. DPH is a first generation antihistamine, an H1-antagonist of the ethanolamine class used for multiple clinical indications including as an antitussive, a nighttime sleep-aid and an antihistamine (for allergy symptoms). Although several OTC analgesic + nighttime sleep-aid combination products are available in US, proposed product will be first combination of naproxen sodium with DPH.

Drug Substance:

Naproxen sodium (2-Naphtaleneacetic acid, 6-methoxy- α -methyl-, sodium salt) 220 mg is used to deliver 200 mg of the active naproxen moiety. Drug substance information is referred in (b) (4) DMF # (b) (4). Letter of authorization has been provided to access the drug substance manufacturers' DMF.

Other drug substance, Diphenhydramine Hydrochloride (DPH) 25 mg is used as nighttime sleep-aid and is obtained from (b) (4) and the manufacturer (b) (4) has submitted DMF # (b) (4) for (b) (4). Letter of authorization has been provided to access the drug substance manufacturers' DMF.

Drug Product:

The final formulation for the drug product, Naproxen Sodium 220 mg + Diphenhydramine Hydrochloride 25 mg (DPH) (Napso/DPH) tablet is selected following a pharmaceutical development study. The finished (b) (4) and total weight of the tablet is 391 mg. Each tablet contains Naproxen Sodium 220 mg and Diphenhydramine Hydrochloride 25 mg (as drug substances), Microcrystalline cellulose NF (b) (4), Povidone USP (b) (4), Talc USP (b) (4), Magnesium stearate NF (b) (4), (b) (4), Carnauba wax NF (b) (4) and Purified water USP (b) (4). The tablets will be packaged in 20, 40, and 80-count in white HDPE containers (b) (4). In addition, 2-count tablets will be packaged in a foil/polyester laminate pouch.

(b) (4) and stability specifications for the drug product are included. The specification for Uniformity of Dosage Units will be based on current USP <905>. However, acceptance criterion T= (b) (4) needs to be explained, since USP <905> requirements do not contain this figure. Specifications for individual impurities are within recommended limits by ICH Q3B for release. Release and stability specifications remain same for naproxen related impurities and consistent with NDA 20-204 for naproxen sodium tablet, (b) (4) g (which has same maximum daily dose limit). However, Release and stability specifications are at different levels for DPH related impurities. (b) (4)

(b) (4) (b) (4)
(b) (4) (b) (4)

The (b) (4) was formed presumably due to the existence of (b) (4) in the drug product. Since there is no monograph diphenhydramine HCl tablet product that can be referenced, the release and shelf life specifications were set based on stability data, EP diphenhydramine HCl monograph and USP diphenhydramine HCl and Pseudoephedrine capsules. The reviewer will need to consult with the toxicology reviewer to confirm whether proposed specifications for DPH have been qualified.

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CMC Initial Quality Assessment
FILING REVIEW FOR NDA 205-352

12-months of stability data for three batches (#6662, #6663 and #6664) have been provided at long term conditions (25°C/60% RH) and accelerated conditions (40°C/75% RH) of the drug product in the proposed bottle (20 and 40 count/38 cc HDPE bottle w/38 mm (b) (4) closure; 80 count/58 cc HDPE bottle w/38 mm- (b) (4) closure; and 2 tablets/printed foil/polyester laminate pouch with (b) (4) seal). In addition, 24-month stability data for the clinical batch (#59541P0) has been included as supportive data. Stress test and photostability tests data are also provided. The applicant has requested 24 month shelf-life of the drug product.

An environmental assessment report with detail analysis has been provided under Other Correspondence (1.12.14) and needs to be consulted to OPQ environmental assessment group for evaluation.

Critical Issues:

Drug substance:

- DMFs (b) (4) and (b) (4) should remain adequate to support the NDA 205-352. It should contain manufacturing process details with appropriate critical process parameters, specifications with impurity profile for the drug substance and stability data to support a retest period.

Drug Product:

- There is detailed formulation development section in 3.2.P which should be evaluated in-depth.
- The applicant should clarify the acceptance criterion for content uniformity testing.
- Determine whether the proposed shelf-life impurity specifications for DPH is acceptable with higher total impurities ((b) (4)%) than total impurities at release ((b) (4)%).

CMC Initial Quality Assessment
FILING REVIEW FOR NDA 205-352

- Has adequate justification been provided for the microbial limits test in the release specification of the drug product? Microbiological Attributes section 3.2.P.2.5 is included and needs a consult review by a microbiologist.
- Is the submitted 12-month stability data for three registration batches of drug product is enough to support the proposed 24-month shelf-life of the drug product in bottle (20 and 40 count/38 cc HDPE bottle w/38 mm (b) (4) closure; 80 count/58 cc HDPE bottle w/38 mm- (b) (4) closure; and 2 tablets/printed foil/polyester laminate pouch with (b) (4) seal)?

Comments and Recommendations:

The application is fileable. Submitted manufacturing facilities have been entered into the EES. The reviewer should confirm the accuracy and completeness of the EES entries. This NDA does not qualify as a QbD submission based on the criteria in the ONDQA interim policy (no design space, PAT, RTRT, reduced end-product testing etc.).

CMC Initial Quality Assessment
FILING REVIEW FOR NDA 205-352

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: #205,352 **NDA Type: 505 (b)(2)(4S)**

Established/Proper Name:
Naproxen Sodium,
Diphenhydramine HCl

Applicant:
Bayer HealthCare LLC,
Consumer Care

Letter Date: 03/20/2013

Stamp Date: 03/20/2013

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		Looks to be in standard eCTD format.
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		NA

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Two facilities identified, all have complete addresses and FEI Numbers.

CMC Initial Quality Assessment
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6.	<p>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.</p>			N/A
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 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		

CMC Initial Quality Assessment
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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		

* 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		

CMC Initial Quality Assessment
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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	Refers to DMFs # [REDACTED] (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Refers to DMFs # [REDACTED] (b) (4)
14.	Does the section contain information regarding the characterization of the DS?		X	Refers to DMFs # [REDACTED] (b) (4)
15.	Does the section contain controls for the DS?		X	Refers to DMFs # [REDACTED] (b) (4)
16.	Has stability data and analysis been provided for the drug substance?		X	Refers to DMFs # [REDACTED] (b) (4)
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	

CMC Initial Quality Assessment
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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		Pharmaceutical development section has adequate information.
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		Data have been included and needs to be evaluated.
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	

CMC Initial Quality Assessment
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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	Needs to be requested based on reviewers judgment.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		Microbiological Attributes section 3.2.P.2.5 is included and needs to be reviewed by a microbiologist.

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		

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. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	X		Needs to be reviewed by a ONDQA biopharm reviewer
35.	Is the dissolution test part of the DP specifications?	X		
36.	Does the application contain the dissolution method development report?	X		
37.	Is there a validation package for the analytical method and dissolution methodology?		X	
38.	Does the application include a biowaiver request?		X	

CMC Initial Quality Assessment
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39.	Does the application include a IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?		X	
41.	Is there any <i>in vivo</i> BA or BE information in the submission?		X	

K. FILING CONCLUSION				
	Parameter	Yes	No	Comment
42.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
43.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		
44.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

{See appended electronic signature page}

Swapan K De
CMC Lead
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Danae D Christodoulou
Acting Branch Chief
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

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

/s/

SWAPAN K DE
04/23/2013

DANAE D CHRISTODOULOU
04/23/2013