

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204016Orig1s000

CHEMISTRY REVIEW(S)

Facility Status View for NDA 204016 Original 1

Displays information for the facilities that are associated to NDA 204016 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.

Time run: 12/21/2015 7:25:27 AM

Overall Manufacturing Inspection Recommendations for NDA 204016 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA-204016-ORIG-1-RESUB-32	HOSPIRA INC	Approve	Complete	12/18/2015

OPF Facility Recommendations for Facilities on NDA 204016 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA-204016-ORIG-1-RESUB-32	3009736169	463719725	LABORATORIOS GRIFOLS SA	(b) (4)	Approve Facility	Complete	12/18/2015
NDA-204016-ORIG-1-RESUB-32	3009736169	463719725	LABORATORIOS GRIFOLS SA	(b) (4)	Approve Facility	Complete	12/18/2015
NDA-204016-ORIG-1-RESUB-32	3005231248	141565163	HOSPIRA BOULDER INC	(b) (4)	Approve Facility	Complete	12/18/2015
NDA-204016-ORIG-1-RESUB-32	3005231248	141565163	HOSPIRA BOULDER INC	(b) (4)	Approve Facility	Complete	12/18/2015
NDA-204016-ORIG-1-RESUB-32	3004591926	827731089	HOSPIRA INC	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	12/18/2015
NDA-204016-ORIG-1-RESUB-32	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Approve Facility	Complete	(b) (4)
NDA-204016-ORIG-1-RESUB-32	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Approve Facility	Complete	(b) (4)

Data refreshed on: 12/21/15 12:15:11 AM

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

Application: NDA 204016/000
Start Date: 31-JAN-2012
Regulatory: 08-JUL-2013

Action Goal:
District Goal: 07-JAN-2013

Applicant: HOSPIRA INC
 275 NORTH FIELD DR DEPT 0389 BLDG H2 2
 LAKE FOREST, IL 60045

Brand Name: ZOLEDRONIC ACID INJECTION
Estab. Name:
Generic Name: ZOLEDRONIC ACID INJECTION

Priority: 5
Org. Code: 150

Product Number; Dosage Form; Ingredient; Strengths
 001; SOLUTION, INJECTION; ZOLEDRONIC ACID; 4MG/100ML

Application Comment: APPLICATION RESUBMITTED AFTER CR. 505(B)(2) (on 10-JAN-2013 by D. MESMER (HFD-800) 3017964023)

FDA Contacts:	L. HSIEH	Prod Qual Reviewer		3017961682
	R. MELLO	Micro Reviewer	(HFD-805)	3017961574
	D. MESMER	Product Quality PM	(HFD-800)	3017964023
	M. FAGBAMI	Regulatory Project Mgr	(HFD-150)	3017961348
	H. SARKER	Team Leader	(HFD-150)	3017961747

Overall Recommendation:	ACCEPTABLE	on 05-FEB-2013	by R. SAFAAI-JAZI	()	3017964463
	WITHHOLD	on 16-NOV-2012	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 31-OCT-2012	by EES_PROD		
	PENDING	on 01-AUG-2012	by EES_PROD		
	PENDING	on 22-FEB-2012	by EES_PROD		

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

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DRUG SUBSTANCE ALTERNATE API RELEASE TESTING SITE (on (b) (4))

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

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-FEB-2012				(b) (4)
OC RECOMMENDATION	23-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO OC	10-JAN-2013				(b) (4)
OC RECOMMENDATION	10-JAN-2013			ACCEPTABLE BASED ON PROFILE	STOCKM

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

Establishment: **CFN:** **FEI:** 3005231248

HOSPIRA BOULDER INC
4876 STERLING DR
BOULDER, CO 803012350

DMF No: **AADA:**

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

Establishment Comment: PERFORMS DRUG SUBSTANCE MANUFACTURING RELEASE TESTING, STABILITY TESTING (on 16-FEB-2012 by D. MESMER (HFD-800) 3017964023)

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

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-FEB-2012				MESMERD
OC RECOMMENDATION	23-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO DO	31-OCT-2012	10-Day Letter			SMITHDE
DO RECOMMENDATION	14-NOV-2012			WITHHOLD	EBUTLER
EI ON 5/2012 REVEALED REPEAT GMP DEFICIENCIES REGARDING PROCESS VALIDATION AND EQUIPMENT CLEANING VALIDATION. IN ADDITION, THE FIRM FAILED TO FILE MULTIPLE FIELD ALERTS. RECOMMEND WITHHOLD UNTIL MEETING WITH FIRM FOR CORRECTIVE RESPONSE				EQUIPMENT CLEANING VALIDATION QA FUNCTIONS (b) (4) (VALIDATION) OR PROCE	
OC RECOMMENDATION	16-NOV-2012			WITHHOLD	SAFAAIJAZIR
OUTSTANDING GMP COMPLIANCE CONCERNS THAT WARRANT A WH AT THIS TIME				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	10-JAN-2013				MESMERD
SUBMITTED TO DO	10-JAN-2013	10-Day Letter			STOCKM
PROFILE IS IN INITIAL STATUS					
DO RECOMMENDATION	10-JAN-2013			ACCEPTABLE	EBUTLER
LAST EI STATUS WAS UPDATED TO VAI BASED ON FIRMS RESPONSE TO OBSERVATIONS AND REGULATORY MEETINGS WITH FIRM; PROFILE CLASS FOR (b) (4) FOUND ACCEPTABLE.				BASED ON FILE REVIEW	
OC RECOMMENDATION	14-JAN-2013			ACCEPTABLE	SHARPT
				DISTRICT RECOMMENDATION	

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

Establishment: CFN: LABORATORIOS GRIFOLS S.A. FEI: 3009736169

(b) (4)
(b) (4), BARCELONA, , SPAIN
DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: THERE ARE (b) (4) BUILDINGS FOR THIS FEI. THE (b) (4) SITE PERFORMS DRUG PRODUCT MANUFACTURING AND IN-PROCESS TESTING (b) (4) PERFORMS FOR DRUG PRODUCT: EXCIPIENT TESTING, COMPONENT TESTING, DRUG PRODUCT TESTING, STABILITY STORAGE AND TESTING. (b) (4) PERFORMS DRUG SUBSTANCE ID TESTING.

(on 16-FEB-2012 by D. MESMER (HFD-800) 3017964023)
PROFILE CHANGED TO (b) (4) PER INVESTIGATOR AND MICRO REVIEW (on (b) (4))

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

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-FEB-2012				MESMERD
SUBMITTED TO DO (b) (4) INSPECTIONAL HISTORY ONLY	23-FEB-2012	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	15-MAR-2012	Product Specific			BRYKMANR
INSPECTION SCHEDULED	30-MAY-2012		11-JUL-2012		PHILPYE
INSPECTION PERFORMED	11-JUL-2012		11-JUL-2012		Simone.Pitts

FORMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED This pre-approval and comprehensive GMP inspection of (b) (4) pharmaceutical manufacturer was conducted according to FACTS Assignment (b) (4)

The inspection covered the manufacturing processes and included a review of the Quality, Production, Materials Management, Facilities & Equipment, Packaging & Labeling and Laboratory Control System for NDA 204016 Zoledronic Acid Injection 4mg/100ml (b) (4) under the profile class (b) (4)

This is the initial inspection of the facility. Please see the EIR for more information regarding other sister facilities.

The current inspection found the firm operating as a (b) (4) manufacturer. At the close of the inspection, a five item FDA-483 was issued citing the following deficiencies: (b) (4)

No samples were collected and no refusals were encountered during the inspection. A copy of the GMP Compliance Summary of Findings Form, Facsimile Coversheet and CDER EES Assihnment sheet are attached to this report.

DO RECOMMENDATION	13-NOV-2012	ACCEPTABLE INSPECTION	BRYKMANR
OC RECOMMENDATION	14-NOV-2012	ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR
SUBMITTED TO OC	10-JAN-2013		MESMERD

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

SUBMITTED TO DO	10-JAN-2013	10-Day Letter		STOCKM
DO RECOMMENDATION	11-JAN-2013		ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	14-JAN-2013		ACCEPTABLE DISTRICT RECOMMENDATION	SHARPT

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Establishment Comment: DRUG SUBSTANCE ALTERNATE API RELEASE TESTING SITE (on (b) (4))
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-FEB-2012				(b) (4)
OC RECOMMENDATION	23-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO OC	10-JAN-2013				(b) (4)
SUBMITTED TO DO PROFILE IS IN INITIAL STATUS	10-JAN-2013	10-Day Letter			STOCKM
DO RECOMMENDATION PROFILE CLASS CTL FINAL UPDATED TO ACCEPTABLE. PREVIOUS THREE DRUG EI'S FOR PROFILE CLASS CTL WERE VAI, NAI, NAI RESPECTIVELY. RECOMMEND APPROVAL BASED ON FIRM'S COMPLIANCE.	05-FEB-2013			ACCEPTABLE BASED ON FILE REVIEW	EBUTLER
DO RECOMMENDATION	05-FEB-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

MEMO TO FILE

NDA: 204016

From: Li-Shan Hsieh Ph.D.
CMC Reviewer, Branch II, Division I, ONDQA

To: Ali Al-Hakim Ph.D.
Branch Chief, Division I, ONDQA

Date: Apr 11, 2013

SUBJECT: EES Acceptable for NDA 204016

The original CMC review for NDA 204016 dated 11-Oct-2012 has recommended Approval for this NDA pending overall recommendation from the Office of Compliance. However, Office of Compliance has issued an overall acceptable recommendation for this application dated 05-Feb-2013. Therefore, the NDA is recommended for approval from CMC perspective.

The EES report is attached to this Memo.

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

Application:	NDA 204016/000	Action Goal:	
Stamp Date:	31-JAN-2012	District Goal:	07-JAN-2013
Regulatory:	08-JUL-2013		
Applicant:	HOSPIRA INC 275 NORTH FIELD DR DEPT 0389 BLDG H2 2 LAKE FOREST, IL 60045	Brand Name:	ZOLEDRONIC ACID INJECTION
		Estab. Name:	
		Generic Name:	ZOLEDRONIC ACID INJECTION
Priority:	5	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	150		001; SOLUTION, INJECTION; ZOLEDRONIC ACID; 4MG/100ML

Application Comment: APPLICATION RESUBMITTED AFTER CR. 505(B)(2) (on 10-JAN-2013 by D. MESMER (HFD-800) 3017964023)

FDA Contacts:	L. HSIEH	Prod Qual Reviewer		3017961682
	R. MELLO	Micro Reviewer	(HFD-805)	3017961574
	D. MESMER	Product Quality PM	(HFD-800)	3017964023
	M. FAGBAMI	Regulatory Project Mgr	(HFD-150)	3017961348
	H. SARKER	Team Leader	(HFD-150)	3017961747

Overall Recommendation:	ACCEPTABLE	on 05-FEB-2013	by R. SAFAAI-JAZI	()	3017964463
	WITHHOLD	on 16-NOV-2012	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 31-OCT-2012	by EES_PROD		
	PENDING	on 01-AUG-2012	by EES_PROD		
	PENDING	on 22-FEB-2012	by EES_PROD		

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

Establishment: CFN: LABORATORIOS GRIFOLS S.A. FEI: 3009736169

(b) (4)
(b) (4) BARCELONA, , SPAIN

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: THERE ARE (b) (4) BUILINGS FOR THIS FEI. THE 2 (b) (4) SITE PERFORMS DRUG PRODUCT MANUFACTURING AND IN-PROCESS TESTING; (b) (4) PERFORMS FOR DRUG PRODUCT: EXCIPEINT TESTING, COMPONENT TESTING, DRUG PRODUCT TESTING, STABILITY STORAGE AND TESTING. (b) (4) PERFORMS DRUG SUBSTANCE ID TESTING.

(on 16-FEB-2012 by D. MESMER (HFD-800) 3017964023)
PROFILE CHANGED TO (b) (4) PER INVESTIGATOR AND MICRO REVIEW (on 01-NOV-2012 by D. SMITH (HFD-323) 3017965321)

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

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-FEB-2012				MESMERD
SUBMITTED TO DO	23-FEB-2012	Product Specific			INYARDA
(b) (4) INSPECTIONAL HISTORY ONLY					
ASSIGNED INSPECTION TO IB	15-MAR-2012	Product Specific			BRYKMANR
INSPECTION SCHEDULED	30-MAY-2012		11-JUL-2012		PHILPYE
INSPECTION PERFORMED	11-JUL-2012		11-JUL-2012		Simone.Pitts
<p>AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED This pre-approval and comprehensive GMP inspection of a (b) (4) pharmaceutical manufacturer was conducted according to FACTS Assignment (b) (4).</p> <p>The inspection covered the manufacturing processes and included a review of the Quality, Production, Materials Management, Facilities & Equipment, Packaging & Labeling and Laboratory Control System for NDA 204016 Zoledronic Acid Injection 4mg/100m (b) (4) under the profile class (b) (4).</p> <p>This is the initial inspection of the facility. Please see the EIR for more information regarding other sister facilities.</p> <p>The current inspection found the firm operating as (b) (4) manufacturer. At the close of the inspection, a five item FDA-483 was issued citing the following deficiencies: (b) (4)</p>					
<p>No samples were collected and no refusals were encountered during the inspection. A copy of the GMP Compliance Summary of Findings Form, Facsimile Coversheet and CDER EES Assihnment sheet are attached to this report.</p>					
DO RECOMMENDATION	13-NOV-2012			ACCEPTABLE INSPECTION	BRYKMANR
OC RECOMMENDATION	14-NOV-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR
SUBMITTED TO OC	10-JAN-2013				MESMERD

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

SUBMITTED TO DO	10-JAN-2013	10-Day Letter		STOCKM
DO RECOMMENDATION	11-JAN-2013		ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	14-JAN-2013		ACCEPTABLE DISTRICT RECOMMENDATION	SHARPT

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 Establishment Comment: DRUG SUBSTANCE ALTERNATE API RELEASE TESTING SITE (on (b) (4))
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-FEB-2012				(b) (4)
OC RECOMMENDATION	23-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO OC	10-JAN-2013				(b) (4)
OC RECOMMENDATION	10-JAN-2013			ACCEPTABLE BASED ON PROFILE	STOCKM

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 Establishment Comment: DRUG SUBSTANCE ALTERNATE API RELEASE TESTING SITE (on (b) (4))
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>	<u>Reason</u>				
SUBMITTED TO OC	22-FEB-2012				(b) (4)
OC RECOMMENDATION	23-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO OC	10-JAN-2013				(b) (4)
SUBMITTED TO DO PROFILE IS IN INITIAL STATUS	10-JAN-2013	10-Day Letter			STOCKM
DO RECOMMENDATION PROFILE CLASS CTL FINAL UPDATED TO ACCEPTABLE. PREVIOUS THREE DRUG EI'S FOR PROFILE CLASS CTL WERE VAI, NAI, NAI RESPECTIVELY. RECOMMEND APPROVAL BASED ON FIRM'S COMPLIANCE.	05-FEB-2013			ACCEPTABLE BASED ON FILE REVIEW	EBUTLER
OC RECOMMENDATION	05-FEB-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAJAZIR

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

/s/

LI SHAN HSIEH
04/12/2013

ALI H AL HAKIM
04/12/2013

MEMO TO FILE

NDA: 204016

From: Li-Shan Hsieh Ph.D.
CMC Reviewer, Division I, ONDQA

To: Nallaperumal Chidambaram Ph.D.
Acting Branch Chief, Division I, ONDQA

Date: November 15, 2012

SUBJECT: EES update for NDA 204016

The CMC review for NDA is recommended for Approval pending overall recommendation from the Office of Compliance. The current EES report indicates a withhold recommendation for the Hospira Boulder facility for NDA 204016, dated 14-Nov-2012. The rest of the facilities have been found Acceptable. The overall application recommendation is not available at this time, dated 15-Nov-2012.

The EES report is attached to this Memo.

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

Application:	NDA 204016/000	Action Goal:	
Stamp Date:	31-JAN-2012	District Goal:	01-JUN-2012
Regulatory:	30-NOV-2012		
Applicant:	HOSPIRA INC 275 NORTH FIELD DR DEPT 0389 BLDG H2 2 LAKE FOREST, IL 60045	Brand Name:	ZOLEDRONIC ACID INJECTION
		Estab. Name:	
		Generic Name:	ZOLEDRONIC ACID INJECTION
Priority:	5	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	150		001; SOLUTION, INJECTION; ZOLEDRONIC ACID; 4MG/100ML
Application Comment:	505(B)(2) (on 13-FEB-2012 by D. MESMER (HFD-800) 3017964023)		

FDA Contacts:	D. MESMER	Project Manager	(HFD-800)	3017964023
	L. HSIEH	Review Chemist		3017961682
	H. SARKER	Team Leader	(HFD-150)	3017961747

Overall Recommendation:	PENDING	on 31-OCT-2012	by EES_PROD
	PENDING	on 01-AUG-2012	by EES_PROD
	PENDING	on 22-FEB-2012	by EES_PROD

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

Establishment: **CFN:** HOSPIRA BOULDER INC
4876 STERLING DR
BOULDER, CO 803012350

FEI: 3005231248

DMF No: **AADA:**

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

Establishment Comment: PERFORMS DRUG SUBSTANCE MANUFACTURING RELEASE TESTING, STABILITY TESTING (on 16-FEB-2012 by D. MESMER (HFD-800) 3017964023)

Profile: (b) (4) **OAI Status:** POTENTIAL OAI

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-FEB-2012				MESMERD
OC RECOMMENDATION	23-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA
SUBMITTED TO DO	31-OCT-2012	10-Day Letter			SMITHDE
DO RECOMMENDATION	14-NOV-2012			WITHHOLD	EBUTLER
EI ON 5/2012 REVELAED REPEAT GMP DEFICIENCIES REGARDING PROCESS VALIDATION AND EQUIPMENT CLEANING VALIDATION. IN ADDITION, THE FIRM FAILED TO FILE MULTIPLE FIELD ALERTS. RECOMMEND WITHHOLD UNTIL MEETING WITH FIRM FOR CORRECTIVE RESPONSE				EQUIPMENT CLEANING VALIDATION QA FUNCTIONS (b) (4) (VALIDATION) OR PROCE	

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 Establishment Comment: DRUG SUBSTANCE ALTERNATE API RELEASE TESTING SITE (on (b) (4))
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-FEB-2012				(b) (4)
OC RECOMMENDATION	23-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
Establishment Comment: DRUG SUBSTANCE ALTERNATE API RELEASE TESTING SITE (on (b) (4))
Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-FEB-2012				(b) (4)
OC RECOMMENDATION	23-FEB-2012			ACCEPTABLE BASED ON PROFILE	INYARDA

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

/s/

LI SHAN HSIEH
11/15/2012

NALLAPERUM CHIDAMBARAM
11/15/2012
I concur.

Memorandum

To: NDA 204-016 (Applicant: Hospira)
From: Haripada Sarker, Ph.D. Date: 11/01/2012
Re: In-use Stability of Transfer Device - Addendum

Subject: Review of In-use Stability Data for Drug Product Transfer Device

Background

Reference is made to the original NDA 204-016 submission dated 31-Jan-2012 for Zoledronic Acid Injection. The NDA is submitted under 505(b)(2) where the listed drug is Zometa approved under NDA 21223. Li Shan Hsieh is the primary CMC reviewer for this NDA.

Two Zoledronic acid 505(b)(2) NDAs, NDA 204-016 (b)(4) are currently under review in the Agency. In NDA 204-016, the drug is supplied in a 4 mg/100 mL (b)(4) plastic bag using a single port delivery system. However, under this NDA a reduction in dose is necessary to treat patients with renal impairment. (b)(4) For safe delivery, FDA recommended the following for proposed commercial container/closure system (Ref. to September 5, 2012 Information Request).

- (b)(4) Use the currently approved preparation instructions as it appears in the label for the listed drug Zometa (Zoledronic Acid) 4 mg/100 mL bottle.

It is noted that the listed drug, Zometa is supplied as a 4 mg/100 mL single-use ready-to-use glass bottle.

In order to be consistent with both Zoledronic acid NDAs, the following IR was sent to this applicant on October 17, 2012.

- Please provide chemical compatibility and in-use stability data for the duration your drug product will be in contact with the sample transfer device(s) that are commonly available, and also provide information that you can gather about materials of construction for those devices.

The applicant provided the following in support of their proposal (ref. NDA 204-016, SD-19).

Table. IV transfer devices and the materials of construction.

Transfer Device Vendor	Device Name	Materials of Construction

In-Use Stability Information:

Hospira Zoledronic Acid, 4mg/100mL Premix bags were spiked with each of the transfer devices described above. It was ensured that the drug solution was in contact with the fluid path of the IV transfer device for a period (b) (4) under ambient conditions. These conditions are considered to be worst case as section 2.3 of the package insert indicates the solution should be (b) (4) after preparation of the reduced dose. The package insert also states the total time between preparation of the reduced dose and end of administration must not exceed (b) (4). Critical attributes such as appearance, pH, potency and impurities were evaluated to demonstrate chemical compatibility. The (b) (4) transfer devices were in contact with Hospira Zoledronic Acid, 4mg/100mL Premix lot 1023802, and the (b) (4) transfer device was in contact with Zoledronic Acid, 4mg/100mL Premix lot 1023803. The transfer device contact solutions were compared to appropriate control solutions from the same lots.

Table. In-use Stability Data

(b) (4)

Evaluation:

Based on the test data provided for representative commercially available transfer device, no significant change in Appearance, pH, Assay and Impurities are observed over the period of (b) (4) at condition under consideration.

Conclusion:

Zoledronic Acid Injection is shown to be compatible with the above transfer devices, and has demonstrated acceptable stability for the in-use period of (b) (4).

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/s/

HARIPADA SARKER
11/02/2012

NALLAPERUM CHIDAMBARAM
11/02/2012



NDA 204016

Hospira Inc.

Li-Shan Hsieh, Ph. D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I/Branch II**

**CMC REVIEW OF NDA 204016
For the Office of Hematology and Oncology Drug Products
Division of Drug Oncology Products I**

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CMC Review Data Sheet

- b) Non-Proprietary Name: Zoledronic Acid Injection
c) Code Name/# (ONDQA only): Hospira 3610
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: bisphosphonate bone resorption inhibitor.
11. DOSAGE FORM: solution
12. STRENGTH/POTENCY: 4 mg/100 mL (0.04 mg/mL)
13. ROUTE OF ADMINISTRATION: Intravenous
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:

USAN/BAN: Zoledronic Acid

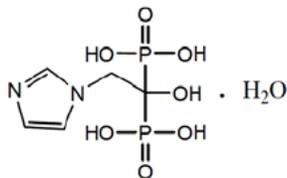
IUPAC Name: [1-hydroxy-2-(1*H*-imidazol-1-yl)ethane-1,1-diy]bis(phosphonic acid) monohydrate

CAS name: Phosphonic acid, P,P'-[1-hydroxy-2-(1*H*-imidzol-1-yl) ethylidene]bis-hydrate (1:1)

CAS Number: 165800-06-6

EPN name: 1-hydroxy-2-(1-imidazolyl) ethylene-1,1 diphosphonic acid monohydrate

CMC Review Data Sheet



Molecular formula: $C_5H_{10}N_2O_7P_2 \cdot H_2O$
 Molecular weight: 290.11 g/mol (monohydrate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		Li-Shan Hsieh
	III			4	Adequate		Li-Shan Hsieh

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
NDA	21223	Reference Listed Drug
IND	113475	(b) (4)

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		
Pharm/Tox	N/A		
Biopharm	BA/BE waiver	10-Sep-2012	Dr. Kareen Riviere
LNC	N/A		
Methods Validation	N/A		
DMEPA*	Pending		
EA	Acceptable	10-Oct-12	Dr. Li-Shan Hsieh
Microbiology	Approval	04-Oct-12	Dr. Robert Mello
CDRH consult	N/A		

*DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 204016

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This New Drug Application for Zoledronic Acid Injection, 0.04 mg/mL (4 mg/100 mL) in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, is recommended for approval from the Chemistry, Manufacturing and Controls perspective, pending overall recommendation from the Office of Compliance and resolution of labeling issues.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

Zoledronic Acid is manufactured and sourced from Hospira Boulder, Inc.. Zoledronic acid is a white to off-white powder and is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents.

There is no compendial monograph available for Zoledronic Acid. Hospira uses the USP general chapter tests wherever applicable, but Hospira in-house methods are applied for all other tests, including assay and impurity tests. The specification includes all the critical drug substance attributes that affect the manufacturing and quality of the drug product. Each lot of active ingredient is tested and is required to meet the specification stated.

The zoledronic acid manufacturing process and process controls, materials control, critical steps and intermediates, process evaluation studies, controls; and manufacturing process development have been reviewed and found Acceptable.

Executive Summary Section

Hospira Boulder, Inc. has placed three lots manufactured for registration purposes on stability under long-term and accelerated conditions. The registration batches were manufactured at pilot scale. Material of construction for packaging of the stability studies simulates the packaging intended for storage and distribution of commercial drug substance.

The test methods used for stability are the same as those used for release testing. The data generated from the long-term (24 M) and accelerated (6 M) stability studies demonstrate that zoledronic acid drug substance is stable. No significant shifts were observed and all results are within the proposed specifications..

The test methods used for stability are the same as those used for release testing.

At this time, Hospira Boulder, Inc. is proposing a retest period of (b) (4) months. Based on provided data, a retest period of (b) (4) months can be granted.

(2) Drug Product

Hospira developed a (b) (4) formulation comparable to the approved Zometa (zoledronic acid) Injection 4 mg/5mL concentrate (NDA 021-223) upon dilution with 0.9% sodium chloride.

Zoledronic Acid Injection (4 mg/100 mL) is a (b) (4) sterile aqueous solution for intravenous (I.V.) administration. The drug product is comprised of a clear, colorless solution, free from visible particulates, presented in 100 ml (b) (4) infusion bags. The bags are closed with a (b) (4) Twist-off closure (b) (4). The composition of each 100 mL drug solution consists of the active ingredient Zoledronic Acid 4 mg (on an anhydrous basis), Mannitol 220 mg, Sodium Citrate 24 mg (b) (4) Sodium Chloride 900 mg in Water for Injection. The pH range is 5.5 to 6.5. This is a (b) (4) product containing no antimicrobial preservatives.

The proposed drug product formulation contains the same active ingredient at the same concentration as the reference drug, Zometa® (zoledronic acid) Injection, 4 mg/5 mL, after admixture with 100 ml of 0.9% sodium chloride, approved March 7, 2003. (b) (4)

(b) (4) Hospira's formulation is a premix considered pharmaceutically equivalent to the admixed RLD with 100 mL of 0.9% sodium chloride

The quality of Zoledronic Acid Injection product has been assessed based on its manufacturing process, process controls, analytical procedures for identification, purity, and strength, sterility, and stability. Based on the stability data, 24 months expiry has been granted when stored at controlled room temperature.

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

Executive Summary Section

- Hypercalcemia of malignancy.
- Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

C. Basis for Approvability or Not-Approval Recommendation

The requirements of 21 CFR 314.50(d)(1) have been adequately met by the applicant.

All drug substance and drug product manufacturing, packaging and control facilities were submitted to EES. An overall recommendation is pending.

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

(See appended electronic signature page)

Li-Shan Hsieh, Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Nallaperumal Chidambaram, Ph.D., Acting Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The following is a summary of the labeling review, pending with the final recommendation made by DMEPA.

1. Package Insert

(a) "Highlights" Section

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	Zoledronic acid Injection
Dosage form, route of administration	(b) (4)
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (201.57(a)(8))	
Whether the drug product is scored	N/A

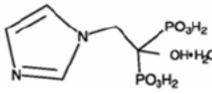
(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths

Item	Information Provided in NDA
Available dosage forms	solution
Strengths: in metric system	4 mg/100 mL
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4) bag

CMC Assessment Section

#11: Description

Item	Information Provided in NDA
Proprietary name and established name	Zoledronic Acid Injection
Dosage form and route of administration	sterile liquid (b) (4) solution for intravenous infusion
Active moiety expression of strength with equivalence statement (if applicable)	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	sodium chloride, USP, (b) (4) mannitol, USP (b) (4) water for injection and sodium citrate, USP, (b) (4)
Statement of being sterile (if applicable)	a sterile liquid
Pharmacological/ therapeutic class	an inhibitor of osteoclastic bone resorption
Chemical name, structural formula, molecular weight	1-Hydroxy-2-imidazol-1-yl-phosphonoethyl phosphonic acid monohydrate. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and its molar mass is 290.1g/Mol 
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	a white crystalline powder

16: How Supplied/Storage and Handling

CMC Assessment Section

Item	Information Provided in NDA
Strength of dosage form	4 mg/100 mL
Available units (e.g., bottles of 100 tablets)	(b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Carton of 1 (b) (4) NDC 0409-4229-01
Special handling (e.g., protect from light)	(b) (4)
Storage conditions	not exceeding 30 C (86 F)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by: Laboratorios Grifols, SA Barcelona, Spain Manufactured for: Hospira Inc. Lake Forest, Illinois 60045 USA

2. Structured Product Labeling (SPL) Drug Listing Data Element

Proprietary name Name(s) of active ingredient(s), dosage form,		
Product Information		
Product Type	HUMAN PRESCRIPTION Drug	DRUG NDC Product Code (Source)
Route of Administration		DEA Schedule
INGREDIENTS		
Name (Active Moiety)	Type	Strength
Name of active ingredient (name of active moiety)	Active	
	Inactive	
Product Characteristics		
Color Name of SPL color		Score
Shape SPLshape		Size
Flavor		Imprint Code
Contains		Symbol
Coating (example: false)		
Packaging		
#	NDC	Package Description
1		
		Multilevel Packaging

3. Immediate container labels

CMC Assessment Section

Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Zoledronic acid Injection
Dosage strength	4 mg/100 mL(0.04 mg/mL)
Net contents (See USP <1> for presentation of strength and content for injections.)	N/A
"Rx only" displayed prominently on the main panel	yes
NDC number (21 CFR 207.35(b)(3)(i)) (Appear prominently in the top third of the principal display panel or it may appear as part of and contiguous to any bar-code symbol)	NDC 0409-4229-01
Lot number and expiration date (21 CFR 201.17)	Yes
Storage conditions	Yes
Bar code (21CFR 201.25)	Yes
Name of manufacturer/distributor	Yes
Instruction for Medication Guide, if any (21CFR 208.24(d)) appears prominently	Yes
And others, if space is available	

4. Carton labeling

Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	Large font size for Zoledronic Acid half the font size for Injection
Dosage strength	4mg/100 mL (0.04 mg/mL)
Net quantity of dosage form	Each bag contains 4.264 mg of zoledronic acid monohydrate
"Rx only" displayed prominently on the main panel	Yes
Lot number and expiration date	Yes
Storage conditions	Yes
Bar code (21CFR 201.25)	Yes
NDC number (21 CFR 207.35(b)(3)(i))(Appear prominently in the top third of the principal display panel or it may appear as part of and contiguous to any bar-code symbol)	Yes, NDC 0409-4229-01
Manufacturer/distributor's name	Yes
Quantitative ingredient information (injectables)	Yes
Statement of being sterile (if applicable)	Yes
"See package insert for dosage information"	Yes, Sterile solution
Special instructions ("Keep out of reach of children" is required for OTC in CFR. Optional for Rx drugs)	Do not mix with calcium-containing solutions. Infusion time must not be less than 15 minutes.

CMC Assessment Section

5. Unit-dose labeling (21 CFR 201.10(i))

Item	Information Provided in NDA
Proprietary name, established name (font size and prominence)	
Dosage strength	
Net content (for injection only. See USP <1> for presentation of strength and content for injections.)	
“Rx only”	
Lot number and expiration date (21 CFR 201.17 & 201.18) (For single-dose containers, the expiration date may properly appear on the individual carton instead of the immediate product container.)	
Bar code (Not required for physician samples)	
NDC number	
Name of manufacturer/distributor	

B. Environmental Assessment Or Claim Of Categorical Exclusion

Since Zoledronic Acid Injection is being submitted as a New Drug Application, the categorical exclusions of 21 CFR 25.31 apply. Zoledronic Acid Injection will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. Therefore, it is excluded from the requirements of 21 CFR 25, since the action requested is both included within an excluded category and meets all of the criteria for this exclusion. Signed environmental impact certification letters issued by Hospira Inc. and Laboratorios Grifols, SA., ^{(b) (4)} facility are provided herein.

Evaluation and Comment:

Acceptable

A request for exclusion of an environmental assessment is submitted base on estimated concentration of the new drug substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb) as per 21 CFR25.31(b).

C. Establishment Evaluation Report

III. List Of Deficiencies Communicated and Resolved

There are no outstanding deficiencies.

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/s/

LI SHAN HSIEH
10/11/2012

NALLAPERUM CHIDAMBARAM
10/11/2012
I concur

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 204-016

Supplement Number and Type: **Established/Proper Name:**

Applicant: Hospira, Inc

Letter Date: 30 January, 2012

Stamp Date: 31 January, 2012

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?	Yes		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Yes		
3.	Are all the pages in the CMC section legible?	Yes		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			No direct CMC issue was included in pre-NDA meeting, except bio-waiver.

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Yes		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			N/A

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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) 	Yes		
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) 	Yes		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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) 	Yes		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	Yes		

* 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?	Yes		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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?	Yes		
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?	Yes		
21.	Is there a batch production record and a proposed master batch record?	Yes		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	Yes		In drug development section
23.	Have any biowaivers been requested?			Fileable from Biopharm. Biowaiver is review issue.
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	Yes		
25.	Does the section contain controls of the final drug product?	Yes		
26.	Has stability data and analysis been provided to support the requested expiration date?			Review issue
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		No	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		No	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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

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

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?	Yes		LoA provided

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	Yes	
	III			Yes	

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

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	Yes		
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.	Yes		No CMC fileability issue.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		No	Describe potential review issues here or on additional sheets

{Haripada Sarker}

3-9-2012

Name of
~~Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer~~
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

Date

{Sarah Pope Miksinski}

Name of
Branch Chief
Division of Pre-Marketing Assessment # 1
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/

HARIPADA SARKER
03/09/2012

LIANG ZHOU on behalf of SARAH P MIKSINSKI
03/09/2012
for BC, Sarah