

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203231Orig1s000

CHEMISTRY REVIEW(S)

NDA 203231

Zoledronic Acid Injection, 4mg/100mL

SAGENT Pharmaceuticals, Inc.

CMC Review # 3

Joyce Crich, Ph.D

Review Chemist

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

**CMC REVIEW OF NDA 203231
For the Division of Drug Oncology Product I**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 203231
2. REVIEW #: 3
3. REVIEW DATE: 9-JUL-2013
4. REVIEWER: Joyce Z Crich
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	30-AUG-2011	30-AUG-2011
NDA Resubmission/After Refusal to File	7	06-JAN-2012	09-JAN-2012
Amendment (revised container and carton labeling)	10	30-MAR-2012	30-MAR-2012
Amendment (Revised container and carton labeling)	13	27-JUN-2012	27-JUN-2012
Amendment (Response to 13-JUN-2012 CMC IR)	14	19-JUL-2012	19-JUL-2012
Amendment (Revised container and carton labeling)	16	06-SEP-2012	06-SEP-2012
Amendment (Revised container and carton labeling)	17	06-SEP-2012	06-SEP-2012
Amendment (Response to 23-AUG-2012 CMC IR)	18	06-SEP-2012	06-SEP-2012
Amendment (Response to 14-SEP-2012 CMC IR)	19	20-SEP-2012	21-SEP-2012
Amendment (Response to 20-SEP-2012 CMC IR)	21	10-OCT-2012	10-OCT-2012
Amendment (Response to 21-SEP-2012 telecon)	20	05-OCT-2012	09-OCT-2012
Amendment (Revised container and carton labeling)	20	05-OCT-2012	09-OCT-2012
Amendment (Revised Package Insert)	22	15-OCT-2012	15-OCT-2012
Amendment (Revised container and carton labeling)	23	17-OCT-2012	17-OCT-2012
Amendment (Response to 23-AUG-2012 CMC IR)	25	11-DEC-2012	11-DEC-2012
Amendment (Response to 01-MAR-2013 Complete Response)	29	04-MAR-2013	04-MAR-2013
Amendment (Response to 03-JUN-2013 Complete Response)	30	03-JUN-2013	03-JUN-2013
Amendment (Response to 01-JUL-2013 CMC IR)	32	02-JUL-2013	02-JUL-2013
Amendment (Response to 03-JUL-2013 CMC IR)	33	05-JUL-2013	05-JUL-2013

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: ACS Dobfar Info S.A.
Address: Casai, CH-7748 Campascio, Switzerland
Representative: Thomas J Moutvic, Sagent Pharmaceuticals Inc
Telephone: 847-908-1613

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zoledronic Acid Injection
- b) Non-Proprietary Name: Zoledronic Acid Monohydrate
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Bisphosphonate, inhibitor for bone resorption

11. DOSAGE FORM: Sterile solution, injection

12. STRENGTH/POTENCY: 4 mg /mL (as zoledronic acid anhydrous)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

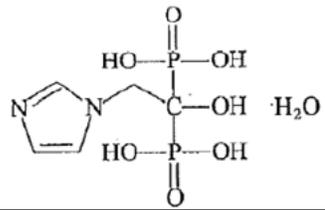
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

CMC Review Data Sheet

Chemical Structure	
Molecular Formula	C ₅ H ₁₀ N ₂ O ₇ P ₂ ·H ₂ O
Molecular Weight	290.11 g/mol (monohydrate) 272.01 g/mol (anhydrous)
United States Adopted Name (USAN)	zoledronic acid
Chemical Name	(1) Phosphonic acid, [1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis-, monohydrate; or (2) (1-Hydroxy-2-imidazol-1-ylethylidene) diphosphonic acid, monohydrate.
Chemical Abstracts Service (CAS) Registry Number	CAS-165800-06-6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II			(b) (4)	3 & 4	Adequate	16-Aug-2012 See section 3.2.S Reviewed by Dr. D. Chowdhury.
	III			4	Adequate	N/A	See sections 1.4.1 & 3.2.P.4.1
	III			4	Adequate	N/A	See sections 1.4.1 & 3.2.P.7
	III			3 & 4	Adequate	17-Feb-2012	Reviewed by Dr. Xuhong Li

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: N/A

18. STATUS:

CMC Review Data Sheet

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	21-FEB-2012	A. Inyard
Pharm/Tox	Acceptable	17-Oct-2012	Dr. Wei Chen
Biopharm	Acceptable	02-APR-2012	Dr. Zedong Dong
LNC	N/A		
Methods Validation	Acceptable	28-DEC-2012 17-APR-2013 24-MAY-2013	Dr. Michael Trehy
DMEPA*	Acceptable with additional comments	19-Oct-2012	Jibril Abdus-Samad
EA	Categorical exclusion (see CMC Review #1)	18-SEP-2012	Dr. Joyce Crich
Microbiology	approval from microbiology product quality standpoint	24-JUL-2012	Dr. Stephen Langille

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 203,231

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval.

Include the following language in the approval letter:

Based on the provided stability data, a 24-month expiration dating period is granted for Zoledronic Acid Injection 4 mg/100mL in the proposed commercial container closure system when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

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

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance zoledronic acid monohydrate is known active pharmaceutical ingredient and is manufactured (b) (4)

(b) (4) Complete manufacturing and controls information is cross-referenced to a DMF. A Letter of Authorization dated 22-DEC-2010 for Zoledronic Acid, Type II DMF # (b) (4) from the DMF holder (b) (4) (b) (4) is provided in support of this application. This DMF was found to be adequate (see Dr. D. Chowdhury's review dated 16-AUG-2012).

Zoledronic acid monohydrate is a white crystalline powder. It has a pH dependent solubility. Zoledronic acid monohydrate exists in several crystal forms. The API supplier produces (b) (4). Other crystal forms are not encountered during production or stability of the API supplier's product.

The stability data shows no trend for impurities up to 6 months under accelerated conditions (40°C ± 2°C, 75% ± 5%RH). The long-term drug substance stability data

Executive Summary Section

support a (b) (4) month retest period under storage conditions of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ($60\% \pm 5\% \text{RH}$). Based on the stability data, the retest period should be no longer than (b) (4) months when the drug substance is stored in an amber Type III glass container with (b) (4) and a (b) (4) cap as immediate packaging, with an aluminium (b) (4) bag as the secondary packaging.

There are no CMC deficiencies related to drug substance.

(2) Drug Product

Zoledronic Acid Injection is a clear, colorless, sterile solution for intravenous infusion with pH value approximately (b) (4). It is available in 4 mg/100 mL dosage strength. The injection solution contains zoledronic acid monohydrate as the active pharmaceutical ingredient equivalent to 4 mg of zoledronic acid anhydrous together with 0.9% Sodium Chloride USP, Mannitol USP, Sodium Citrate (b) (4) USP and Water for Injection USP.

The drug product is filled in (b) (4) bags equipped with one (b) (4) tube (b) (4) and twist off port (b) (4). These bags are then contained in aluminium (b) (4) over-wrapping to protect the product from light and to reduce the water permeation.

Formulation development of Zoledronic Acid Injection was performed by ACS DOBFAR INFO SA at site Campascio, Switzerland, which is also the proposed commercial site for the drug product manufacturing and release testing, packaging, labeling, stability testing and release. The main steps of the manufacturing process consist of (b) (4). Standard release specifications for an injection solution dosage form have been proposed.

During the first review cycle, the applicant submitted the stability data from three primary batches for Zoledronic Acid Injection 4 mg/100mL up to 12 months at $25^{\circ}\text{C}/40\% \text{RH}$ (long term storage condition) and up to 6 months at $40^{\circ}\text{C}/15\% \text{RH}$ (accelerated condition) in the proposed commercial primary stability container closure system in the original NDA submission. At end of the first review cycle, the applicant provided updated stability data up to 24 months at $25^{\circ}\text{C}/40\% \text{RH}$ and 6 months at $40^{\circ}\text{C}/15\% \text{RH}$ in Amendment SN0024. Due to the deficiencies related to the analytical methods identified during the Method Validations conducted by FDA's Division of Pharmaceutical Analysis (DPA) in St. Louis which resulted in a Complete Response Letter dated 01-MAR-2013 for this NDA, an appropriate expiration dating period can not be determined at that time.

In the resubmission dated 03-JUN-2013, the applicant addressed all the deficiencies identified in the first review cycle. Based on the provided stability data, a 24-month expiration dating period is granted for Zoledronic Acid Injection 4 mg/100mL in the

Executive Summary Section

proposed commercial container closure system when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

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

Zoledronic Acid Injection is indicated for the treatment of (i) hypercalcemia of malignancy; (ii) multiple myeloma and bone metastases from solid tumors in conjunction with standard antineoplastic therapy.

Zoledronic Acid Injection 4 mg/100 mL is dosed as a single – use intravenous infusion over no less than 15 minutes, and 4 mg as retreatment after a minimum of 7 days for hypercalcemia of malignancy, or 4 mg as retreatment every 3-4 weeks for multiple myeloma and bone metastases from solid tumors.

This product is not intended for use with patients with reduced renal function (renal impairment).

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

Based on the provided stability data, a 24-month expiration dating period is granted for Zoledronic Acid Injection 4 mg/100mL in the proposed commercial container closure system when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed established name Zoledronic Acid Injection.

Methods validation has been completed by the FDA Laboratory in St. Louis, MO.

The CMC revisions to the package insert have been incorporated and the revised container labels are found to be acceptable from the CMC perspective.

The Office of Compliance issued an overall “acceptable” recommendation dated 21-FEB-2012 for the facilities used for manufacturing and control of the drug substance and drug product.

Executive Summary Section

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

(See appended electronic signature page)

Joyce Z Crich, Ph.D., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Ali Ai-Hakim, Ph.D., Branch Chief, Branch II, Division of New Drug Quality
Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

14 Page(s) has been Withheld in Full as b4 (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/

JOYCE Z CRICH
07/09/2013

ALI H AL HAKIM
07/09/2013

CMC Review Data Sheet

Memo to File

To: NDA 203231

From: Joyce Z Crich, Ph.D

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

Subject: Addendum to CMC Review # 2

Date: Feb 11, 2013

This addendum to the CMC review #2 for NDA 203,231 is written to update the files based on results of methods validation studies performed by FDA's Division of Pharmaceutical Analysis (DPA), St. Louis.

NDA 203,231 was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zoledronic Acid Injection, 4 mg per 100 mL. A tentative approval was granted under 21 CFR 314.105, with a shelf life of 12 months on 09-NOV-2012. It should be noted that since the listed drug upon which this NDA relies is subject to a period of patent and/or exclusivity protection, a final approval of the application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired. Before the Tentative Approval Letter was issued, a request for the validation of the regulatory methods was made by the reviewer due to some concerns on the methods, and the same was stated in the Agency's Tentative Approval Letter, that the validation of the regulatory methods had not been completed and that the Agency expects applicant's continued cooperation to resolve any problems that may be identified. Refer to Agency's *Tentative Approval Letter* dated 09-NOV-2012 in DARRTS.

The Methods Validation Report from DPA, FDA St. Louis Lab became available on 28-DEC-2012. Based on the results contained in this report, this NDA is not recommended for approval from a chemistry, manufacturing and controls (CMC) standpoint, due to significant CMC deficiencies identified in the validation of the regulatory methods for this NDA. Therefore, the current recommendation from a CMC standpoint is that a complete response letter be issued. An appropriate expiration dating period should be determined once the deficiency noted has been resolved.

Executive Summary Section

Review Notes

FDA's Division of Pharmaceutical Analysis (DPA, FDA St. Louis Lab) performed Methods Validation on HPLC method for Assay, Unknown and Known Impurities upon request from the reviewer, and provided a Methods Validation Report. Refer to Methods Validation Report Review dated 28-DEC-2012 in DARRTS. The overall conclusion from this validation report is that **the methods are unacceptable for regulatory purposes**. Following is the summary of the findings from the report:

1. HPLC Method for Assay (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-7), is not acceptable for quality control and regulatory purposes, due to (i) inadequate System Suitability as the resolution between [REDACTED]^{(b) (4)} did not pass because of [REDACTED]^{(b) (4)} due to sample overloading, (ii) using unacceptable system suitability placebo solution which causes shifts in retention time of the [REDACTED]^{(b) (4)} comparing the standard solution placebo which is also used in the method.
2. HPLC Method for Unknown Impurities (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-8.2), is not acceptable for quality control and regulatory purposes, due to the same reasons as describe in 1. Note: Due to sample overloading and observed [REDACTED]^{(b) (4)}, DPA modified the method and observed a previously unobserved and unreported impurity [REDACTED]^{(b) (4)} at an average amount of [REDACTED]^{(b) (4)}% in the drug product samples provided by the applicant.
3. HPLC Method for Known Impurities (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-8.1), is not acceptable for quality control and regulatory purposes, due to (i) the incorrect description of buffer preparation which caused unrepeatable chromatograph results, (ii) incorrect calculation formula which is not agreed with the standard solution preparation per the method.

The CMC reviewer concurs with the conclusion of DPA's Methods Validation Report that the analytical methods for Assay, Unknown Impurities and Known Impurities of drug product are unacceptable for quality control and regulatory purposes, based on the principles stated in CDER's *Reviewer Guidance on Validation of Chromatographic Methods, Nov 1994*. The findings from DPA's Methods Validation as listed above support the CMC reviewer's concerns on the analytical methods and validation in sections 3.2 P.5.2 and 3.2.P.5.3, and on the inconsistent stability data submitted in the original NDA, and in the amendment SN0013 respectively. The discovery of an unknown impurity at [REDACTED]^{(b) (4)} by DPA's modified method also indicates that the HPLC Method for Unknown Impurities (Method ID: MCP429.USP-8.2) is not adequate to detect unknown impurities and is not stability indicating, as this unknown impurity was not reported by the applicant in any batch analysis and stability studies including forced degradation studies; additional information on the origin and the level of the impurity in stability samples need to be determined. Note: before the validation results of regulatory methods became available, there were great efforts from the reviewer and the review team in communicating with the applicant to resolve CMC issues, which resulted in a recommendation

Executive Summary Section

of granting a shelf-life of 12 months for Zoledronic Acid Injection 4 mg/100mL at the time of tentative approval. Refer to the Agency's *Tentative Approval Letter* dated 09-NOV-2012. For additional comments and concerns, refer to CMC Review # 1 and #2 in DAARTS dated 05-OCT-2012 and 19-OCT-2012 respectively.

Consequently, the analytical results that have been obtained thus far for release and stability also cannot be relied upon because the regulatory methods have been verified to be not suitable for assay and impurities. Therefore, the potential impact on safety and efficacy of the drug product can not be evaluated.

Based on the above and until new methods for potency and known/unknown impurities are developed, validated and all impurities are accounted with established acceptance criteria, this application can not be recommended for full approval from the standpoint of chemistry, manufacturing and controls, as it does not meet requirement stated in 21 CFR 314.50 (d)(1)(ii)(a).

The following comments are to be included in the action letter:

The following deficiencies were noted during method validation, and the following methods have been determined to be unacceptable for regulatory purposes. Due to these deficiencies, the Agency is not able to confirm the strength, identity, quality, purity and potency of the proposed drug product as required under 21 CFR 314.50(d)(1).

- 1. HPLC Method for Assay (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-7), is not acceptable for quality control and regulatory purposes, due to (i) inadequate System Suitability as the resolution between (b)(4) did not pass because of (b)(4) due to sample overloading, (ii) using unacceptable system suitability placebo solution which causes shifts in retention time of the (b)(4) (b)(4) comparing the standard solution placebo which is also used in the method.*
- 2. HPLC Method for Unknown Impurities (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-8.2), is not acceptable for quality control and regulatory purposes, due to the same reason as describe in 1. Note: Due to sample overloading and observed (b)(4) (b)(4), DPA modified the method and observed a previously unobserved and unreported impurity (b)(4) at an average amount of (b)(4) % in the drug product samples you provided.*
- 3. HPLC Method for Known Impurities (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-8.1), is not acceptable for quality control and regulatory purposes, due to (i) the incorrect description of buffer preparation which caused unrepeatable chromatograph results, (ii) incorrect calculation formula which is not agreed with the standard solution preparation per the method.*

In order to address these deficiencies, redevelop and revalidate your regulatory methods for assay, unknown and known impurities, and provide updated regulatory specifications for drug product as well as updated batch analysis data and stability data.

Executive Summary Section

Additionally, based on the above deficiencies, the applicant's request under amendment SN 0024 (dated 12-DEC-2012) to extend the expiration dating period from 12 months to 24 months can not be granted at this time.

Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Joyce Z Crich, Ph.D., 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:

Sarah Pope Miksinski, Ph.D. Acting Director, Division I of New Drug Quality Assessment I (DNDQA I), ONDQA

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

/s/

JOYCE Z CRICH
02/11/2013

NALLAPERUM CHIDAMBARAM
02/11/2013
I concur.

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application: NDA 203231/000

Action Goal:

App Date: 30-AUG-2011

District Goal: 10-SEP-2012

App No: 09-NOV-2012

Applicant: ACS DOBFAR INFO SA
1901 NORTH ROSELLE RD STE 700
SCHAUMBURG, IL 601953176

Brand Name: ZOLEDRONIC ACID INJECTION

Estab. Name:

Generic Name: ZOLEDRONIC ACID INJECTION

Priority: 5

Product Number; Dosage Form; Ingredient; Strengths

App Code: 150

001; SOLUTION, INJECTION; ZOLEDRONIC ACID; 4MG/100ML

Application Comment: 505(B)(2) (on 13-FEB-2012 by D. MESMER (HFD-800) 3017964023)

Contacts:	D. MESMER	Project Manager	(HFD-800)	3017964023
	J. CRICH	Review Chemist		3017963882
	H. SARKER	Team Leader	(HFD-150)	3017961747

Final Recommendation:	ACCEPTABLE	(b) (4)	by A. INYARD	(HFD-323)	3017965363
	PENDING	on 13-FEB-2012	by EES_PROD		
	ACCEPTABLE	(b) (4)	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 05-OCT-2011	by EES_PROD		

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: ACS DOBFAR S.P.A. (PLANT #2)
 CAMPASCIO
 CH-7748 CAMPASCIO, SWITZERLAND
FEI: 3004537783

F No: **AADA:**

Capabilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURING, TESTING, PACKAGING, RELEASE AND STABILITY STUDIES; LAST INSPECTION
 (b) (4)

File: APPLICANT SITES FACILITY NAME AS ACS DOBFAR INFO SA (on 13-FEB-2012 by D. MESMER (HFD-800) 3017964023)
 (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>
MITTED TO OC	05-OCT-2011				MESMERD
MITTED TO DO	06-OCT-2011	10-Day Letter			SMITHDE
RECOMMENDATION	(b) (4)			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
RECOMMENDATION	(b) (4)			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE
REQUEST CANCELLED	01-NOV-2011			REFUSE TO FILE	MESMERD
MITTED TO OC	13-FEB-2012				MESMERD
MITTED TO DO	13-FEB-2012	10-Day Letter			INYARDA
RECOMMENDATION	(b) (4)			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
RECOMMENDATION	(b) (4)			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
File No: (b) (4) **AADA:**
Capabilities: DRUG SUBSTANCE MANUFACTURER
Establishment Comment: PERFORMS MANUFACTURING AND QC TESTING FOR DRUG SUBSTANCE. ALTERNATE CONTACT: (b) (4)
 (b) (4)
File: NON-STERILE API BY CHEMICAL SYNTHESIS **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>	
MITTED TO OC	05-OCT-2011				MESMERD
RECOMMENDATION	(b) (4)			ACCEPTABLE BASED ON PROFILE	SMITHDE
QUEST CANCELLED	01-NOV-2011			REFUSE TO FILE	MESMERD
MITTED TO OC	13-FEB-2012				MESMERD
RECOMMENDATION	(b) (4)			ACCEPTABLE BASED ON PROFILE	INYARDA

NDA 203231

Zoledronic Acid Injection, 4mg/100mL

SAGENT Pharmaceuticals, Inc.

CMC Review # 2

Joyce Crich, Ph.D

Review Chemist

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

**CMC REVIEW OF NDA 203231
For the Division of Drug Oncology Product I**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 203231
2. REVIEW #: 2
3. REVIEW DATE: 19-OCT-2012
4. REVIEWER: Joyce Z Crich
5. PREVIOUS DOCUMENTS: N/A
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Amendment (Response to 14-SEP-2012 CMC IR)	19	20-SEP-2012	21-SEP-2012
Amendment (Response to 20-SEP-2012 CMC IR)	21	10-OCT-2012	10-OCT-2012
Amendment (Response to 21-SEP-2012 telecon)	20	05-OCT-2012	09-OCT-2012
Amendment (Revised container and carton labeling)	20	05-OCT-2012	09-OCT-2012
Amendment (Revised Package Insert)	22	15-OCT-2012	15-OCT-2012
Amendment (Revised container and carton labeling)	23	17-OCT-2012	17-OCT-2012

7. NAME & ADDRESS OF APPLICANT:

Name: ACS Dobfar Info S.A.
 Address: Casai, CH-7748 Campascio, Switzerland
 Representative: Thomas J Moutvic, Sagent Pharmaceuticals Inc
 Telephone: 847-908-1613

8. DRUG PRODUCT NAME/CODE/TYPE:

CMC Review Data Sheet

- a) Proprietary Name: Zoledronic Acid Injection
 b) Non-Proprietary Name: Zoledronic Acid Monohydrate
 c) Code Name/# (ONDQA only): N/A
 d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Bisphosphonate, inhibitor for bone resorption

11. DOSAGE FORM: Sterile solution, injection

12. STRENGTH/POTENCY: 4 mg/mL (as zoledronic acid anhydrous)

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

Chemical Structure	
Molecular Formula	C ₅ H ₁₀ N ₂ O ₇ P ₂ ·H ₂ O
Molecular Weight	290.11 g/mol (monohydrate) 272.01 g/mol (anhydrous)
United States Adopted Name (USAN)	zoledronic acid
Chemical Name	3-Quinolinecarbonitrile, 4-[(2, 4-dichloro-5-methoxyphenyl) amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl) propoxy]-, hydrate (1:1).

CMC Review Data Sheet

Chemical Abstracts Service (CAS) Registry Number	CAS-165800-06-6
---	-----------------

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)	3 & 4	Adequate	16-Aug-2012	See section 3.2.S Reviewed by Dr. D. Chowdhury.
	III			4	Adequate	N/A	See sections 1.4.1 & 3.2.P.4.1
	III			4	Adequate	N/A	See sections 1.4.1 & 3.2.P.7
	III			3 & 4	Adequate	17-Feb-2012	Reviewed by Dr. Xuhong Li

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: N/A

18. STATUS:

CMC Review Data Sheet

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	21-FEB-2012	A. Inyard
Pharm/Tox	Acceptable	17-Oct-2012	Dr. Wei Chen
Biopharm	Acceptable	02-APR-2012	Dr. Zedong Dong
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy	pending	pending
DMEPA*	Acceptable with additional comments	19-Oct-2012	Jibril Abdus-Samad
EA	Categorical exclusion (see CMC Review #1)	18-SEP-2012	Dr. Joyce Crich
Microbiology	approval from microbiology product quality standpoint	24-JUL-2012	Dr. Stephen Langille

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 203,231

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA. Include the following language in the approval letter:
Based on the provided stability data, a 12-month expiration dating period is granted for Zoledronic Acid Injection 4 mg/100mL in the proposed commercial container closure system when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance zoledronic acid monohydrate is known active pharmaceutical ingredient and is manufactured (b) (4)

(b) (4) Complete manufacturing and controls information is cross-referenced to a DMF. A Letter of Authorization dated 22-DEC-2010 for Zoledronic Acid, Type II DMF # (b) (4) from the DMF holder (b) (4) (b) (4) is provided in support of this application. This DMF was found to be adequate (see Dr. D. Chowdhury's review dated 16-AUG-2012).

Zoledronic acid monohydrate is a white crystalline powder. It has a pH dependent solubility. Zoledronic acid monohydrate exists in several crystal forms. The API supplier produces (b) (4). Other crystal forms are not encountered during production or stability of the API supplier's product.

Executive Summary Section

The stability data shows no trend for impurities up to 6 months under accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$, $75\% \pm 5\%\text{RH}$). The long-term drug substance stability data support a ^{(b) (4)} month retest period under storage conditions of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ($60\% \pm 5\%\text{RH}$). Based on the stability data, the retest period should be no longer than ^{(b) (4)} months when the drug substance is stored in an amber Type III glass container with ^{(b) (4)} and a white ^{(b) (4)} cap as immediate packaging, with an aluminium ^{(b) (4)} bag as the secondary packaging.

There are no CMC deficiencies related to drug substance.

(2) Drug Product

Zoledronic Acid Injection is a clear, colorless, sterile solution for intravenous infusion with pH value approximately ^{(b) (4)}. It is available in 4 mg/100 mL dosage strength. The injection solution contains zoledronic acid monohydrate as the active pharmaceutical ingredient equivalent to 4 mg of zoledronic acid anhydrous together with 0.9% Sodium Chloride USP, Mannitol USP, Sodium Citrate ^{(b) (4)} USP and Water for Injection USP.

The drug product is filled in ^{(b) (4)} bags equipped with one ^{(b) (4)} tube ^{(b) (4)} and twist off port ^{(b) (4)}. These bags are then contained in aluminium ^{(b) (4)} over-wrapping to protect the product from light and to reduce the water permeation.

Formulation development of Zoledronic Acid Injection was performed by ACS DOBFAR INFO SA at site Campascio, Switzerland, which is also the proposed commercial site for the drug product manufacturing and release testing, packaging, labeling, stability testing and release. The main steps of the manufacturing process consist of ^{(b) (4)}. Standard release specifications for an injection solution dosage form have been proposed.

The applicant submitted the stability data from three primary batches for Zoledronic Acid Injection 4 mg/100mL up to 12 months at $25^{\circ}\text{C}/40\% \text{RH}$ (long term storage condition) and up to 6 months at $40^{\circ}\text{C}/15\% \text{RH}$ (accelerated condition) in the proposed commercial primary stability container closure system in the original NDA submission. Those stability data does not support the proposed 24 months shelf-life for the drug product due to the trend of degradation under the accelerated condition. However, based on the real time stability data under long term storage condition, a shelf-life of 12 months can be granted for Zoledronic Acid Injection 4 mg/100mL in the proposed commercial container closure system at controlled room temperature. During the review cycle, the applicant provided updated stability data up to 18 months at $25^{\circ}\text{C}/40\% \text{RH}$ and 6 months at $40^{\circ}\text{C}/15\% \text{RH}$ in Amendment SN0013. Due to the inconsistency in the levels of degradation products reported between two submissions and unacceptable calculation for degradation products in SN0013, a shelf-life can not be granted based on the updated stability data.

Executive Summary Section

(b) (4)

The final revised drug product Package Insert (Amendment SN0021 dated 15-Oct-2012) and Container Labeling (Amendment SN0022 dated 17-Oct-2012) indicate that the drug product is not intended for use with patients with reduced renal function. (b) (4)

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

Zoledronic Acid Injection is indicated for the treatment of (i) hypercalcemia of malignancy; (ii) multiple myeloma and bone metastases from solid tumors in conjunction with standard antineoplastic therapy.

Zoledronic Acid Injection 4 mg/100 mL is dosed as a single – use intravenous infusion over no less than 15 minutes, and 4 mg as retreatment after a minimum of 7 days for hypercalcemia of malignancy, or 4 mg as retreatment every 3-4 weeks for multiple myeloma and bone metastases from solid tumors.

This product is not intended for use with patients with reduced renal function (renal impairment).

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

Based on the provided stability data, a 12-month expiration dating period is granted for Zoledronic Acid Injection 4 mg/100mL in the proposed commercial container closure system when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed established name Zoledronic Acid Injection.

Methods validation is pending evaluation by the FDA Laboratory in St. Louis, MO.

The CMC revisions to the package insert have been incorporated and the revised container labels are found to be acceptable from the CMC perspective.

Executive Summary Section

The Office of Compliance issued an overall “acceptable” recommendation dated 21-Feb-2012 for the facilities used for manufacturing and control of the drug substance and drug product.

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

(See appended electronic signature page)

Joyce Z Crich, Ph.D., 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

7 Page(s) has been Withheld in Full as b4 (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/

JOYCE Z CRICH
10/19/2012

NALLAPERUM CHIDAMBARAM
10/19/2012
I concur

Memorandum

NDA 203,231

Submission Date: January 9, 2012

Brand Name: Zometa®

Generic Name: zoledronic acid

Formulation: Aqueous Solution, single-use, ready-to-use bag for intravenous infusion

Strength: 4 mg/100 mL

Reviewer: Wei Chen, Ph.D.

Acting Team Leader: Todd Palmby, Ph.D.

Applicant: Sagent Pharmaceuticals, Inc.

Submission Type: 505(b)(2)

Dosing regimen: 4 mg administered by intravenous infusion (b) (4)

Indications: Hypercalcemia of malignancy; multiple myeloma and bone metastasis from solid tumors

This 505(b)(2) submission is for a new formulation of a single-use, ready-to-use bag containing 4 mg of zoledronic acid dissolved in 100 mL of infusion solution. The basis of submission for this application is the reference listed drug (RLD) product Zometa® (Zoledronic Acid) Injection, 4mg /5mL and 4 mg/100 mL (Novartis Pharmaceuticals Corporation). No nonclinical study reports were submitted with this application.

The CMC review team asked for input from the pharmacology/toxicology discipline for the proposed acceptance criterion of a "Single Unknown Impurity" in the drug product of (b) (4) % at release, and no more than (NMT) (b) (4) % for shelf life. We sent the following request to the Applicant on June 13, 2012:

"The proposed acceptance limit for "single unknown impurity" in the drug product specification may not be acceptable for genotoxic or carcinogenic impurities. Therefore, you may choose to evaluate genotoxic potential of unknown impurities, or reduce the limit for "single unknown impurity" to NMT (b) (4) %, at which the daily exposure would be (b) (4) with the recommended dose of 4 mg/day".

The Applicant's response to our request was received on July 19, 2012, which stated that a chemical assessment of the manufacturing process for zoledronic acid did not identify any genotoxic alerts, and that the proposed the specification for the "Any unspecified degradation product" was NMT (b) (4) %, which was consistent with ICH Q3B. With this proposed specification, the total daily intake for a single unknown impurity is less than (b) (4). From a pharmacology/toxicology perspective, the proposed specification of NMT (b) (4) % for any unidentified degradant in the drug product is acceptable given the

compliance with ICH Q3B, the patient population, the administration schedule, and the Reference Listed Drug's specification for "*single unknown impurity*".

No nonclinical studies are needed to support the approval of the proposed zoledronic acid product at this time. No changes to the Reference Listed Drug's package insert were recommended in sections containing nonclinical data. There are no issues from the Pharmacology/Toxicology discipline that would preclude approval of this zoledronic acid product for the proposed indications.

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

/s/

WEI CHEN
10/17/2012

TODD R PALMBY
10/17/2012

I concur that the proposed level of NMT (b) (4) % for any "single unknown impurity" in the drug product is acceptable for the reasons described in Dr. Chen's review. I also concur with Dr. Chen's conclusion that there are no remaining Pharmacology/Toxicology issues that would preclude approval of NDA 203231.

NDA 203231

Zoledronic Acid Injection, 4mg/100mL

SAGENT Pharmaceuticals, Inc.

Joyce Crich, Ph.D

Review Chemist

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

**CMC REVIEW OF NDA 203231
For the Division of Drug Oncology Product I**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 203231
2. REVIEW #: 1
3. REVIEW DATE: 21-SEP-2012
4. REVIEWER: Joyce Z Crich
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	30-AUG-2011	30-AUG-2011
NDA Resubmission/After Refusal to File	7	06-JAN-2012	09-JAN-2012
Amendment (revised container and carton labeling)	10	30-MAR-2012	30-MAR-2012
Amendment (Revised container and carton labeling)	13	27-JUN-2012	27-JUN-2012
Amendment (Response to 13-JUN-2012 CMC IR)	14	19-JUL-2012	19-JUL-2012
Amendment (Revised container and carton labeling)	16	06-SEP-2012	06-SEP-2012
Amendment (Revised container and carton labeling)	17	06-SEP-2012	06-SEP-2012
Amendment (Response to 23-AUG-2012 CMC IR)	18	06-SEP-2012	06-SEP-2012
Amendment (Response to 14-SEP-2012 & 20-SEP-2012 CMC IR)	pending	pending	pending
Amendment (Response to 21-SEP-2012 telecon)	pending	pending	pending
Amendment (Revised container and carton labeling)	pending	pending	pending

7. NAME & ADDRESS OF APPLICANT:

Name: ACS Dobfar Info S.A.
 Address: Casai, CH-7748 Campascio, Switzerland
 Representative: Thomas J Moutvic, Sagent Pharmaceuticals Inc
 Telephone: 847-908-1613

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zoledronic Acid Injection
- b) Non-Proprietary Name: Zoledronic Acid Monohydrate

CMC Review Data Sheet

- c) Code Name/# (ONDQA only): N/A
 d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
 10. PHARMACOL. CATEGORY: Bisphosphonate, inhibitor for bone resorption
 11. DOSAGE FORM: Sterile solution, injection
 12. STRENGTH/POTENCY: 4 mg /mL (as zoledronic acid anhydrous)
 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

Chemical Structure	
Molecular Formula	C ₅ H ₁₀ N ₂ O ₇ P ₂ ·H ₂ O
Molecular Weight	290.11 g/mol (monohydrate) 272.01 g/mol (anhydrous)
United States Adopted Name (USAN)	zoledronic acid
Chemical Name	3-Quinolinecarbonitrile, 4-[(2, 4-dichloro-5-methoxyphenyl) amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl) propoxy]-, hydrate (1:1).
Chemical Abstracts Service (CAS) Registry Number	CAS-165800-06-6

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)	II	(b) (4)	(b) (4)	3 & 4	Adequate	16-Aug-2012	See section 3.2.S Reviewed by Dr. D. Chowdhury.
	III			4	Adequate	N/A	See sections 1.4.1 & 3.2.P.4.1
	III			4	Adequate	N/A	See sections 1.4.1 & 3.2.P.7
	III			3 & 4	Adequate	17-Feb-2012	Reviewed by Dr. Xuhong Li

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: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	21-FEB-2012	A. Inyard
Pharm/Tox	Impurity limits in drug product & a toxicological risk assessment on the extractables of container closure system are acceptable	Email communication dated 07-JUN-2012 & 23-AUG-2012	Dr. Wei Chen Dr. Todd Palmby
Biopharm	Acceptable	02-APR-2012	Dr. Zedong Dong
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy	pending	pending
DMEPA*	pending	pending	Jibril Abdus-Samad
EA	Categorical exclusion (see review)	18-SEP-2012	Dr. Joyce Crich
Microbiology	approval from microbiology product quality standpoint	24-JUL-2012	Dr. Stephen Langille

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 203,231

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application cannot be recommended for approval from a chemistry, manufacturing, and controls (CMC) standpoint until the following deficiency is satisfactorily resolved:

[REDACTED] (b) (4)

In addition to the above, labeling issues are pending.

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

The drug substance zoledronic acid monohydrate is known active pharmaceutical ingredient and is manufactured [REDACTED] (b) (4)

[REDACTED] Complete manufacturing and controls information is cross-referenced to a DMF. A Letter of Authorization dated 22-DEC-2010 for Zoledronic Acid, Type II DMF # [REDACTED] (b) (4) from the DMF holder [REDACTED] (b) (4), [REDACTED] (b) (4) is provided in support of this application. This DMF was found to be adequate (see *Dr. D. Chowdhury's review dated 16-AUG-2012*).

Zoledronic acid monohydrate is a white crystalline powder. It has a pH dependent solubility. Zoledronic acid monohydrate exists in several crystal forms. The API supplier produces [REDACTED] (b) (4). Other crystal forms are not encountered during production or stability of the API supplier's product.

Executive Summary Section

The stability data shows no trend for impurities up to 6 months under accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$, $75\% \pm 5\%\text{RH}$). The long-term drug substance stability data support a (b) (4) month retest period under storage conditions of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ($60\% \pm 5\%\text{RH}$). Based on the stability data, the retest period should be no longer than (b) (4) months when the drug substance is stored in an amber Type III glass container with (b) (4) liner and a white (b) (4) cap as immediate packaging, with an aluminium (b) (4) bag as the secondary packaging.

There are no CMC deficiencies related to drug substance.

(2) Drug Product

Zoledronic Acid Injection is a clear, colorless, sterile solution for intravenous infusion with pH value approximately (b) (4). It is available in 4 mg/100 mL dosage strength. The injection solution contains zoledronic acid monohydrate as the active pharmaceutical ingredient equivalent to 4 mg of zoledronic acid anhydrous together with 0.9% Sodium Chloride USP, Mannitol USP, Sodium Citrate (b) (4) USP and Water for Injection USP.

The drug product is filled in (b) (4) bags equipped with one (b) (4) tube (b) (4) and twist off port (b) (4). These bags are then contained in aluminium (b) (4) over-wrapping to protect the product from light and to reduce the water permeation.

Formulation development of Zoledronic Acid Injection was performed by ACS DOBFAR INFO SA at site Campascio, Switzerland, which is also the proposed commercial site for the drug product manufacturing and release testing, packaging, labeling, stability testing and release. The main steps of the manufacturing process consist of (b) (4). Standard release specifications for an injection solution dosage form have been proposed.

The applicant submitted the stability data from three primary batches for Zoledronic Acid Injection 4 mg/100mL up to 12 months at $25^{\circ}\text{C}/40\% \text{RH}$ (long term storage condition) and up to 6 months at $40^{\circ}\text{C}/15\% \text{RH}$ (accelerated condition) in the proposed commercial primary stability container closure system in the original NDA submission. Those stability data does not support the proposed 24 months shelf-life for the drug product due to the trend of degradation under the accelerated condition. However, based on the real time stability data under long term storage condition, a shelf-life of 12 months can be granted for Zoledronic Acid Injection 4 mg/100mL in the proposed commercial container closure system at controlled room temperature. During the review cycle, the applicant provided updated stability data up to 18 months at $25^{\circ}\text{C}/40\% \text{RH}$ and 6 months at $40^{\circ}\text{C}/15\% \text{RH}$ in Amendment SN0013. Due to the inconsistency in the levels of degradation products reported between two submissions and unacceptable

Executive Summary Section

calculation for degradation products in SN0013, a shelf-life can not be granted based on the updated stability data.

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

Zoledronic Acid Injection is indicated for the treatment of (i) hypercalcemia of malignancy; (ii) multiple myeloma and bone metastases from solid tumors in conjunction with standard antineoplastic therapy.

Zoledronic Acid Injection 4 mg/100 mL is dosed as a single – use intravenous infusion over no less than 15 minutes, and 4 mg as retreatment after a minimum of 7 days for hypercalcemia of malignancy, or 4mg as retreatment every 3-4 weeks for multiple myeloma and bone metastases from solid tumors. Dose reduction is required for patient with renal impairment.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

Based on the provided stability data, a 12-month expiration dating period is granted for Zoledronic Acid Injection 4 mg/100mL in the proposed commercial container closure system when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed established name Zoledronic Acid Injection.

Methods validation is pending evaluation by the FDA Laboratory in St. Louis, MO.

Executive Summary Section

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 30-Aug-2012 are acceptable from the CMC perspective.

(b) (4)



The Office of Compliance issued an overall “acceptable” recommendation dated 21-Feb-2012 for the facilities used for manufacturing and control of the drug substance and drug product.

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

(See appended electronic signature page)

Joyce Z Crich, Ph.D., 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

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/s/

JOYCE Z CRICH
10/05/2012

NALLAPERUM CHIDAMBARAM
10/05/2012
I concur

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

NDA Number: 203-
231

Supplement Number and Type:

Established/Proper Name: Not
proposed

Applicant: Sagent
Pharmaceuticals, Inc.

Letter Date: 6 January, 2012
(Resubmission)

Stamp Date: 9 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 pre-NDA meeting is noted for this resubmission.

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.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	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.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	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. See biopharm filing review in DARRTS.
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 PROVIDED?	COMMENTS
(b) (4)	II		(b) (4)	Yes	
	III			Yes	
	III			Yes	
	III			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

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/s/

HARIPADA SARKER
03/09/2012

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

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

OND Division: Division of Drug Oncology Products
NDA: 203-231
Applicant: Sagent Pharmaceuticals, Inc.
Letter Date: 8 February, 2012
Stamp Date: 9 February, 2012 (Resubmission)
PDUFA Goal Date: 9 December, 2012 (standard)
Trade name: Not proposed
Established Name: Zoledronic Acid Injection
Dosage Form/Strength: Aqueous Solution- 4 mg/ 100 mL.
Route of Administration: IV
Indication: Hypercalcemia of malignancy. Multiple myeloma, bone metastases from solid tumors in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

Regulatory Filing For 505 (b) (2)
Related IND/DMF DMF # [REDACTED] (b) (4)

Reference Listed Drug (RLD) NDA 21-223 (Zometa)

Assessed by:
Haripada Sarker

Yes No

ONDQA Fileability: x

Comments for 74-Day Letter: x

Background Summary

The application introduces the drug product, Zoledronic Acid Injection by Sagent Pharmaceuticals. The drug product, Zoledronic Acid Injection 4 mg/ 100 mL Ready-to-Infuse Solution contains zoledronic acid, a bisphosphonic acid which is indicated for multiple myeloma, bone metastases from solid tumors in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

The basis of submission for this application is the reference listed drug (RLD) product Zometa® (Zoledronic Acid) Injection, 4mg /5mL, approved in a New Drug Application (NDA 021223; Novartis

Pharmaceuticals Corporation) in March 7, 2003. Later, a modified strength, 4 mg/100 mL single-use ready-to-use bottle was introduced under NDA 21-223 supplement.

No pre-NDA meeting is noted with CMC issue. The CMC information of the NDA is submitted as per cTDQ format. However, the qos under Module 2 is presented as per J format, which is similar to question/answer based ANDA submission.

The NDA was previously refused to file due to lack of insufficient DP stability data. Please refer to the RTF letter (1/9/2012) and the CMC assessment (11/1/2011) in DARRTS. The current assessment is a duplicate of that previous CMC assessment, and has been updated to cover resolution of the previous CMC filing issues.

(b) (4)

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Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		

12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √ √		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CB ER LNC DMEPA/ODS EER

Have all DMF References been identified? Yes (√) No ()

DMF Number	Holder	Description	LOA Included
(b) (4)			Yes
			Yes

Comments and Recommendations

The application is fileable, no 74-Day Letter issues regarding drug product stability have been identified at this point. Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex.

Haripada Sarker
CMC Lead

February 22, 2012
Date

Sarah Pope Miksinski, Ph.D.
Branch Chief

February 22, 2012
Date

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/s/

HARIPADA SARKER
02/22/2012

SARAH P MIKSINSKI
02/22/2012

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

OND Division: Division of Drug Oncology Products
NDA: 203-231
Applicant: Sagent Pharmaceuticals, Inc.
Letter Date: 30 August, 2011
Stamp Date: 30 August, 2011
PDUFA Goal Date: 30 June, 2012 (standard)
Trade name: Not proposed
Established Name: Zoledronic Acid Injection
Dosage Form/Strength: Aqueous Solution- 4 mg/ 100 mL.
Route of Administration: IV
Indication: Hypercalcemia of malignancy. Multiple myeloma, bone metastases from solid tumors in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

Regulatory Filing For 505 (b) (2)
Related IND/DMF DMF # [REDACTED] (b) (4)

Reference Listed Drug (RLD) NDA 21-223 (Zometa)

Assessed by:
Haripada Sarker

Yes No

ONDQA Fileability: x

Comments for 74-Day Letter: x

Background Summary

The application introduces the drug product, Zoledronic Acid Injection by Sagent Pharmaceuticals. The drug product, Zoledronic Acid Injection 4 mg/ 100 mL Ready-to-Infuse Solution contains zoledronic acid, a bisphosphonic acid which is indicated for multiple myeloma, bone metastases from solid tumors in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

The basis of submission for this application is the reference listed drug (RLD) product Zometa® (Zoledronic Acid) Injection, 4mg /5mL, approved in a New Drug Application (NDA 021223; Novartis Pharmaceuticals Corporation) in March 7, 2003. Later, a modified strength, 4 mg/100 mL single-use ready-to-use bottle was introduced under NDA 21-223 supplement.

No pre-NDA meeting is noted with CMC issue. The CMC information of the NDA is submitted as per cTDQ format. However, the qos under Module 2 is presented as per J format, which is similar to question/answer based ANDA submission.

(b) (4)

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Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	6 months DP long term stability data to support 24 months shelf-life.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		

12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √ √		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CB ER LNC DMEPA/ODS EER

Have all DMF References been identified? Yes (√) No ()

DMF Number	Holder	Description	LOA Included
(b) (4)			Yes
			Yes

Comments and Recommendations

The application is not fileable and following filing issue has been identified.

1. The proposed drug product shelf-life of 24 months based on 6 months of long term and accelerated stability data are not sufficient to support a commercially viable shelf-life. Also note that as per GRMPs, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

Haripada Sarker
CMC Lead

October 31, 2011
Date

Sarah Pope Miksinski, Ph.D.
Branch Chief

October 31, 2011
Date

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/s/

HARIPADA SARKER
10/31/2011

SARAH P MIKSINSKI
11/01/2011