

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201195Orig1s000

CHEMISTRY REVIEW(S)

NDA 201-195

Docetaxel Injection

20 mg/0.5 mL and 80 mg/2 mL

Accord Healthcare, Inc.
Durham, NC

Division of Oncology Drug Products
Office of Oncology Drug Products

Joyce Z. Crich, Ph, D

Review Chemist

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

CMC REVIEW OF NDA 201-195
For the Division of Drug Oncology Products (HFD-150)

Table of Contents

CMC Review Data Sheet.....4

The Executive Summary8

I. Recommendations.....8

 A. Recommendation and Conclusion on Approvability 8

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... 8

II. Summary of CMC Assessments8

 A. Description of the Drug Product(s) and Drug Substance(s)..... 8

 (1) Drug Substance Satisfactory8

 B. Description of How the Drug Product is Intended to be Used..... 10

 C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative.....10

CMC Assessment.....11

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....11

 S. DRUG SUBSTANCE 11

 S.1 General Information11

 S.2 Manufacture11

 S.3 Characterization11

 S.4 Control of Drug Substance11

 S.5 Reference Standards or Materials11

 S.6 Container Closure System.....11

 S.7 Stability11

 P. DRUG PRODUCT 11

 P.1 Description and Composition of the Drug Product11

 P.2 Pharmaceutical Development.....11

 P.2.1 Components of the Drug Product.....12

 P.2.2 Drug Product.....12

 P.2.2.1 Formulation Development12

 P.2.2.2 Overages13

 P.2.2.3 Physicochemical and Biological Properties13

 P.2.3 Manufacturing Process Development13

 P.2.4 Container Closure System.....13

 P.2.5 Microbiological Attributes.....13

 P.2.6 Compatibility13

 P.3 Manufacture13

 P.4 Control of Excipients13

 P.5 Control of Drug Product13

 P.5.1 Specification13

 P.5.2 Analytical Procedures14

 P.5.3 Validation of Analytical Procedures14

P.5.4 Batch Analyses 14

P.5.5 Characterization of Impurities..... 14

P.5.6 Justification of Specification..... 15

P.6 Reference Standards or Materials..... 16

P.7 Container Closure System..... 16

P.8 Stability 16

 P.8.1 Stability Summary and Conclusion..... 16

 P.8.2 Postapproval Stability Protocol and Stability Commitment..... 18

 P.8.3 Stability Data 18

A. APPENDICES 18

 A.1 Facilities and Equipment (biotech only) 18

 A.2 Adventitious Agents Safety Evaluation 18

 A.3 Novel Excipients..... 18

R. REGIONAL INFORMATION 18

 R1 Executed Batch Records..... 18

 R2 Comparability Protocols 18

 R3 Methods Validation Package 19

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 120

 A. Labeling & Package Insert..... 20

 B. Environmental Assessment Or Claim Of Categorical Exclusion 25

 C. Establishment Evaluation Report..... 25

III. List Of Deficiencies to be Communicated.....27

CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 201-195
2. REVIEW #: 2
3. REVIEW DATE: 27-MAY-2011
4. REVIEWER: Joyce Z Crich, Ph.D
5. PREVIOUS DOCUMENTS:

Previous Documents
CMC Review #1

Document Date
19-OCT-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Amendment (Class 2 resubmission)	14	07-DEC-2010	10-DEC-2010
Amendment (Response to FDA TCON 11-APR-2011CMC IR)	21	18-APR-2011	19-APR-2011
Amendment (Revised container and carton labeling)	20	16-MAR-2011	17-MAR-2011
Amendment (Revised container and carton labeling)	22	25-APR-2011	27-APR-2011
Amendment (Revised container and carton labeling)	23	10-MAY-2011	11-MAY-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Accord Healthcare, Inc.
Address: 1009 Slate Road, Suite 210-B, Durham, ND
27703
Representative: Samir Mehta, Ph.D.
Telephone & Fax: 919-941-7878 & 919-941-7881

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name: Docetaxel Injection
- c) Code Name/# (ONDQA only): N/A

CMC Review Data Sheet

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 20 mg/0.5 mL and 80 mg/2 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

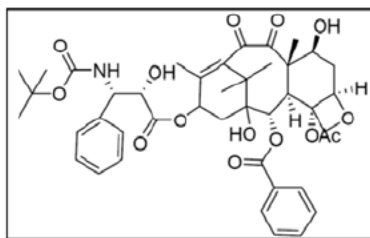
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5 β -20-epoxy-1,2a,4,7 β ,10 β ,13a-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate

US Adopted Name (USAN): Docetaxel

International Non-proprietary Name (INN): Docetaxel

Laboratory Codes: SPT1141



CMC Review Data Sheet

Chemical Formula: C43H53NO14
 Molecular Weight: 807.88
 CAS Number: 114977-28-5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs (no changes from CMC Review #1):

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	Jul. 23, 2008
	III		3	Adequate	Aug. 17, 2006	
	III		4	Adequate		
	III		4	Adequate		

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 (no changes from CMC Review #1):

DOCUMENT	Date	Location	DESCRIPTION
Original	Dec. 8, 2006	Volume 1.1	Original Type II DMF (b) (4) for docetaxel
CMC Review #1	Jul. 24, 2008	DARRTS	CMC Review of DMF (b) (4) and Amendments prior to July 1, 2009
CMC Review	Dec. 10, 2009	DARRTS	CMC Review of DMF (b) (4) Amendment 3 (Feb. 19, 2009)
IQA	Feb. 25, 2010	DARRTS	CMC Initial Quality Assessment

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	04-OCT-2010	Office of Compliance
Pharm/Tox	pending		M. E. Brower
Biopharm	Biowaiver granted	22-JUL-2010	A. Dorantes
LNC	N/A	N/A	N/A
Methods Validation	N/A, according to the current ONDQA policy	19-OCT-2010	H. T. Chang
DMEPA*	Original DMEPA comments Revised C/C labels received	06-APR-2011 11-MAY-2011	L. Holmes
EA	Categorical exclusion granted	03-OCT-2010	H. T. Chang
Microbiology	Approval	05-OCT-2010	J. Metcalfe

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 201-195

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this NDA is recommended for approval with a 12 month shelf life for the drug product (b) (4) 25°C ((b) (4) 77°F) or room temperature; excursions permitted to 15°C - 30°C (59°F - 86°F), [see USP Controlled Room Temperature] and protected from bright light.

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)

This second-cycle CMC review addresses deficiencies in drug product and in labeling (PI/PPI and Container/Carton) that were identified in the first-cycle review. All other information may be found in the Chemistry Review #1 dated 19-OCT-2010, by Huai T. Chang, Ph.D.

(1) Drug Substance

Satisfactory

See Chemistry Review #1 dated 19-OCT-2010, by Huai T. Chang, Ph.D.

(2) Drug Product

Satisfactory

The proposed drug product Docetaxel Injection has been developed relative to the Reference Listed Drug (RLD) TAXOTERE® Injection Concentrate of Sanofi-Aventis U.S. LLC (NDA 20-449 approved in May 1996). Docetaxel is used for the treatment of various types of cancers including breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer. It is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions.

Docetaxel Injection will be supplied in two presentations and one strength: 20 mg/0.5 mL and 80 mg/2 mL (both are 40 mg/mL). Each presentation is a two-vial formulation intended for single-dose administration. For each presentation, one carton contains two vials packed together in a blister. One vial is Docetaxel Injection and the other accompanying vial is Diluent for Docetaxel Injection.

Executive Summary Section

Drug Product Docetaxel Injection—Two-Vial Formulation

Strength	Vial #1: Docetaxel Injection	Vial #2: Diluent for Docetaxel Injection
Docetaxel Injection 20 mg/0.5 mL	20 mg/0.5 mL Docetaxel in Dehydrated Alcohol and Polysorbate 80	1.5 mL of PEG 400 in Water for Injection
Docetaxel Injection 80 mg/2 mL	80 mg/2 mL Docetaxel in Dehydrated Alcohol and Polysorbate 80	6.0 mL of PEG 400 in Water for Injection

Docetaxel Injection has the same active ingredient, drug concentration, dosage form, route of administration, and dosing regime, and is intended for the same indications as TAXOTERE. Accord’s proposed drug product is formulated slightly differently from TAXOTERE. The proposed product contains two additional inactive ingredients not found in TAXOTERE. Citric acid, which acts as a pH modifying agent, is present in the Docetaxel Injection, and polyethylene glycol 400, (b) (4), is present in the Diluent. Dehydrated alcohol is also present in the concentrate in Accord’s drug product, but is a component of the Diluent in TAXOTERE. These inactive ingredients are listed in the Inactive Ingredient Database (IIG) and have been previously approved for use in the same route of administration, and at levels higher than those in the proposed product.

The applicant states that the proposed drug product is considered equivalent to the reference drug and requests a biowaiver of in-vivo studies. The request was granted by Biopharmaceutics in a review dated 21-JUL-2010.

In the resubmission of 07-DEC-2010 and the subsequent amendment of 19-APR-2010 after the tele-conference of 11-APR-2011, the applicant provided adequate responses to address the five deficiencies for drug product identified in the first-cycle review. The related review comments and CMC evaluation for those complete responses can be found in the sections P.5 and P.8 of this review. Note: these deficiencies were the basis for the Not-Approval Recommendation for this NDA in the first-cycle review. For detailed information, see Section C. Basis for Approvability or Not-Approval Recommendation under Summary of CMC Assessments in Chemistry Review #1 dated 19-OCT-2010, by Huai T. Chang, Ph.D.

Further, the applicant addressed all the issues related to labeling (PI/PPI and Container/Carton) in the Amendment of 11-MAY-2011.

Based on the additional stability data provided in this second-cycle review, a 12 month shelf life will be granted for this drug product when stored at 25° C (77° F) or room temperature; excursions permitted to 15°C - 30°C (59°-86°F) [see USP Controlled Room Temperature], with protection from bright light.

Executive Summary Section

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

The drug product both 20 mg/0.5 mL and 80 mg/2 mL presentations is prepared for use in a three-step sequence: 1) initial dilution, 2) final dilution, and 3) intravenous administration.

Initial dilution involves aseptic withdrawal of the Diluent for Docetaxel Injection using a syringe, and transfer to the Docetaxel Injection vial. This mixture of Docetaxel Injection and Diluent is mixed by repeated inversion of the vial for at least 45 seconds. The initial dilution results in a solution of 10 mg/mL docetaxel for both presentations. This “initial diluted solution” is to be used immediately or within 8 hours when stored at room temperature or refrigerator conditions.

Final dilution involves withdrawal of a dose of the initial diluted solution and transfer to an intravenous infusion bag or bottle containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. The concentration of docetaxel in this “final dilution solution” should be in the range of 0.3 mg/mL to 0.74 mg/mL depending on the dosage prescribed. This solution should be administered intravenously within 4 hours of preparation if stored at 2°C to 25°C.

C. Basis for Approvability or Not-Approval Recommendation

There are no outstanding Chemistry, Manufacturing and Controls issues for this NDA.

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

Joyce Z Crich, Ph.D, CMC Reviewer, Branch II, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

B. Endorsement Block:

(See appended electronic signature page)

Haripada Sarker, Ph.D., CMC Lead, Division of New Drug Quality Assessment I, ONDQA

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I, ONDQA

C. CC Block: entered electronically in DFS

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/s/

JOYCE Z CRICH
05/31/2011

SARAH P MIKSINSKI
06/01/2011

Memorandum

To: NDA 201-195
cc: Haripada Sarker, Ph.D., Huai T. Change, Ph.D.
From: William Adams, acting for Sarah Pope Miksinski, Ph.D.
Date: 19 Oct 2010
Re: Final CMC Recommendation for NDA 201-195

NDA 201-195 (Docetaxel Injection) was submitted by Accord Healthcare, Inc. as a 505(b)(2) application on 22 Dec 2009 and was granted a standard review by the Agency. The Chemistry, Manufacturing and Control (CMC) Review has evaluated information in the original application dated 22 Dec 2009 and in amendments dated 16 Feb, 07 May and 14 Jun 2010. CMC deficiencies identified during the review have been sent to the applicant in Information Letters dated 06 May, 29 June and 02 Aug 2010.

The 07 May 2010 amendment is a response to the Information Request letter dated 06 May 2010. ONDQA is still awaiting a response to the latter two Information Request letters. In addition, a commitment, made at a 06 May 2008 pre-NDA meeting (minutes dated 19 Jun 2008), to submit updated drug product stability study results by 22 May 2010 (midcycle of the NDA review per the GRMP milestones) has not been met. In the absence of complete CMC information, the review concluded that the application was Not Adequate for approval and that a Complete Response letter should be issued to the applicant.

The 15 Feb and 14 Jun 2010 amendments provided updated labels and labeling. The Information Request letter dated 29 Jun 2010 informed the applicant that the submitted labels and labeling could not be reviewed due to CMC deficiencies which are listed in the letter.

CMC Review, section IV - List of Deficiencies cites the deficiencies from the unanswered Information Request letters; provides comments on the CMC sections of the labels and labeling; and includes a comment regarding a Comparability Protocol for change of drug substance supplier. These items summarized as follows:

- Revisions to and justification of criteria in the drug product specification for various impurities and degradation products are needed.
- Updated long term drug product stability data to support the label storage statement and proposed expiry period should be submitted.
- Revision of the drug product established name (to delete the word [REDACTED] ^{(b) (4)}) is recommended.
- Revision of the comparability protocol for change of drug substance supplier to submit the change as a prior approval supplement is recommended.

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

/s/

WILLIAM M ADAMS

10/19/2010

William Adams for Sarah Pope Miksinski

NDA 201-195

**Docetaxel Injection
20 mg/0.5 mL and 80 mg/2 mL**

**Accord Healthcare, Inc.
Durham, NC**

**Division of Oncology Drug Products
Office of Oncology Drug Products**

Huai T. (Ted) Chang, Ph.D.

**Office of New Drug Quality Assessment
Center for Drug Evaluation and Research**

Table of Contents

Table of Contents	2
CMC Review Data Sheet	4
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of CMC Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used	10
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	11
A. Reviewer’s Signature.....	11
B. Endorsement Block.....	12
C. CC Block.....	12
Chemistry, Manufacturing and Control Assessment	13
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data.....	13
S. DRUG SUBSTANCE [Docetaxel, (b) (4)].....	14
S.1 General Information.....	14
S.2 Manufacture	15
S.3 Characterization	27
S.4 Control of Drug Substance.....	34
S.5 Reference Standards or Materials	40
S.6 Container Closure System.....	41
S.7 Stability	42
P. DRUG PRODUCT [Docetaxel Injection, Intas Pharmaceuticals, Ltd].....	47

P.1	Description and Composition of the Drug Product.....	47
P.2	Pharmaceutical Development	51
P.3	Manufacture	77
P.4	Control of Excipient.....	102
P.5	Control of Drug Product	108
P.6	Reference Standards or Materials	128
P.7	Container Closure System.....	128
P.8	Stability	130
A.	APPENDICES	140
A.1	Facilities and Equipment (biotech only).....	140
A.2	Adventitious Agents Safety Evaluation	140
A.3	Novel Excipient	141
R.	REGIONAL INFORMATION	141
R.1	Executed Batch Records	141
R.2	Comparability Protocols	142
R.3	Methods Validation Package	142
II.	Review of Common Technical Document-Quality (Ctd-Q) Module 1	142
A.	Labeling & Package Insert.....	142
B.	Environmental Assessment or Claim of Categorical Exclusion	146
III.	Establishment Evaluation Report.....	146
IV.	List of Deficiencies to be Communicated.....	148

CMC Review Data Sheet

1. NDA 201-195
2. REVIEW #: 1
3. REVIEW DATE: October 8, 2010
4. REVIEWER: Huai T. (Ted) Chang, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
pre-IND 101904 Meeting Minutes	Jun. 19, 2008 (meeting on May 6, 2008)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Subject Title
NDA 201-195	Dec. 22, 2009	Original submission
Amendment	May 7, 2010	Response to IR May 6, 2010 (Quantity of excipients)

7. NAME & ADDRESS OF APPLICANT:

Name	Accord Healthcare, Inc.
Address	1009 Slater Road Suite 210-B Durham, NC 27703 TEL: 919-941-7878 FAX: 919-941-7881
Representative	Samir Mehta, Ph.D.

8. DRUG PRODUCT NAME/CODE/TYPE:

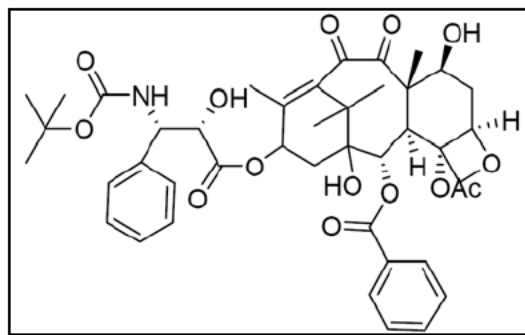
Proprietary Name	N/A
Non-Proprietary Name (USAN)	Docetaxel Injection

Chemistry Review Data Sheet

Code Names	N/A
Chemistry Type	1
Submission Priority	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: Anti-cancer
INDICATION: breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, head and neck cancer.
11. DOSAGE FORM: Solution for Injection
12. STRENGTH/POTENCY: 20 mg/0.5 mL and 80 mg/2 mL
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
- Chemical Names: (2R,3S)-N-carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5 β -20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate
- US Adopted Name (USAN): Docetaxel
International Non-proprietary Name (INN): Docetaxel
Laboratory Codes: SPT1141

Chemistry Review Data Sheet



Chemical Formula: $C_{43}H_{53}NO_{14}$
 Molecular Weight: 807.88
 CAS Number: 114977-28-5

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	Jul. 23, 2008
	III			3	Adequate	Aug. 17, 2006
	III			4	Adequate	
	III			4	Adequate	

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under “Comments”)

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	Date	Location	DESCRIPTION
Original	Dec. 8, 2006	Volume 1.1	Original Type II DMF (b) (4) for docetaxel
CMC Review #1	Jul. 24, 2008	DARRTS	CMC Review of DMF (b) (4) and Amendments prior to July 1, 2009
CMC Review	Dec. 10, 2009	DARRTS	CMC Review of DMF (b) (4) Amendment 3 (Feb. 19, 2009)
IQA	Feb. 25, 2010	DARRTS	CMC Initial Quality Assessment

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	STATUS/ REVIEWER
EES	“Acceptable”	Oct. 4, 2010	Office of Compliance
LNC	--	--	--
Methods Validation	Not Applicable	--	--
OSE DMETS	Not Applicable	--	--
EA	Category exclusion granted	Aug. 3, 2010	H. T. Chang
Pharmacology/ Toxicology	“Not Approval”	Sep. 9, 2010	M. E. Brower
Biopharmaceutics	Biowaiver granted	July 22, 2010	A. Dorantes
Microbiology	Approval	Oct. 5, 2010	J. Metcalfe

The CMC Review for NDA 201-195

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended “*not to be approved in its present form*” from a CMC perspective.

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

There are no Phase 4 commitments.

II. Summary of CMC Assessments

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

DRUG SUBSTANCE *Satisfactory*

The drug substance docetaxel is manufactured by (b) (4)® (b) (4) who describes the CMC in DMF (b) (4). The DMF has been reviewed and found adequate (by T. Ocheltree July 23, 2008) to be used for the manufacturing of Docetaxel Injection. A (b) (4) letter of authorization, dated Oct. 1, 2009, for Accord to reference DMF (b) (4) is provided in the NDA.

The drug substance is manufactured (b) (4)
The bulk drug substance is a white to off-white powder and has been characterized adequately using elemental analysis, UV, IR, MS, NMR, XRD, and HPLC. Four process-related/degradation impurities are identified and specified. Specifications for both release and stability are established and are deemed adequate to ensure the quality of drug substance. Certificate of analysis for two exhibit batches meeting the release specifications are provided.

Docetaxel is insoluble in water, but freely soluble in ethanol and tetrahydrofuran. It is hygroscopic, and sensitive to light and temperature. Docetaxel drug substance (b) (4)

Storage at 5±3°C is recommended. The re-test period is (b) (4)

Executive Summary Section

DRUG PRODUCT *Non-satisfactory*

The proposed drug product Docetaxel Injection has been developed as a generic equivalent to the Reference Listed Drug (RLD) TAXOTERE[®] Injection Concentrate of Sanofi-Aventis U.S. LLC (NDA 20-449 approved in May 1996). Docetaxel is used for the treatment of various types of cancers including breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer. It is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions.

Docetaxel Injection will be supplied in two presentations and one strength: 20 mg/0.5 mL and 80 mg/2 mL (40 mg/mL). Each presentation is a two-vial formulation intended for single-dose administration. For each presentation, one carton contains two vials packed together in a blister. One vial is Docetaxel Injection (“Concentrate”) and the other accompanying vial is Diluent for Docetaxel Injection (“Diluent”).

Drug Product Docetaxel Injection—Two-Vial Formulation

Strength	Vial #1: Docetaxel Injection	Vial #2: Diluent for Docetaxel Injection
Docetaxel Injection 20 mg/0.5 mL	20 mg/0.5 mL Docetaxel in Dehydrated Alcohol and Polysorbate 80	1.5 mL of PEG 400 in Water for Injection
Docetaxel Injection 80 mg/2 mL	80 mg/2 mL Docetaxel in Dehydrated Alcohol and Polysorbate 80	6.0 mL of PEG 400 in Water for Injection

Docetaxel Injection has the same active ingredient, drug concentration, dosage form, route of administration, and dosing regime, and is intended for the same indications as TAXOTERE. Accord’s proposed drug product is formulated slightly different from TAXOTERE. The proposed product contains two additional inactive ingredients not found in TAXOTERE. Citric acid, which acts as a pH modifying agent, is present in the Docetaxel Injection, and polyethylene glycol 400, (b) (4) is present in the Diluent. Dehydrated alcohol is present in the concentrate in Accord’s drug product, but is a component of the Diluent in TAXOTERE. These inactive ingredients are listed in the Inactive Ingredient Database (IID) and have been previously approved for use in the same route of administration, and at levels higher than those in the proposed product.

The applicant states that the proposed drug product is considered equivalent to the reference drug and requests a biowaiver of *in-vivo* studies. The request is granted by Biopharmaceutics on Jul. 21, 2010.

The reasons for “Non-satisfactory” assessment are discussed in section C, Basis for Approvability or Not-Approval Recommendation.

Executive Summary Section

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

The drug product both 20 mg/0.5 mL and 80 mg/2 mL presentations are prepared for use in a three-step sequence: 1) initial dilution, 2) final dilution, and 3) intravenous administration.

Initial dilution involves aseptic withdrawal of the Diluent using a syringe, and transfer to the Concentrate vial. This mixture of Concentrate and Diluent is mixed by repeated inversion of the vial for at least 45 seconds. The initial dilution results in a solution of 10 mg/mL docetaxel for both presentations. This “initial diluted solution” is to be used immediately or within 8 hours when stored at room temperature or refrigerator conditions.

Final dilution involves withdrawal of a dose of the initial diluted solution and transfer to an intravenous infusion bag or bottle containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. The concentration of docetaxel in this “final dilution solution” should be in the range of 0.3 mg/mL to 0.74 mg/mL depending on the dosage prescribed. This solution should be administered intravenously within 4 hours of preparation if stored at 2°C to 25°C.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has *not* provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The submitted draft labels *do not* have adequate information as required. Therefore, this NDA is recommended “not to be approved in its present form” from a CMC perspective until the following issues are resolved:

1. Information Request (IR) letter dated Jun. 29, 2010: Revise the drug product release specification to include single criteria for purity and related substances to be used at release and on stability. Include a justification for the proposed criteria.
2. IR letter dated Jun. 29, 2010: In section 3.2.P.2 Table 18: Comparator Comparison Stability Study, the levels of impurity (b) (4) at 3 and 6 months are lower at 40±2°C/75±5% RH than at 25±2°C/60±5% RH. However, other impurity levels are generally higher at the higher temperature than at the lower temperature. Explain this apparent discrepancy.
3. IR letter dated Jun. 29, 2010: Either provide additional stability data and information to support the proposed storage condition (b) (4) in the absence of light) or revise the proposed label storage statement to indicate a condition supported by the submitted long-term stability studies. The current stability information is not sufficient to support storage (b) (4)
4. IR letter dated June 29, 2010: Provide additional long term stability data to support the proposed initial drug product expiry period. The submitted 6 month data is not

Executive Summary Section

sufficient to support approval [REDACTED] (b) (4)

5. IR letter dated Jun. 29, 2010: You have failed to meet the commitment in the pre-NDA agreement dated May 6, 2008 in which you were to file updated stability data prior to the mid-cycle date (May 22, 2010). It is expected that this data will be provided in the resubmission. Any submission of additional stability data after the resubmission may be considered a major amendment.
6. IR letter dated Aug. 2, 2010: Using the analytical method in your NDA, two new impurity peaks identified as RRT (b) (4) and RRT (b) (4) and the acceptance criteria for these two compounds are set at NMT (b) (4). This acceptance criterion is above the identification threshold of 0.2% set by ICH Q3B(R2) based on the maximum daily dose of 180 mg/person. Please identify these two impurity peaks. If the impurity peaks at RRT (b) (4) and RRT (b) (4) cannot be identified, their levels should be adequately justified (e.g., based on nonclinical studies), or reduced to meet the ICH Q3B(R2) reporting threshold. If the impurity peaks at RRT (b) (4) and RRT (b) (4) are identified to be impurities in the RLD, their levels should be reduced not to exceed the levels in the RLD; levels above the RLD should be adequately justified based on nonclinical or clinical studies.
7. Labeling issues: The established name for the drug product should be revised from [REDACTED] (b) (4) to “docetaxel injection” throughout the labels and labeling. In packaging insert, section 11 Description, both citric acid and polysorbate 80 should be included in the description of Docetaxel Injection. Both excipients are not present in the RLD but are new in this NDA. The finalization of labels and labeling is pending the review of all disciplines including CMC, DMEPA, clinical pharm and clinical.
8. Section R.2 Comparability Protocols: The applicant’s proposal for [REDACTED] (b) (4) is not acceptable. This type of change is a major change and should be submitted as a prior approval supplement.

III. Administrative

A. Reviewer’s Signature

/s/ Huai T. (Ted) Chang, Ph.D.
CMC Reviewer, Branch III
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

/s/ Sarah M. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Executive Summary Section

B. Endorsement Block

CMC Reviewer: Huai T. (Ted) Chang, Ph.D.
CMC Lead: Haripada (Hari) Sarker, Ph.D.
Branch Chief: Sarah M. Pope Miksinski, Ph.D.
Project Manager: Kim J. Robertson

C. CC Block

Orig. NDA 201-195
HFD-150/Division File
Filename: CMC Review-NDA 201195 Accord Docetaxel.doc

140 Pages have 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/

HUAI T CHANG
10/19/2010

WILLIAM M ADAMS
10/19/2010
William Adams for Sarah Pope Miksinski

**Initial Quality Assessment
Branch V
Pre-Marketing Assessment Division III
Office of New Drug Quality Assessment**

OND Division: Division of Drug Oncology Products
NDA: 201-195
Applicant: Accord Healthcare, Inc.
Letter Date: 21 December, 2009
Stamp Date: 22 December, 2009
PDUFA Goal Date: 22 October, 2010 (standard)
Mid-Cycle Review Data 22 May, 2010 (standard)
Tradename: Not proposed
Established Name: Docetaxel Injection
Dosage Form/Strength: Solution; 20mg/0.5 mL and 80mg/2 mL per vial
Route of Administration: IV
Indication: Treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

Regulatory Filing For 505 (b) (2)
Related IND IND 101,904

Assessed by: Haripada Sarker

Yes No

ONDQA Fileability: x

Comments for 74-Day Letter: x

Background Summary

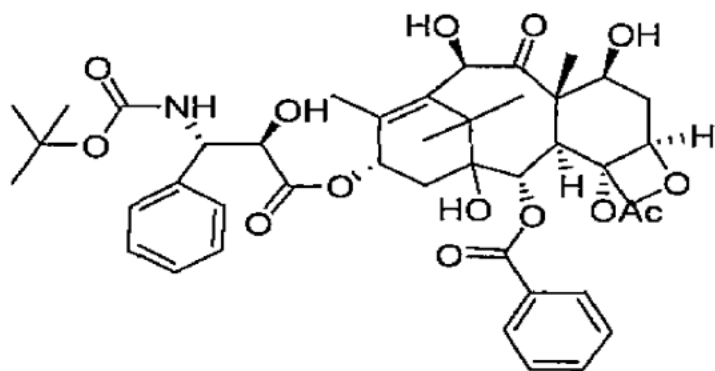
The application introduces the drug product, Docetaxel Injection, which is supplied as 40mg/ml solution concentrate of two strengths (20mg/0.5 mL and 80mg/2 mL) in vials. The final package consists of two vials in which one is drug product vial and other is diluent vial for drug product. Drug Product is a clear yellow to brownish yellow viscous solution. The product has to be reconstituted with Diluent to make Docetaxel injection concentrate, which is then reconstituted with 5% Dextrose injection or 0.9% Sodium Chloride Injection before administration.

It is noted that Taxotere® under NDA 20-449 is considered as the reference listed drug (RLD), where the formulation is equivalent (40mg base/mL), except that a different excipient is used in the DP for this NDA from Accord Healthcare. Docetaxel (Taxotere) injection by Sanofi Aventis was previously approved by the agency under NDA 20-449 (May 14, 1996), for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.

In pre-NDA meeting dated June 4, 2008 under IND 101904 several CMC issues related to DP batches and stability were discussed. The CMC information of the NDA is submitted fully in paper as well as partially electronic, which is apparently a question based OGD like submission in non CTDQ format.

Drug Substance (DS)

The DS is a (b) (4) Applicant referred to DMF (b) (4) (Type II) by (b) (4) ® (b) (4) for DS CMC information. In the NDA submission, applicant provided brief DS information regarding identity, physico-chemical properties and specifications. Docetaxel is an optically active compound. It is a semi-synthetic drug substance made from natural precursor 10-deacetylbaccatin III. Docetaxel is highly lipophilic and practically insoluble in water. As the structural formula of docetaxel has multiple stereogenic centers, many isomers are theoretically possible. However, docetaxel drug substance in solid form is very stable. In solution, docetaxel is known to undergo pH assisted epimerization at C7, leading to the formation of (b) (4) Couple of DS structurally related impurities are indicated in the submission. Request has been made to office of compliance to provide inspection report for the DS related sites listed in the submission. The DS is identified with following structure.



DS Critical Issues

- In solution, docetaxel is known to undergo pH assisted epimerization, leading to the formation of variety of isomers. Degradation product of docetaxel should be evaluated as per ICH Q3A (R).
- EER information for DS needs to be re-examined for accuracy.
- (b) (4) is the new DS manufacturer of Docetaxel from (b) (4). The cross-referred DMF (b) (4) for DS information should be evaluated as per ICH Q3A (R) to support the NDA.

Drug Product (DP)

The finished drug product is a solution, and the proposed product will also be accompanied with a diluent vial. Docetaxel Anhydrous (API) in (b) (4) solution at 40 mg/mL in single-dose vials containing 20 mg/0.5 mL or 80 mg/2 mL is termed as injection concentrates. The injection concentrate requires dilution prior to use. The (b) (4) contain Polysorbate 80 NF and

Alcohol (b) (4) for Injection USP/EP. A comparative composition between the RLD and the DP of this submission is provided. Following is the comparative formulations of the reference product and proposed product - **product vial**.

Ingredient		Proposed product: Docetaxel injection concentrate	Reference product: Taxotere	Proposed product: Docetaxel injection concentrate	Reference product: Taxotere
		Per 0.5 mL	Per 0.5 mL	Per 2 mL	Per 2 mL
Active ingredient	Docetaxel (anhydrous)	20 mg	20 mg	80 mg	80 mg
Inactive ingredients	Citric acid (anhydrous)	q.s. to pH	--	q.s. to pH	--
	Dehydrated alcohol	30 mg	--	120 mg	--
	Polysorbate 80	(b) (4)	520 mg	(b) (4)	2080 mg
Total volume		0.5 mL	0.5 mL	2 mL	2 mL

Following is the comparative formulations of the reference product and proposed product - **diluent vial**.

Ingredient	For 20 mg/0.5 mL product		For 80 mg/2 mL product	
	Proposed product: Diluent for Docetaxel injection concentrate 20 mg	Reference product: Diluent for Taxotere 20 mg	Proposed product: Diluent for Docetaxel injection concentrate 80 mg	Reference product: Diluent for Taxotere 80 mg
Dehydrated alcohol	--	13% w/w	--	13% w/w
PEG 400	13% w/v	--	13% w/v	--
Water for injection	q.s. to 1.5 mL	q.s. to 1.5 mL	q.s. to 6 mL	q.s. to 6 mL

This initial diluted solution (10 mg/mL) needs to be further diluted with an appropriate volume of either 0.9% Sodium Chloride Solution or 5% Dextrose Solution to produce a final dilution for IV infusion. Applicant utilizes the DP pharmaceutical development experiences of RLD to develop Docetaxel injection for this submission. The manufacturing and controls for RLD and the DP appears to be very similar.

The proposed DP manufacturing site is listed below:

Intas Pharmaceuticals Limited,
Ahmedabad 382 210,
Gujarat, India.

Docetaxel Injection (b) (4) 40 mg/mL (20 mg/0.5 mL) will be packaged in 5 mL clear glass vials (20 mm) with grey elastomeric serum stoppers (20 mm) and aluminum crimp caps (20 mm).

Docetaxel Injection (b) (4) 40 mg/mL (80 mg/2 mL) will be packaged in 15 mL clear glass vials (20 mm) with grey elastomeric serum stoppers (20 mm) and aluminum crimp caps (20 mm).

Two different acceptance criteria for DP impurities are proposed for release and for stability specification as following.

Degradation Products	DP Release Limits	DP Stability Limits
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Stability Summary for both Docetaxel concentrate and Diluent are provided for long term and accelerated conditions as following.

Batch number	Batch size	Packaging	Storage condition	Orientation	Completed (and proposed test intervals)	Conclusion
Diluent for Docetaxel injection concentrate 1.5 mL						
J1927 and J1955	(b) (4)	(b) (4)	Accelerated 40 ± 2°C / 75 ± 5 % RH	Inverted	0, 1, 2, 3, 6	Complies with specification up to six months.
			Long Term 25 ± 2°C / 60 ± 5 % RH	Inverted	0, 3, 6, (9, 12, 18, 24, 36)	Complies with specification up to six months, further study is ongoing.
Diluent for Docetaxel injection concentrate 6.0 mL						
J1930 and J1954	(b) (4)	(b) (4)	Accelerated 40 ± 2°C / 75 ± 5 % RH	Inverted	0, 1, 2, 3, 6	Complies with specification up to six months.
			Long Term 25 ± 2°C / 60 ± 5 % RH	Inverted	0, 3, 6, (9, 12, 18, 24, 36)	Complies with specification up to six months, further study is ongoing.

Applicant provided 6 months stability data for both long term and accelerated conditions, which may be a fileability issue, however, due to prior commitment by the Agency in pre-NDA meeting, the applicant was allowed to make a stability update prior to mid-cycle review date. Applicant also provided DP stability in solution (ref. 3.2.S.7, Module 3, vol 1) at different pH and at temperature. In solution condition, (b) (4) No stability data on infusion solution are provided.

No statistical analysis is included to support the proposed DP expiration dating. Applicant indicated to update the stability data as available. The Applicant proposes a (b) (4) expiration dating period

for the Docetaxel concentrate, when stored (b) (4) in absence of light.

Drug Product Critical Issues

- New degradants in DP concentrate (finished dosage form) and infusion solution, when compared with RLD specification.
- Check EES of DP sites for accuracy.
- DMFs for DS manufacturing and container/closure systems need to be reviewed for adequacy of the NDA.
- Two different acceptance criteria for DP impurities are proposed for release and for stability specification. Enough justification should be provided to qualify the level.
- Provide stability test data on drug product infusion solution over the period of intended storage time.
- Provide in-use stability data for the drug product infusion solution.
- Justification of (b) (4) expiration based on 6-months stability data in the submission and an update. Whether ICH Q1E can be applied for this extrapolation to justify the proposed expiration.
- The DP labeling, applicant proposes DP storage at (b) (4) in absence of light. Justify the broad range of storage temperature.

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?	√		Ref. p-6, Vol. 1, under other correspondence
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?	√		Pending review of stability update.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Review issue.
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

		✓ ✓ ✓ ✓	Biopharm Statistics (stability) OCP/CDRH/CBER LNC DMEPA EER
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Have all DMF References been identified? Yes (✓) No ()

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

Comments and Recommendations

The application is fileable, however, two 74-Day Letter issues regarding drug product stability have been identified at this point (see below). Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex. Please send the following comments with 74-day letter regarding stability data for the DP infusion solution.

1. Provide stability test data on drug product infusion solution over the period of intended storage time.
2. Provide in-use stability data for the drug product infusion solution.

Haripada Sarker
 Pharmaceutical Assessment Lead (PAL)

February 18, 2010
 Date

Sarah Pope Miksinski, Ph.D.
 Branch Chief

February 18, 2010
 Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201195	ORIG-1	ACCORD HEALTHCARE INC	DOCETAXEL INJECTION 20 MG and 80 MG

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
02/25/2010

Sarah Pope Miksinski
02/25/2010