CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201195Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	201,195
Supporting document/s:	11
Applicant's letter date:	December 7, 2010
CDER stamp date:	December 10, 2010, Re-submission January 12, 2011
Product:	Docetaxel Injection
Indication:	Breast cancer, NSCLC, Prostate cancer, Gastric cancer, SCCHN
Applicant:	Accord Healthcare, Inc. USA
Review Division:	Division of Drug Oncology Products
Reviewer:	Margaret E. Brower, Ph.D.
Supervisor/Team Leader:	Haleh Saber, Ph.D.
Division Director:	Robert Justice, M.D.
Project Manager:	Kim Robertson

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

Recommending Approval.

Background and Regulatory History
Docetaxel Injection was submitted as a 505(b)(2) by Accord Healthcare, Inc., for the same clinical indications as Taxotere, the reference listed drug (RLD). Docetaxel Injection will be administered IV using the same dosages and schedule as the reference listed drug.

A Complete Response Letter was sent to the Applicant on October 22, 2010. The following paragraph includes the non-clinical deficiencies documented in the Complete Response Letter.

> Using the analytical method in your NDA, there are two new impurity peaks identified as RRT (b) (4) and RRT (b) (4) The acceptance criteria for these two compounds are set at NMT (b) (4) These acceptance criteria are above the 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) threshold. If the impurity peaks at RRT (b) (4) and RRT (b) (4) are identified to be an impurity 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.

Applicant Response to non-clinical deficiencies submitted with Complete Response Letter [December 7, 2010 (SDN 14)]:

1. Impurity with elution of RRT (b) (4) has been lowered to NMT (b) (4) at release, as well as following shelf-life, in accordance with the ICH Q3B (R2) threshold limit of 0.2%, based on the maximum daily dose of 180 mg/person.
   Agency position: This impurity is within the ICH Q3B(R2) threshold. The proposed specification is acceptable.

2. Impurity with elution of RRT (b) (4) was identified via HPLC/LCMS as (b) (4) formed from the secondary degradation of (b) (4) at higher temperatures. The Applicant increased the limit of this impurity from NMT (b) (4) (NDA submission dated December 21, 2009) to NMT (b) (4) (response to Complete Response Letter dated December 7, 2010), to NMT (b) (4) in their response to information request (IR) dated January 20, 2011.

In their response to the IR, dated January 20, 2011, the Applicant documented the limit of this impurity in the side-by-side impurity comparison of Docetaxel Injection with the reference listed drug (RLD) (see table). The highest documented limit of the impurity was (b) (4) in the Applicant's drug product after 6 months at 25ºC/60% relative humidity, compared to the (b) (4) limit of the impurity in the RLD at expiry (end of shelf life).

Stability study comparing Docetaxel Injection at 6 month shelf life to Taxotere at expiry* (25±2º/60±5% relative humidity)

Impurity	Docetaxel Injection/Batch #				Taxotere/Batch #		
	K0971	K1204	K0972	K1205	D7C992	D7D348	D7G097
(b) (4)							

* Comparative time differs between initial and final assay at ~expiry for batches of RLD. Batches D7C992, D7D348, and D7G097 of Taxotere = 2, 11, and 3 months as time from initial to final assay.

The Applicant conducted a nonclinical rodent study in an attempt to qualify the (b) (4) However, the study cannot be used to set an acceptable specification limit for this impurity.

Agency position:
The specification limit of the (b) (4) should be lowered to NMT (b) (4) in the Applicant's drug which is approximately equal to the highest shelf-life specification of the impurity observed in the RLD (b) (4) (see table).

During the April 11, 2011 telecommunication with the Applicant, we recommended lowering the shelf-life specification limit of the (b) (4) to NMT (b) (4), as noted above. The Applicant accepted these changes, and submitted the revised drug product release and shelf-life specification on April 18, 2011.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The content of the pharmacology/toxicology sections of the label is similar to that of the reference drug, Taxotere.

1.2 Brief Discussion of Nonclinical Findings

The impurity at RRT (b) (4) was identified by the Applicant as (b) (4), formed from the secondary degradation of (b) (4) at higher temperatures.

The highest shelf-life stability limit of the (b) (4) impurity in the RLD is (b) (4), as indicated in the Applicant's side-by-side impurity comparison of Docetaxel Injection with the reference listed drug (RLD). The limit of the impurity at (b) (4) of the maximum daily dose (MDD) of docetaxel (180 mg) administered to a 60kg human, is (b) (4) The Applicant has proposed to increase the threshold limit of the (b) (4) impurity to (b) (4) in the drug product. Therefore, the proposed impurity limit of the MDD administered to a 60kg human is increased to (b) (4) an increase of (b) (4) fold on a daily basis.

The Applicant conducted a 28-day multiple dose toxicology study to qualify the (b) (4) The impurity and Docetaxel Injection drug product containing (b) (4) of the impurity were administered at the same doses daily for 28 days in the Wistar rat. A suitable design would have been comparing Docetaxel Injection containing the impurity at the proposed specification limit of (b) (4) to the RLD Taxotere. No bridge to Taxotere was provided in the toxicology study. The study cannot be used to justify the proposed (b) (4) impurity limit of (b) (4) Other study limitations were noted as well, including limited organ histopathology.

Results of the toxicology study indicate that the impurity alone is marginally more toxic when administered to rodents compared to Docetaxel Injection with undetectable (b) (4) Animals administered 0.2mg/kg of the impurity exhibited an increase in hepatobiliary enzymes, and renal, uterine, and ocular histopathology findings which were not observed with the Docetaxel Injection drug product; hepatobiliary enzymes were increased in lower doses as well.

Study title: Comparative Repeated Dose 28 day Intravenous Toxicity Study of Docetaxel impurity at RRT (b) (4) 40 mg/mL (test substance) and Docetaxel Injection concentrate 40 mg/mL (reference substance) in Wistar rats

Key Study Findings:

● Toxicities associated with Impurity RRT (b) (4) are comparable to those of Docetaxel Injection with exceptions noted below:
- ● While not dose dependent, increase in hepatobiliary enzymes (possible cholestasis) was observed with all doses of impurity
- ● Significant increase in uterine weight at mid-dose
- ● Histopathologic findings observed with 0.2mg/kg impurity included hyperplasia and pyelonephritis of kidney, hyperplasia of uterus and eye; findings not observed with Docetaxel Injection drug product

● Since the study was not designed to show comparable toxicities between Taxotere and Docetaxel Injection with the proposed impurity level for (b) (4) the study cannot be used to set an acceptable specification limit for the impurity.

Study no.:	10108
Study report location:	Appendix 12, Response to Complete Response Letter
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 23, 2010
GLP compliance:	Yes
QA report:	Yes
Drug, lot #, and % purity:	•Docetaxel impurity at RRT (b) (4) in PEG 400, 40mg/mL, batch # ASDCTP1125, 98.4% purity •Docetaxel Injection concentrate in PEG 400, 40mg/mL, batch # ASDCTP1124, 99.6% purity •PEG 400 control, batch # ASDCTP1126

Methods:

Doses:	0.05, 0.1, 0.2mg/kg
Frequency of dosing:	Daily for 28 days, 14-day recovery
Route of administration:	IV bolus, tail vein
Dose concentration:	0.1mg/mL
Formulation/vehicle	NaCL 0.9% w/v
Species/Strain:	Wistar rat
Number/Sex/Group:	5 rats/sex/group (See table)
Age:	7-8 weeks
Weight:	202-208g males; 159-165g females
Satellite groups:	Recovery (5 rats/sex/group; See table)
Notes on study design:	1. Histopathology limited to liver, kidney, lungs, salivary gland, pancreas, stomach, mesenteric lymph node, spleen, thyroid, adrenals, uterus, pituitary, and eyes. 2. Reticulocyte counts not measured.

Note: An amendment to the study report (dated November 19, 2010) provided additional data regarding dose formulation preparation. Dose concentrations remained constant at 0.1mg/mL; individual dose volume was adjusted according to body weight of animal.

Tables in this section were generated by the reviewer

Group		**Dose (mg/kg/day)**
G1	Control	0
G2	Impurity LD	0.05
G3	Impurity MD	0.1
G4	Impurity HD	0.2
G5	Docetaxel Injection LD	0.05
G6	Docetaxel Injection MD	0.1
G7	Docetaxel Injection HD	0.2
G8	Recovery control	0
G9	Recovery impurity	0.2[a]
G10	Recovery Docetaxel Injection	0.2[a]

Abbreviations: Impurity = Docetaxel Impurity at RRT (b) (4) LD= low dose; MD = mid dose; HD = high dose; G = group

[a] *An IR requesting clarification of recovery group dosing was sent to the Applicant on March 4, 2011, as a result of contradictory statements in experimental design. The Applicant confirmed that the high dose (0.2mg/kg) was administered to recovery groups G9 and G10. Ten pages of the final report were amended and submitted, which raises questions about the QA audit of the study.*

Study parameters

Observation	**Time of assessment**
Mortality	2X daily
Clinical observations	2X daily
Body weight	Predose, weekly thereafter
Food consumption	Weekly
Ophthalmology	Predose, prior to terminal and recovery sacrifice
Hematology	Day 29, Day 43
Clinical chemistry	
Urinalysis	
Organ weights	Dosing phase sacrifice: 28 days Recovery phase sacrifice: 14 days following dosing (day 43)
Gross pathology	
Histopathology	

Parameters	0.05mg/kg				0.1mg/kg				0.2mg/kg			
	Impurity		DI		Impurity		DI		Impurity		DI	
	M	F	M	F	M	F	M	F	M	F	M	F
Mortality	None											
Clinical observations	Unremarkable											
Body weight	Unremarkable											
Food consumption	Unremarkable											
Ophthalmoscopy	Unremarkable											
Hematology (d29) [a]												
WBC	↓25		↓19		↓14		↓14				↓12	
Platelets	↓23		↓12		↓10		↓9		↓12		↓13	
Clotting time	↓12	↓10	↓9	↓9	↓12	↓10	↓20	↓10	↓12		↓12	↓19
Clinical chemistry (d29) [a]												
Glucose	↑42		↑21		↑52				↑42		↑23	
Total bilirubin	↑36		↑36				↑11		↑22		↑11	
GGT	↑62	↑82							↑80			
ALP		↑89		↑53		↑76		↑44		↑21		↑35
Urinalysis	UR											
Organ weight (absolute-d29)[a]												
Spleen									↑14		↑5	
Uterus		↑65		↑65		↑170		↑52		↑41		↑40
Liver		↓14		↓10		↓9		↓11		↓13		↓14
Thymus		↑11		↑16		↑29		↑14		↑19		↑14
Gross pathology	None noted by study author											
Histopathology	See histopathology table (Control and high dose only)											

[a] Percent change from concurrent control
Abbreviations: Impurity = Docetaxel impurity at RRT (b) (4); DI = Docetaxel Injection; M = males; F = females

Triglycerides were comparatively depressed at day 29 in all doses of impurity and Docetaxel Injection dose groups. Organ weights were determined for adrenals, ovaries, uterus, kidneys, brain, heart, spleen, liver and thymus. Most findings in table above are not dose-dependent.

Histopathology was limited to liver, kidney, lungs, salivary gland, pancreas, stomach, mesenteric lymph node, spleen, thyroid, adrenals, uterus, pituitary, and eyes. Grading of findings was not indicated. Histopathology was limited to control and high dose animals; histopathology was not conducted on target organs at the low-dose and mid-dose.

In the following table, histopathology findings were documented in impurity high-dose groups only if similar findings were not observed in the concurrent Docetaxel Injection group, or findings were observed at an increased incidence in the impurity groups.

Histopathological incidence N=5/sex/dose

Finding/organ	Impurity HD incidence	
	M	F
Kidney/hyperplasia	1	
/pyelonephritis	1	
Spleen/congestion	2	
Thyroid/Atrophy		1
Uterus/hyperplasia, hypertrophy		2
Eye/hyperplasia	2	1

HD = high dose

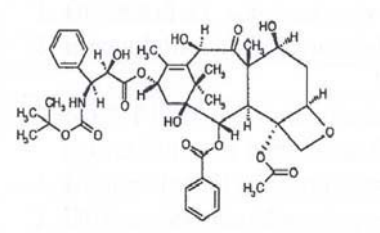
The incidence of noted histopathological findings were not observed in the Docetaxel Injection high-dose group.

2 Drug Information

2.1 Drug: Docetaxel Injection (Reference Listed Drug: Taxotere)

2.1.1 CAS Registry Number	114977-28-5
2.1.2 Generic Name	docetaxel
2.1.3 Code Name	none
2.1.4 Chemical Name	(2R,3S)-N-benzoyl-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β, 20-Epoxy-1,2ά , 4, 7β, 10β , 13ά-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate
2.1.5 Molecular Formula/Molecular Weight	$C_{43}H_{53}NO_{14}$/861.9
2.1.6 Manufacturing site	Intas Pharmaceuticals Limited Ahmedabad, Gujarat, India

2.1.7 Structure



2.1.8 Pharmacologic class: Microtubule inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s: IND 101,904, NDA 20,449

Integrated Summary and Safety Evaluation

Docetaxel Injection was submitted as a 505(b)(2) by Accord Healthcare, Inc., for the same clinical indications as Taxotere, the reference listed drug. Non-clinical issues included drug product impurities. In the December 2009 NDA submission, the Applicant compared batches of Docetaxel Injection to batches of the reference listed drug (Taxotere) at expiry to determine impurity specification. The CMC review team considered the impurity methodology used in this determination to be valid and reliable. Specification limits proposed for 3 of 5 impurities were qualified (see NDA review 1). The remaining 2 impurities (i.e., impurity peaks at RRT (b) (4) and RRT (b) (4) were not structurally identified; the acceptance criteria for these compounds were set at NMT (b) (4), which is above the ICH Q3B(R2) threshold of 0.2%. It should be noted that the specification limits of the RLD were not available for these impurities in the 2009 NDA data (see table).

Impurity specification comparison of Docetaxel Injection and Taxotere NDA 201,195 submitted December 21, 2009

Impurity	Accord		Taxotere	
	Release	Shelf-life	Release	Shelf-life
(b) (4)				

Abbreviations: N/A = not available (unidentified impurity)

In the Complete Response (CR) Letter, dated October 22, 2010, the Applicant was asked to identify the impurities, and reduce their levels, or justify the proposed specification limits of the unidentified impurities.

In the response to non-clinical deficiencies submitted with the CR Letter, dated December 7, 2010, the Applicant lowered the specification limit of the impurity with elution of RRT (b) (4) from (b) (4) to NMT (b) (4) at release, and following shelf-life, in accordance with the ICH Q3B (R2) threshold limit of 0.2%.

The impurity with elution of RRT (b) (4) was identified as (b) (4) formed from the secondary degradation of (b) (4) at higher temperatures. The Applicant raised the specification limit of this impurity from (b) (4) basing this

increase on a non-clinical study conducted to qualify the impurity. However, the study was not designed to show comparable toxicities between the RLD (Taxotere) and Docetaxel Injection with the proposed impurity level for RRT (b) (4) In addition, the results indicated that the (b) (4) impurity alone is marginally more toxic when administered to rodents compared to Docetaxel Injection. In response to an IR dated January, 2011, the Applicant again raised the proposed limit of this impurity from (b) (4)

The highest shelf-life specification of the (b) (4) impurity in 3 batches of the RLD is (b) (4), as indicated in the Applicant's side-by-side comparison of impurities with 4 batches of Docetaxel Injection. The specification limit of the C, D-seco docetaxel (RRT (b) (4)) should be lowered to NMT (b) (4) in the Applicant's drug which is approximately equal to the highest shelf-life specification of the impurity observed in the RLD (b) (4) The impurity is considered qualified at (b) (4) The Applicant has agreed to lower the shelf-life specification of the impurity with elution of RRT (b) (4) from (b) (4) to NMT (b) (4)

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/s/

MARGARET E BROWER
06/02/2011

HALEH SABER
06/02/2011

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Product:	Docetaxel Injection
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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

Not Approvable.

Two impurities are above the threshold defined in ICH Q3B(R2). The Applicant did not respond to the information request addressing this issue.

> Using the analytical method in your NDA, there are two new impurity peaks identified as RRT (b) (4) and RRT (b) (4) The acceptance criteria for these two compounds are set at NMT (b) (4). This acceptance criteria is above the 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) threshold. If the impurity peaks at RRT (b) (4) and RRT (b) (4) are identified to be an impurity 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.

This NDA cannot be approved until the impurity issue is adequately addressed.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The drug label has not been finalized given that a CR letter will be forwarded to the Applicant. The content of the pharmacology/toxicology sections of the label should be similar to that of the reference drug.

1.2 Brief Discussion of Nonclinical Findings

Docetaxel Injection was submitted as a 505(b)(2) by Accord Healthcare, Inc., for the same clinical indications as Taxotere, the reference listed drug (RLD). Docetaxel Injection will be administered IV using the same dosages and schedule as the reference listed drug.

No additional non-clinical studies were submitted with this 505(b)(2) application. Non-clinical issues address differences from the reference listed drug. These include drug product impurities, changes in the docetaxel:PS80 ratio, and the addition of drug product excipients. These issues are briefly discussed below.

The shelf-life specification of five Docetaxel Injection drug product impurities are above the ICH Q3B(R2) threshold of 0.2%. While the specification for three of these impurities, (b) (4) are above the ICH Q3B(R2) threshold, levels are not above those of the RLD, using validated analytical methods. Practices for establishing the comparative adequacy of purity methods were followed by the Applicant for these three impurities. Therefore, the specification limits set for impurities (b) (4) are acceptable. Two impurities have not been structurally identified (i.e., impurity peaks at RRT (b) (4) and RRT (b) (4)); the acceptance criteria for these compounds is set at NMT (b) (4), which is above the ICH Q3B(R2) threshold of 0.2%. These impurities must be identified and/or adequately qualified. Alternatively, their levels may be reduced to meet the threshold defined in ICH Q3B(R2). See Integrated Summary and Safety Evaluation for further information.

Docetaxel Injection can not be approved as a 505(b)(2) until the impurity issue is adequately addressed.

In June, 2009, Sanofi submitted a Citizen's Petition (CP) to the Agency which indicated that changes in the ratio of docetaxel:PS80 different from that of Taxotere may affect the release of the unbound fraction of docetaxel (i.e. pharmacokinetics), which may change the safety profile (e.g. neutropenia) and effectiveness of the drug product compared to Taxotere. Sanofi requested that the Agency require a clinical pharmacokinetic study for these 505(b)(2) or ANDA drug formulations. The ratio of docetaxel:PS80 for the marketed Taxotere 1- and 2-vial formulations is (b) (4) The ratio of docetaxel: PS80 for the proposed Accord 505(b)(2) formulation is (b) (4) The Clinical Pharmacology review of the Applicant formulation indicated that differences in the ratio of docetaxel:PS80 between Taxotere and Docetaxel Injection are not likely to have a significant clinical impact on the pharmacokinetics of docetaxel.

Citric acid and polyethylene glycol have been added to the proposed formulation. Citric acid is added to the drug product as a pH adjusting agent (b) (4) Polyethylene glycol (PEG 400) is added to the diluent vial at 13% w/v. These excipients have been previously included in several approved drug

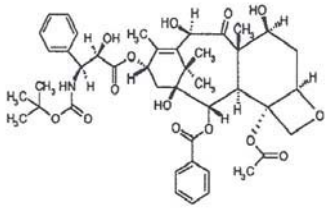
products. The addition of citric acid and polyethylene glycol are not safety issues at specified levels.

2 Drug Information

2.1 Drug: Docetaxel Injection (Reference Listed Drug: Taxotere)

2.1.1 CAS Registry Number	114977-28-5
2.1.2 Generic Name	docetaxel
2.1.3 Code Name	none
2.1.4 Chemical Name	(2R,3S)-N-benzoyl-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β, 20-Epoxy-1,2α , 4, 7β, 10β , 13α-hexahydroxytax-11-en-9-one 4-10-dicetate 2-benzoate
2.1.5 Molecular Formula/Molecular Weight	$C_{43}H_{53}NO_{14}$/861.9
2.1.6 Manufacturing site	Intas Pharmaceuticals Limited Ahmedabad, Gujarat, India

2.1.7 Structure



2.1.8 Pharmacologic class: Microtubule inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s: IND 101,904, NDA 20,449

2.3 Clinical Formulation

2.3.1 Drug Formulation

Docetaxel Injection is supplied as a 40mg/mL solution concentrate with strengths of 20mg/0.5mL and 80mg/2mL. Two vials (drug product and diluent) are supplied with the final package. The drug product must be reconstituted with the diluent to produce Docetaxel Injection concentrate, which is then reconstituted with 5% Dextrose injection or 0.9% Sodium Chloride Injection prior to administration.

Comparison of the reference product and proposed product – **drug product vial**

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

Comparison of the reference product and proposed product – **diluent vial**

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

2.3.2 Comments on Novel Excipients

None

2.3.3 Comments on Impurities/Degradants of Concern

Two Docetaxel Injection drug product impurities have not been structurally identified (i.e., impurity peaks at RRT (b) (4) and RRT (b) (4)); the acceptance criteria for these compounds is set at NMT (b) (4) which is above the ICH Q3B(R2) threshold of 0.2%. The Applicant has not responded to an information request forwarded on August 2, 2010, asking for identification of these unidentified impurity peaks, or reduction of specification levels to ≤0.2% (see Executive Summary).

> Using the analytical method in your NDA, there are two new impurity peaks identified as RRT (b) (4) and RRT (b) (4) The acceptance criteria for these two compounds are set at NMT (b) (4) This acceptance criteria is above the 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) threshold. If the impurity peaks at RRT (b) (4) and RRT (b) (4) are identified to be an impurity 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.

2.4 Proposed Clinical Population, Exclusivity, and Dosing Regimen

Docetaxel Injection will be administered IV at the doses and schedule of the RLD.

2.5 Regulatory Background

Taxotere (NDA 20,449), the reference listed drug (RLD), was approved on May 15, 1996, for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during antracycline-based adjuvant therapy. On December 23, 1999, Taxotere was approved as a single agent for the treatment of advanced or metastatic non-small cell lung cancer after failure of platinum containing chemotherapy at the recommended dose of 60-100mg/m^2 administered iv once every three weeks. As an adjuvant therapy, Taxotere was approved on May 19, 2004 in combination with prednisone for the treatment of androgen independent (hormone refractory) metastatic prostate cancer at a recommended dose of 75mg/m^2 administered once every 3weeks in combination with 5mg oral prednisone BID. In 2005, Taxotere was approved in combination with cisplatin and 5-FU for the treatment of gastric adenocarcinoma. Taxotere (with cisplatin and flurouracil) is also approved for induction treatment of locally advanced SCCHN.

As indicated above, Docetaxel Injection, the 505(b)(2) NDA application submitted by Accord Healthcare, Inc. is indicated for the same clinical patient population as Taxotere.

3 Studies Submitted - None

3.1 Studies Reviewed - None

3.2 Studies Not Reviewed - None

3.3 Previous Reviews Referenced - None

4 Pharmacology

4.1 Primary Pharmacology - None

4.2 Secondary Pharmacology - None

4.3 Safety Pharmacology - None

5 Pharmacokinetics/ADME/Toxicokinetics - None

6 General Toxicology - None

6.1 Single-Dose Toxicity - None

6.2 Repeat-Dose Toxicity - None

7 Genetic Toxicology - None

8 Carcinogenicity - None

9 Reproductive and Developmental Toxicology - None

10 Special Toxicology Studies - None

11 Integrated Summary and Safety Evaluation

Docetaxel Injection was submitted as a 505(b)(2) by Accord Healthcare, Inc., for the same clinical indications as Taxotere, the reference listed drug. Taxotere (NDA 20,449) has been approved for the treatment of patients with locally advanced or metastatic breast cancer, advanced or metastatic NSCLC, hormone refractory metastatic prostate cancer, gastric adenocarcinoma, and locally advanced SCCHN. Docetaxel Injection will be administered IV using the same dosages and schedule as the reference listed drug.

No additional non-clinical studies were submitted with this 505(b)(2) application. Non-clinical issues address differences from the reference listed drug. These include drug product impurities, changes in the docetaxel:PS80 ratio, and the addition of drug product excipients. These issues are addressed below.

A. Drug Product Impurities:

The Applicant has compared batches of Docetaxel Injection to batches of the reference listed drug (Taxotere) at expiry to determine impurity specification. The CMC review team (T. Chang, Ph.D, H. Sarker, Ph.D. and M. Adams, Ph.D.) consider the impurity methodology used in this determination to be valid and reliable.

The shelf-life specification of five Docetaxel Injection drug product impurities are above the ICH Q3B(R2) threshold of 0.2%. While the specification for three of these impurities, (b) (4) are above the ICH Q3B(R2) threshold, levels are not above those of the RLD, using validated analytical methods. Practices for establishing the comparative adequacy of purity methods were followed by the Applicant for these three impurities. Therefore, the specification limits set for impurities (b) (4) are acceptable. Two impurities have not been structurally identified (i.e., impurity peaks at RRT (b) (4) and RRT (b) (4)); the acceptance criteria for these

compounds is set at NMT (b) (4), which is above the ICH Q3B(R2) threshold of 0.2% (see table below).

On August 2, 2010, an information request was forwarded to Accord Healthcare, Inc. asking that the Applicant identify the two unidentified impurity peaks, or reduce the specification limits to ≤0.2%. The Applicant has not responded to this information request.

The information request stated that if the impurity peaks cannot be identified, their levels should be reduced to meet the ICH Q3B(R2) threshold of 0.2%, or adequately justified (e.g. based on nonclinical studies). If the impurity peaks can be identified to be an impurity in the RLD, their levels should be reduced not to exceed the levels in the RLD (see table below). Levels of these impurities above the RLD should be adequately justified based on nonclinical or clinical studies.

Comparison of drug product impurities as provided by Accord Healthcare, Inc.

Impurity	Accord		Taxotere	
	Release	Shelf-life	Release	Shelf-life
(b) (4)				

Abbreviations: N/A = not available (unidentified impurity)

B. Citizens Petition from innovator of Reference Listed Drug:

In June, 2009, Sanofi submitted a Citizen's Petition (CP) to the Agency which indicated that changes in the ratio of docetaxel:PS80 different from that of Taxotere may affect the release of the unbound fraction of docetaxel (i.e. pharmacokinetics), which may change the safety profile (e.g. neutropenia) and effectiveness of the drug product compared to Taxotere. Sanofi requested that the Agency require a clinical pharmacokinetic study for these 505(b)(2) or ANDA drug formulations. The ratio of docetaxel:PS80 for the marketed Taxotere 1- and 2-vial formulations is (b) (4)

The ratio of docetaxel: PS80 for the proposed Accord 505(b)(2) formulation is (b) (4) The Clinical Pharmacology review of the Applicant formulation by J. Moon, Ph.D., indicated that differences in the ratio of docetaxel:PS80 between Taxotere and Docetaxel Injection are not likely to have a significant clinical impact on the pharmacokinetics of docetaxel.

C. Drug product excipients:

Citric acid and polyethylene glycol have been added to the proposed formulation. Citric acid is added to the drug product as a pH adjusting agent at levels of (b) (4) Polyethylene glycol (PEG 400) is added to the diluent vial at 13% w/v. These excipients have been previously included in several approved drug products. The addition of citric acid and polyethylene glycol are not safety issues at specified levels.

12 Appendix/Attachments - None

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/

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09/09/2010

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