CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208870Orig1s000

PRODUCT QUALITY REVIEW(S)

ADDENDUM
NDA 208870 Quality Review
From: Danae Christodoulou, ATL

The applicant, JDI amended the application on 8/4/2017 with the revised drug product release and stability specifications, as agreed upon with FDA during this review cycle. The release limit for the reducing agent stannous chloride was tightened from (b) (4) mcg/ml (as the lower limit) so that the stability specification of (b) (4) mcg/ml is met. Attached are the updated specification sheets.
ATTACHMENT 1

Drug Product Specifications for Release testing

JDI Internal code	506791	
Standard	House	
Revision #	7	
Approval Date	August 01, 2017	
Test	**Method** **(Type of Method)**	**Acceptance Criteria**
Tests applicable on the Lyophilized product		
Description	Organoleptic	(b) (4)
Appearance	Organoleptic	Free from visible contamination
Clarity of Solution & Completeness	MTD-GEN-005, (Visual)	Reconstituted solution must have the appearance of purified water Reconstitution Time: NMT (b) (4)
Identification of Stannous	MTD-GEN-004, (Colorimetry)	Test paper turns blue
Identification A of Exametazime	MTD-LC-001, (Colorimetry)	Solution becomes purple-pink
Identification B of Exametazime	MTD-LC-001, (HPLC)	Retention time of main peak is within (± (b) (4)%) of the Reference Standard retention time
Exametazime Assay	MTD-LC-001, (HPLC)	(b) (4) mg/vial
Content Uniformity	MTD-LC-001, (HPLC)	AV NMT (b) (4) Meets USP <905> Requirements
Impurities and Degradation Products	MTD-LC-002, (HPLC)	Total: NMT (b) (4)% Individual impurities: - (b) (4) NMT (b) (4)% - Any unspecified impurity: NMT (b) (4)% - Impurity A: NMT (b) (4)%
	MTD-LC-012, (HPLC)	- (b) (4) NMT (b) (4)%
Stannous Chloride Content	MTD-GEN-006, (Polarography)	(b) (4) µg/vial (expressed as Sn)
Total (b) (4) Content	MTD-AA-001, (Atomic Absorption)	(b) (4) µg/vial (expressed as (b) (4)

JDI Internal code	506791	
Standard	House	
Revision #	7	
Approval Date	August 01, 2017	
Test	**Method** **(Type of Method)**	**Acceptance Criteria**
[redacted] (b) (4)		
Bacterial Endotoxins	USP <85> and SOP 1684	NMT (b) (4) EU/mL
Particulate Matter	USP <788>	NMT (b) (4) particules/vial for particles ≥ 10µm
		NMT (b) (4) particules/vial for particles ≥ 25µm
Sterility	USP <71>	Sterile
Tests applicable on the Reconstituted Product: Technetium Tc 99m Exametazime Injection		
pH	MTD-GEN-005 (USP <791>)	(b) (4)
Radiochemical Purity (within 30 min post reconstitution)	MTD-RCP-001 USP Product Monograph (TLC)	NLT (b) (4) % of Total Radioactivity as primary Tc-Exametazime lipophilic complex
		NMT (b) (4) % of Total Radioactivity as (b) (4) (b) (4)
Biological distribution	MTD-BIO-001 USP Product Monograph	NLT (b) (4) % of Radioactivity in brain
		NMT (b) (4) % of Radioactivity in intestines
		NMT % of Radioactivity in liver
		In Not Less Than (b) (4) animals

ATTACHMENT 2

Drug Product Specifications for Stability testing

JDI Internal code	**506791**	
Standard	**House**	
Revision #	**7**	
Approval Date	**August 01, 2017**	
Test	**Method** **(Type of method)**	**Acceptance Criteria**
Tests applicable on the Lyophilized product		
Description	Organoleptic	White powder or white plug
Appearance	Organoleptic	Free from visible contamination
Container	Organoleptic	No change in appearance of inner walls and stopper
Clarity of Solution & Completeness	MTD-GEN-005, (Visual)	Reconstituted solution must have the appearance of purified water Reconstitution Time: NMT (b)(4) minute
Exametazime Assay	MTD-LC-001, (HPLC)	(b)(4) mg/vial
Impurities and Degradation Products	MTD-LC-002, (HPLC)	Total: NMT (b)(4) % Individual impurities: - (b)(4): NMT (b)(4) % - Any unspecified impurity: NMT (b)(4) % - Impurity A: NMT (b)(4) %
	MTD-LC-012 (HPLC)	(b)(4) NMT (b)(4) %
Stannous Chloride Content	MTD-GEN-006, (Polarography)	NLT (b)(4) µg/vial (expressed as Sn)
(b)(4)		
Bacterial Endotoxins	USP <85> and SOP 1684	NMT (b)(4) EU/mL
Sterility	USP <71>	Sterile
Tests applicable on the Reconstituted Product: Technetium Tc 99m Exametazime Injection		
pH	MTD-GEN-005 (USP <791>)	(b)(4)

JDI Internal code	506791	
Standard	House	
Revision #	7	
Approval Date	August 01, 2017	
Test	**Method** **(Type of method)**	**Acceptance Criteria**
Radiochemical Purity (within 30 min post reconstitution)	MTD-RCP-001 USP Product Monograph, (TLC)	NLT (b) (4)% of Total Radioactivity as primary Tc-Exametazime lipophilic complex
		NMT (b) (4)% of Total Radioactivity as (b) (4) (b) (4)
Biological distribution	MTD-BIO-001 USP Product Monograph	NLT (b) (4)% of Radioactivity in brain
		NMT % of Radioactivity in intestines
		NMT % of Radioactivity in liver
		In Not Less Than (b) (4) animals

Recommendation: APPROVAL

NDA 208870
Review # 1

Drug Name/Dosage Form	Kit for the preparation of Technetium Tc 99m Exametazime (b) (4)
Strength (kit)	0.5 mg per vial
Strength Tc 99m exametazime	74- 370 MBq / mL (2-10 mCi / mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Jubilant DraxImage Inc.
US agent, if applicable	Aziz Nutritdinov, INC Research LLC, Cincinnati, OH

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	7/20/2016	ALL
Labeling	10/5/2016, 10/31/2016	Drug Product
Amendment	12/19/2016	Biopharmaceutics
Amendment	1/9/2017, 2/2/2017	Drug Product, Process, Biopharmaceutics
Amendment	2/21/2017, 2/28/2017	Drug Product, Process
Amendments	3/2/2017, 3/3/2017, 3/14/2017	Microbiology
Amendment	3/8/2017	Process
Amendment	3/30/2017	Drug Substance and Product
Amendment	3/31/2017	Drug Product
Amendments	4/7/2017, 4/21/2017, 4/28/2017	Drug Product
Amendment, Labeling	6/30/2017	Drug Product
Labeling	7/7/2017	Drug Product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	New Drug API
Drug Product	Dhanalakshmi Kasi	DNDP II
Process	Dhanalakshmi Kasi	DNDPII
Microbiology	Samata Tiwari	OPF
Facility	Michael Klapal	OPF
Biopharmaceutics	Poonam Delvadia	ONDP-Biopharmaceutics
Regulatory Business Process Manager	Thao Vu	OPRO
Application Technical Lead	Danae Christodoulou	DNDPII
Laboratory (OTR)	NA	
ORA Lead	NA	
Environmental Analysis (EA)	Dhanalakshmi Kasi	DNDPII

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	5/27/2011	Sufficient information in NDA
	Type III			Adequate	6/15/2017	Sufficient information in NDA
	Type III					Drug Substance
	Type III					Drug Substance
	Type V			Adequate	4/25/2017	
	Type V			Adequate	10/3/2016	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Label RLD	NDA 19829	Ceretec™
Pre-IND	123604	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	Completed	*In vitro* BE Acceptable	3/31/2017	Satish Misra

Executive Summary

I. Recommendations and Conclusion on Approvability:

The NDA is recommended for approval from a Quality and Microbiology perspective. There are no pending deficiencies and all manufacturing facilities have received "Acceptable" cGMP recommendation. Bioequivalence to the referenced approved product Ceretec™ has been established by evaluation of physiochemical properties and *in vitro* studies on %labeling efficiency (%LE) and % cell efflux radioactivity (%CER) comparisons of the proposed product and the reference drug, Ceretec™.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	(b) (4) Leukocytes labeled scintigraphy as an adjunct in the localization of (b) (4) intra-abdominal infection, inflammatory bowel diseas (b) (4)
Duration of Treatment	**NA – Diagnostic Imaging Agent**
Maximum Daily Dose	259 - 925 megabecquerels (MBq) [7-25 millicuries] (mCi)
Alternative Methods of Administration	**None**

B. Quality Assessment Overview

Jubilant DraxImage (JDI) submitted the current NDA as a 505(b)(2) application relying on the approved drug Ceretec™, NDA 19829, by GE Healthcare. Both drugs have the same formulation, strength, dosage form, and route of administration. JDI proposed only one of the two indications approved for Ceretec™, leukocyte labeled scintgraphy as an adjunct in localizing sites of infection. The mechanism of action, dosimetry, biodistribution, pharmacodynamics and pharmacokinetics of Tc 99m Exametazime (b) (4) have been previously described in the approved GE Healthcare's NDA for Ceretec™. No non-clinical and clinical data have been submitted in support of this NDA. JDI requested a waiver from *in vivo* bioavailability/bioequivalence (BA/BE) studies comparing the proposed product and the reference drug, Ceretec™, under the provision of 21 CFR 320.22(b)(1)(i) and (ii). In addition, JDI provided physicochemical properties comparison as well as an *in vitro* equivalence study for White Blood Cell labeling efficiency using the proposed drug product and the reference approved drug as a study comparator. Dr. Poonam Delvadia reviewed the *in-vitro* studies in support of establishing bioequivalence, and Dr. Satish Mishra the statistics supporting the studies. The *in vitro* studies in support of demonstrating bioequivalence were found adequate.

Dr. Martin Haber reviewed the ligand exametazime, [redacted] Tc 99m exametazime is used to radiolabel leukocytes for scintigraphy of infection or inflammation. Exametazime is a racemate ligand, (oxime) and contains two chiral centers with four theoretical stereoisomers. The precursor to the drug substance consists of [redacted] The other two stereoisomers [redacted]. See chemical structures in Dr. Martin Haber's review p.3. The manufacturing process [redacted] he chemical structure was elucidated by FT-IR, HNMR, C NMR, Mass Spectrometry and X-Ray single crystal diffraction analysis. No polymorphs were identified.

Specifications include clarity of saline solution, identification by IR and HPLC, melting point ([redacted]°C), loss on drying (NMT [redacted]%), pH of saline solution [redacted]), assay (HPLC, ≥ [redacted]%), impurities (total: NMT [redacted]%), enantiomeric excess (chiral HPLC, NMT [redacted]%), heavy metals (NMT [redacted]ppm), residual solvents and bacterial endotoxins. Specified impurities are: [redacted] NMT [redacted]%; Impurity A, NMT [redacted]%; and [redacted] NMT [redacted]%. Any unspecified impurity is NMT [redacted]%. Impurity A is [redacted] During review of analytical methods, representative chromatograms for assay, impurities, [redacted] determination, enantiomeric excess were requested and reviewed. The methods were found adequate for their intended use. Reference standards have been developed by JDI for exametazime, [redacted] impurity A and [redacted] Batch analysis results were presented for 3 lots and a retest date of [redacted]months was granted.

Dr. Dhanalakshmi Kasi re[redacted]wed the drug product and process. The composition of the kit (one vial) is 0.5 mg of [redacted] HMPAO) per vial, 4.5 mg NaCl [redacted] 7.6 mcg $SnCl_2.2H_2O$ as a reducing agent. The end user takes the lyophilized vial and reconstitutes it with 5 mL of USP 0.9% NaCl for Injection, containing 10 mCi - 54 MCi of Tc 99m Sodium Pertechnetate [redacted] USP.

The referenced approved drug, Ceretec™, consists of three vials. The additional vial 2 contains 0.003 M Na_2HPO_4 and NaH_2PO_4 in 0.9% NaCl and vial 3 contains 1 mL of 1% methylene blue. [redacted] The shelf life of Tc 99m exametazime complex is only 30 min and it is increased to 4 [redacted] h by adding methylene blue as the stabilizer when used for cerebral imaging by GE.

In the original submission, JDI did not include the quantitative composition of Tc 99m exametazime after reconstitution, details of the radiolabeling procedure, and the type of Tc 99m generator used. The information was amended to the application after a series of information requests and teleconferences with the applicant. The final composition of Tc 99m exametazime is 0.5 mg [redacted] HMPAO, [redacted] mg NaCl, 7.6 mcg $SnCl_2.2H_2O$, Tc 99m exametazime $7.3x10^{-6}$ (10 mCi) -$1.7x10^{-4}$ mg (54mCi) and [redacted]ml WFI. Eluate from

(b) (4) generators (b) (4) was used within 2h from elution. For radiolabeling procedure see drug product review, p. 37. Critical quality attributes for the drug product are appearance, assay, impurity profile, stannous chloride content, moisture content, (b) (4) radiolabeling efficiency and physiochemical properties such as osmolality, density, specific gravity and viscosity and the test results were comparable to the referenced drug. Tc 99m exametazime complies with the USP monograph.
The exametazime kit is sterilized (b) (4) glass vial with a (b) (4) rubber stopper with (b) (4) sealed under N_2. No extractables were found from the stopper and no leachables study was performed. The pH of the solution is high (9.0-9.8) and there is a potential of leachable (b) (4) from the vial. However, no interference(s) were noted for the radiolabeling reaction, except for (b) (4).
The applicant was asked to revise the limit for $SnCl_2$ in their specification from (b) (4) mcg/mL to (b) (4) mcg/mL not to fail the stability test limit of (b) (4) mcg/mL and agreed. With respect to the radiochemical purity specification (RCP) for the reconstituted solution, the product complies with the USP specification, NLT (b) (4) % at release and NLT (b) (4) % after leukocyte labeling. After production of 10 batches the applicant agreed to revisit this specification. The applicant submitted analytical data and chromatogram traces to support use of the ITLC (per USP monograph) method which was validated against the HPLC method. The stability specification limits are the same as the release specification limits except the impurity limits (b) (4) NMT (b) (4) %, Impurity A + (b) (4) NMT (b) (4) %, any unspecified impurity: NMT (b) (4) %), (b) (4) (NMT (b) (4) %) and water content limit (b) (4) %). Stannous chloride content (NLT (b) (4) mcg/vial (expressed as Sn) is lower than the release specification limitasexpected. A shelf life of 12 months was granted for the kit and a 30 minute expiry was granted for the reconstituted drug product Tc 99m exametazime. With respect to microbiological controls, the process and product quality attributes were reviewed by Dr. Samata Tiwari and found adequate. (b) (4) which meets stability and microbial quality criteria.
The manufacturing facilities are: Jubilant Draximage Inc., Kirkland, Canada (exametazime manufacture and drug product testing), Jubilant HollisterStier (JHS) in Kirkland Canada (drug product manufacture, packaging release and stability testing). Pre-approval inspections were conducted, 483 issued and the applicant responded adequately. (b) (4) are testing facilities and were evaluated by profile. Overall cGMP recommendation was "Acceptable". See Facilities review by Michael Klapal.

The applicant submitted a biowaiver request per 21 CFR 320.22(b)(1)(i) and (ii). The biopharmaceutics review team determined that the biowaiver request was not applicable but rather the *in vitro* BE data submitted for demonstrating bioequivalence between the proposed and reference drug can be evaluated under 21 CFR 320.24(b)(6) which states: "Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence". As such, the comparative physicochemical properties and the *in vitro* studies in support of BE, % labeling efficiency (%LE) and % efflux radioactivity (%CER) for radiolabeled leukocytes for the proposed drug versus Ceretec™ were evaluated. See comparisons of formulations and critical physicochemical properties in the

biopharmaceutics review p. 7-9 by Dr. Poonam Delvadia. In the pre-IND meeting package dated 9/28/2015 and 10/15/2015, the applicant submitted the detailed *in vitro* BE protocol and proposed % labeling efficiency (%LE) and % cell efflux radioactivity [%CER] as the metrics to address bioequivalence. The Agency advised the applicant by written responses: (1) to collect %CER data over multiple time points to calculate and use area under the curve (AUC) as the endpoint for *in vitro* equivalence assessment; (2) to use two one-sided t-test (TOST) procedure with 90% confidence interval (CI) around the geometric mean ratio of products for each end point to conclude BE instead of the proposed paired t-test with null and alternative hypotheses to support the claim of bioequivalence; and (3) to provide power calculations (80% to 90%) and relevant sample sizes based on varied estimates of the variability in %LE and %CER. The applicant provided responses to some of the above comments in the response letter dated May 16, 2016. In the NDA submission, the Applicant refined the *in vitro* equivalence study protocol and made the following minor technical adjustments to the original protocol proposed in the pre-IND meeting package: (1) sample size changed from 16 to 30 blood samples; (2) use of heparin as anticoagulant instead of acid citrate dextrose (ACD); and (3) addition of Hespan® or hetastarch [6% Hydroxyethyl starch (HES)] in the blood collection tube as a sedimentation agent. See the protocol steps for radiolabeling of leukocytes for the *in vitro* BE study in p. 11-12 of Dr. Delvadia's review.

Percent labeling efficiency (%LE) was calculated by: $\%LE = [A/(A+B)]\times 100$
Where A: Radioactivity of the cells (measured after leukocytes were treated with reconstituted Tc 99m exametazime centrifuged, precipitated and separated in tube A) and B: Radioactivity of the supernatant separated in tube B
The %LE data for the test and reference drug were subjected to equivalency test using one-tailed paired t-test at α of 0.05.
The labeled leucocytes sample was tested for cell viability using the trypan blue dye method. The number of cells with blue color (C) and those which have excluded the dye (D) were counted in a hemocytometer.

Percent cell viability was calculated by % cell viability = $(D\times 100)/(C+D)$.
To measure Percent Cell Efflux Radioactivity, the precipitated leukocytes (button) were broken up and re-suspended in 3 ml of supernatant and subsequently divided in four samples centrifuged and separated from supernatant. Radioactivity was measured for the corresponding tubes containing leukocytes (E) and supernatant (F).

Percent cell efflux radioactivity (%CER) was calculated by: $\%CER = (F\times 100)/(E+F)$.
Based on the %CER vs time profile, Cmax and AUC (trapezoidal method) were calculated and used for statistical *in vitro* BE analysis comparing the test and the reference drug.
Dr. Satish Misra (statistician, CDER/OTS) was consulted to assess the data pooling for both %LE and %CER (C_{max} and AUC) across both reference and test drug. In the statistical review dated 3/31/2017 in DAARTS, Analysis of Variance (ANOVA) in SAS software, determined that %LE and %CER (C_{max} and AUC) can be pooled as there is not significant effect of the reference drug lot # and test lot # in fast and fed state. The same conclusion was reached by the biopharmaceutics reviewer by performing statistical

analysis using Phoenix software. Refer to the biopharmaceutics review p. 24-26. In conclusion, the proposed product is bioequivalent to the reference drug, Ceretec™, with respect to two clinically relevant *in vitro* endpoints, % labeling efficiency (%LE) and % cell efflux radioactivity (%CER – C_{max} and AUC).

C. Special Product Quality Labeling Recommendations (NDA only)

The tradename "DRAX Exametazime" is under review at this time. The established name is: "Kit for the preparation of tecnetium Tc 99m exametazime for leukocyte labeling (b) (4)

The reconstitution procedure and radiolabeling of leukocytes is supported by CMC data (see drug product review p. 37).

D. Final Risk Assessment

Initial Risk Identification			**Review Assessment**		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Radionuclidic identity/purity	Tc 99m (b) (4)	<25 Low	Tc 99m eluted from approved generator	<25 Acceptable	None
Radiochemical identity/purity	Tc 99m (b) (4)	<25 Low	Eluate complies to USP monograph for [Tc 99m] (b) (4)	<25 Acceptable	None
Chemical purity (exametazime)	(b) (4) Limit radio-labeling of related substance	<60 Mode-rate	Controlled by specs. (b) (4) ≤ (b) (4)% Imp. A ≤ (b) (4)% (b) (4) ≤ (b) (4)% Unsp. Imp. ≤ (b) (4)% Total (b) (4)%	<25 Acceptable	None
Chirality (exametazime)	Route of synthesis	<60 Mode-rate	Enantiomeric excess ± (b) (4)%	<25 Acceptable	None
KIT					
Strength	Sufficient excess for successful radio-labeling	<60	Fill and Cont. Unif. 0.5 mg	<25 Acceptable	None
Appearance	Free of foreign particu-lates	<25	No interferences to radiolabeling reaction from foreign particulates Visual examination	<25 Acceptable	None
Assay, exametazime	As in Strength	<60	Controlled by spec.	<25 Acceptable	None
Reducing agent ($SnCl_2$)	Reducing agent for	>60 High	Controlled by release and stability	<25 Acceptable	None

	Tc 99m successful radio-labeling		specs (b) (4) mg/ml (release)		
(b) (4)	Interfere with radio-labeling	>60 High	Controlled (b) (4)	<25 Acceptable	None
Particulates	Patient safety	>60 High	USP <788>	<25 Acceptable	None
Bacterial Endotoxin	Patient safety	>60 High	USP<85> ≤ (b) (4) EU/ml	<25 Acceptable	None
Sterility	Patient safety	>60 High	USP<70>	<25 Acceptable	None
Tc 99m exametazime					
Radiochemical purity (RCP)	RCP sufficient for imaging	<60	≥ (b) (4) % per USP ≤ % other Tc species	<25 Acceptable	Applicant agreed to test 10 batches post approval and set RCP: Tc 99m exametazime ≥ (b) (4) % and radiolabeled WBC ≥ (b) (4) %
pH	Should be as ref. drug	<60	Limit (b) (4)	<25 Acceptable	None
Appearance	Patient safety	<60	Free of particulates Visual examination	<25 Acceptable	None
Endotoxin	Patient safety	>60 High	Controlled by components specs USP<85> ≤ (b) (4) EU/ml	<25 Acceptable	None
Sterility	Patient safety	>60 High	Post-release testing USP<71>	<25 Acceptable	None

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BIOPHARMACEUTICS

Product Background

NDA/ANDA: NDA-208870-ORIG-1

Applicant Name: Jubilant DraxImage Inc.

Type of NDA: 505(b)(2) Submission

Drug Product Name: Kit for the Preparation of Technetium (Tc 99m) Exametazime (b) (4)

Dosage Form: Lyophilized (b) (4)

Strength: 0.5mg of Exametazime / vial

Route of Administration: Intravenous

Reference Drug: NDA 019829 (CERETEC™; Kit for the Preparation of Technetium Tc 99m Exametazime Injection; Approved on Dec 30, 1988)

NDA 208870 is submitted as a 505(b)(2) application for the use of kit for the preparation of technetium Tc 99m exametazime (b) (4) as a radioactive diagnostic agent indicated for white blood cell (WBC; Leukocytes) labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease.[1] The Applicant relies for the approval of this NDA on FDA's previous finding of safety and efficacy for the reference drug Ceretec™.[2] The reference drug, Ceretec™ by GE Healthcare (N019829), is indicated as an adjunct in the detection of altered regional cerebral perfusion in stroke in addition to the above indication proposed for the current submission.[3] Since the Applicant proposed only the leukocyte labeled scintigraphy indication, (b) (4) as determined by the Agency during the IND (#123604) stage.[4] In the submission dated 07/20/2016 [0001(1)], the proposed labeling by the Applicant included (b) (4)

(b) (4)

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[1] Global Submit – N208870 – 0019(19) dated 03/30/2017. Module 1.14.1.3. Draft Labeling Text – Updated March 30, 2017. (Accessed on March 31, 2017)
[2] Global Submit – N208870 – 0001(1) dated 07/20/2016. Module 1.2. Cover Letter – Initial Submission (July 19, 2016) – Sequence 0001. (Accessed on March 23, 2017)
[3] Drugs@fda – NDA 019829 – Ceretec™ Drug Labeling. (Accessed on March 21, 2017)
[4] DARRTS – IND 123604 – REV-CLINICAL-21(Primary Review) dated 09/18/2014 by Davis, Phillip B. (Accessed on March 21, 2017)
[5] Global Submit – N208870 – 0001(1) dated 07/20/2016. Module 1.14.1.3. Draft Labeling Text – Initial Submission (July 19, 2016). (Accessed on March 23, 2017)

(b) (4)

.[6] The Applicant agreed with the Agency's suggestion and updated the drug labeling (b) (4) for the use as diagnostic agent in intra-abdominal infection and inflammatory bowel disease.

The proposed product is a kit for the preparation of technetium Tc 99m exametazime (b) (4) The kit comprises of: (1) five individual vials of sterile, non-pyrogenic, and lyophilized mixture of exametazime (b) (4) HMPAO; drug substance; Figure 1], stannous chloride dehydrate, and sodium chloride; (2) (b) (4) radiation labels (b) (4) (3) five labeling efficiency/radiochemical purity worksheets; (4) one leukocyte labeling schematic; and (5) one package insert.[1] The lyophilized (b) (4) requires reconstitution with 0.9% NaCl solution containing sodium pertechnetate Tc 99m [obtained on elution of sodium pertechnetate Tc 99m from generator with 0.9% NaCl (b) (4) USP] prior to use.[7] When technetium Tc 99m pertechnetate is added to exametazime in the presence of stannous reductant (b) (4)

[1,7,8] This lipophilic complex, the active moiety, when added to the leukocyte rich plasma prepared from patient's blood sample by a defined protocol provided in the drug labeling (ex-vivo radiolabeling of leukocytes) is taken up by leukocytes (and selectively retained in neutrophils). Leukocytes with trapped labeled drug when re-injected in patients intravenously, *ex vivo* radiolabeled leukocytes localize to intra-abdominal infection sites and serve the diagnostic purpose in scintigraphy.

(b) (4)

This submission includes a request for waiver of *in vivo* bioavailability/bioequivalence (BA/BE) studies comparing the proposed test product and the reference drug, Ceretec™, under the provision of 21 CFR 320.22(b)(1)(i) and (ii).[9] To support the biowaiver request, in addition to evidences meeting 21 CFR 320.22(b)(1) requirements, the Applicant provided

[6] Global Submit – N208870 – 0005(5) dated 09/15/2016. Module 1.11.4. Response to FDA Information Request – dated September 7th, 2016. (Accessed on March 23, 2017)
[7] Global Submit – N208870 – 0001(1) dated 07/20/2016. Module 3.2.P.2. Drug Product. (Accessed on March 23, 2017)
[8] Global Submit – N208870 – 0001(1) dated 07/20/2016. Module 3.2.P.2. Components of the Drug Product. (Accessed on March 23, 2017)
[9] Global Submit – N208870 – 0001(1) dated 07/20/2016. Module 1.12.15. Request for Waiver of In Vivo Bioavailability Studies. (Accessed on March 23, 2017)

physicochemical properties and performed *in vitro* equivalence study on two clinically relevant endpoints % labeling efficiency (% LE) and % cell efflux radioactivity (% CER) comparing the proposed (test) and reference drug (reference, Ceretec™) products.[7,8,10] However, the information submitted in support of the biowaiver request is evaluated as the information for demonstration of bioequivalence and not biowaiver request and the reasoning for this is discussed in detail under the section "***Demonstration of Bioequivalence Based on In Vitro Studies***". The below biopharmaceutics review focuses on the evaluation of the qualitative and quantitative sameness of active and inactive ingredients and comparative physicochemical properties comparing the proposed product and the reference drug, as well as the *in vitro* BE study submitted for the proposed kit for the preparation of technetium Tc 99m exametazime (b) (4) This evaluation can be found under the section "***Demonstration of Bioequivalence Based on In Vitro Studies***".

Review Summary

The Applicant submitted a biowaiver request under the provision of 21 CFR 320.22(b)(1) supported by qualitative and quantitative sameness of active and inactive ingredients, comparative physiochemical properties, and *in vitro* bioequivalence (BE) study for the approval of the proposed Kit for the Preparation of Technetium (Tc 99m) Exametazime (b) (4) As discussed in detail in the review body under the section "**Demonstration of Bioequivalence Based on *In Vitro* Studies**", the above biopharmaceutics information submitted in support of the approval is evaluated as the data supporting the demonstration of bioequivalence [under 21 CFR 320.24(b)(6)] and not biowaiver request due to the presence of *in vitro* BE study. The information submitted by the Applicant demonstrated the qualitative and quantitative sameness of active and inactive ingredients, and physicochemical equivalence with respect to pH, osmolality, density, specific gravity, viscosity, lipophilicity, and enantiomeric excess between the proposed and reference drug product. Further, the *in vitro* BE study conducted by the Applicant with respect to two clinically relevant end points percent labeling efficiency (%LE) and % cell efflux radioactivity [%CER; peak concentration (C_{max}) and area under the curve (AUC)] demonstrated bioequivalence [met the BE criteria of 90% confidence interval of geometric mean ratios of each endpoint being within 80%-125%] between the proposed and reference drug which was confirmed by the analysis in Phoenix software (Build 7.0.0.2535) by the reviewer. The Applicant adequately responded to the three biopharmaceutics information requests during the review cycle.

Based on the comprehensive biopharmaceutics information submitted by the Applicant and confirmation of BE between the proposed and reference drug by the reviewer, the NDA 208870 ***is recommended for Approval*** from a Biopharmaceutics perspective.

[10] Global Submit – N208870 – 0001(1) dated 07/20/2016. **Module 3.2.P.2. RES.MNT.SDY.025 – In Vitro Equivalence Study for the Evaluation of the Labeling Efficiency of the WBC.** (Accessed on March 26, 2017)

List Submissions being reviewed (Table):

SEQUENCE #	SUBMISSION(S) DATE	MODULE #	SUBMISSION DOCUMENT(S) REVIEWED
0001(1)	07/20/2016	1.2	Cover Letter
		1.12.15	Request for waiver of in vivo BA/BE studies
		3.2.P.2	Components of the Drug Product
		3.2.P.2	Drug Product
		3.2.P.2	RES.MNT.SDY.025 - *In Vitro* Equivalence Study
0007(7)	10/31/2016	1.11.4	Response to Filing Review Issues Dated Sep 15, 2016
		3.2.P.2	Appendices – *In Vitro* Equivalence Study
0008(8)	12/19/2016	3.2.P.2	Pharmaceutical Development – *In Vitro* Equivalence Study Datasets
0010(10)	01/19/2017	1.11.4	Response to Biopharmaceutics Information Request dated Dec 05, 2016 and Jan 13, 2017
0011(11)	02/02/2017	3.2.P.1	Description and Composition of the Drug Product
0017(17)	03/08/2017	1.11.4	Response to Information Request dated Mar 02, 2017

Highlight Key Outstanding Issues from Last Cycle: No pending issues (All biopharmaceutics information request (IRs) were addressed in review cycle and discussed in detail under the section "***Demonstration of Bioequivalence Based on In Vitro Studies***").

Concise Description Outstanding Issues Remaining: No pending issues (All biopharmaceutics information request (IRs) were addressed in review cycle and discussed in detail under the section "***Demonstration of Bioequivalence Based on In Vitro Studies***").

BCS Designation

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: *Not Applicable. The proposed product is an injectable solution.*

Bridging of Formulations

Reviewer's Assessment: *The to-be-marketed proposed product is the same as that of the formulation used in in vitro BE study. Therefore, the need of bridging data is not applicable.*

Demonstration of Bioequivalence Based on In Vitro Studies

The Applicant included a biowaiver request of *in vivo* bioavailability/bioequivalence (BA/BE) study for the proposed test product under the provision of 21 CFR 320.22(b)(1)(i) and (ii).[9] To support the biowaiver request, in addition to evidences meeting 21 CFR 320.22(b)(1) requirements, the Applicant provided comparative physicochemical properties and performed *in vitro* bioequivalence study on two clinically relevant endpoints % labeling efficiency (% LE) and

% cell efflux radioactivity (% CER) comparing the proposed (test) and reference drug (reference, Ceretec™) products.[7,8,10]

Though the Applicant has submitted a biowaiver request, the biopharmaceutics review team for this submission is of opinion that since the *in vitro* BE study is submitted in support of demonstration of bioequivalence between the proposed and reference drug, the biowaiver request made under the provision of 21 CFR 320.22(b)(1)(i) and (ii) is not applicable. Further, the *in vitro* BE data submitted for demonstrating bioequivalence between the proposed and reference drug can be evaluated under 21 CFR 320.24(b)(6) which states "Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence". Therefore, the comparative physicochemical properties and *in vitro* bioequivalence study are reviewed under 21 CFR 320.24(b)(6). Additionally, the submitted information on qualitative and quantitative sameness with respect to active and inactive ingredients between the proposed and reference drug is also evaluated as supportive information.

The evaluation on the Applicant's claim of (1) qualitative and quantitative sameness of active and inactive ingredients between the proposed and reference drug; (2) comparative physicochemical properties; and (3) *in vitro* bioequivalence are described below for the assessment of the bioequivalence between the proposed and reference drug.

1. QUALITATIVE AND QUANTITATIVE SAMENESS OF ACTIVE AND INACTIVE INGREDIENTS:

As mentioned above, the Applicant has submitted a biowaiver request under the provision of 21 CFR 320.22(b)(1),[11] and accordingly a drug product's *in vivo* BA/BE is self-evident if the product meets following criteria:

(i) The drug product is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and
(ii) The drug product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application (NDA) or abbreviated new drug application (ANDA).

However, as explained above, the information submitted by the Applicant to support biowaiver request is evaluated in the review as the information in support of the demonstration of bioequivalence between the proposed and reference drug. The qualitative and quantitative sameness of active and inactive ingredients in support of the demonstration of bioequivalence is evaluated below.

[11] 21 CFR 320.22 Criteria for Waiver of Evidence of In Vivo Bioavailability or Bioequivalence (Accessed on March 31, 2017)

The proposed test product and the reference drug according to the Applicant are chemically and pharmaceutically equivalent and both have the same formulation, strength, dosage form, and route of administration.[12] The Applicant states the proposed product is considered to be self-evident since it is a parenteral solution intended for administration by injection after reconstitution and contains the same active and inactive ingredients in the same concentration as the reference drug Cerectec™.[9] Table 1 provides the composition of the proposed drug product prior to lyophilization (1mL), and reconstituted drug product (5mL), as well as the composition of reference drug, Ceretec™ (lyophilized powder composition). Based on Table 1, the proposed drug product is chemically and pharmaceutically equivalent (Parenteral solution after reconstitution) to the reference drug, Ceretec™, and contains the same active and inactive ingredients in the same concentration as the reference drug, Ceretec™. Further based on Ceretec™ drug labeling[3] and the information on the reconstitution provided for the proposed drug product,[1,13] for both the proposed test and reference drug, lyophilized (b) (4) exametazime is reconstituted using approximately 30 mCi of Tc 99m pertechnetate in 5.0 mL sodium chloride (0.9%) injection. This further supports the sameness of the reconstituted drug products across the proposed test and reference drug.

Table 1. Composition of the Proposed Test and Reference (Ceretec™) Drug Products

Ingredients	Composition of the proposed test drug product[13]				Composition of the reference drug product (Ceretec)		Function
	Composition of the drug product per unit (1mL) prior to lyophilization		Composition of the reconstituted drug product (5mL)		Composition of lyophilized Ceretec™ based on Ceretec™ drug labeling[3]	Composition of the reconstituted Ceretec™ (5mL)	
	Amount per vial	%w/w	Amount per vial	%w/w	Amount per vial	Amount per vial	
Active Substance(s)							
Exametazime	0.5mg	0.050%	(b) (4)		0.5mg	(b) (4)	Active ingredient
Tc-Exametazime	-	-			-		Active complex
Excipients							
Sodium chloride	4.5mg	0.446%			4.5mg		(b) (4)
Stannous chloride dehydrate (b) (4)	7.6µg	0.001%			7.6µg		Reducing agent

[12] Global Submit – N208870 – 0001(1) dated 07/20/2016. Module 1.2. Cover Letter – Initial Submission (July 19, 2016) – Sequence 0001. (Accessed on March 26, 2017)
[13] Global Submit – N208870 – 0011(11) dated 02/02/2017. Module 3.2.P.1. Description and Composition. (Accessed on March 26, 2017)

Sterile elute from Tc 99m generator (Tc 99m in 0.9% NaCl) [a,b]	-	-	(b) (4)	-		Forms active complex with Exametazime
Nitrogen	Head space fill	Head space fill		Head space fill		(b) (4)
Total Quantity	(b) (4)	100.000%	(b) (4)	100.000%	-	-

(b) (4)

2. COMPARATIVE PHYSICOCHEMICAL PROPERTIES:

Comparative physicochemical testing was performed on three primary batches of the proposed product (Lot #s 4L263, 5B142, and 5F648 manufactured at commercial scale of (b) (4) and one batch of the reference drug, Ceretec™ (Lot # 12880163).[7] Both the proposed (test) and the reference drug products were reconstituted in normal saline [0.9% sodium chloride (NaCl)] for physicochemical equivalence testing. Though reconstitution is not performed with Tc 99m pertechnetate in 5 mL of NaCl injection USP (0.9%), the reconstitution with only normal saline (without Tc 99m pertechnetate) for physicochemical equivalence testing is relevant since it is used as a diluent for eluting Tc 99m generator which is subsequently employed for reconstituting lyophilized (b) (4) formulation of both the proposed test product and the reference drug. Further, according to this reviewer, it is not practical to measure physicochemical properties of the radiopharmaceutical due to safety concerns. The reconstituted proposed and reference drug products were compared with respect to osmolality, density, specific gravity, viscosity, lipophilicity, and enantiomeric excess. The results in Table 2 indicate that both the proposed and reference drug products are similar with respect to the measured physicochemical attributes. It is noted that products are not compared with respect to relevant physicochemical property, pH, in Table 2. However, the pH information provided in Table 3 was extracted from the Applicant's response to one of the CMC information request[14] and the Ceretec™ drug labeling[3]. The measurement of pH was performed using both normal saline and sodium Tc 99m pertechnetate in normal saline. Based on the results in Table 3, it is evident that pH is not affected by the

[14] Global Submit – N208870 – 0017(17) dated 03/08/2017. Module1.11.4. Response to Information Request dated Mar 02, 2017. (Accessed on March 27, 2017)

presence of Tc 99m pertechnetate and same is expected for other physicochemical properties mentioned in Table 2. The pH of the drug products reconstituted with sodium Tc 99m pertechnetate in normal saline is similar for both the proposed product and reference drug. The physicochemical equivalence is demonstrated for the proposed product based on the results in Table 2 and 3 and the proposed product is expected to have similar safety profile as the reference drug. The reviewer based on the above information agrees with the Applicant that the proposed drug product demonstrates physicochemical equivalence when compared to the reference drug, Ceretec™.

Table 2. Comparison of Physicochemical Attributes Between the Proposed Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4) and the Reference Drug, Ceretec™

Kit for the Preparation of Technetium Tc99m Exametazime (b) (4)					
Test Description	Manufacturer	Jubilant DraxImage			GE Healthcare
	Lot Number	4L263	5B142	5F648	12880163
Osmolality		22 mOsm/kg	21 mOsm/kg	29 mOsm/kg	23 mOsm/kg
Density		1.010 g/mL	1.007 g/mL	1.008 g/mL	1.007 g/mL
Specific Gravity		1.002	1.000	1.000	0.999
Viscosity		1.00 cSt	1.01 cSt	1.01 cSt	1.02 cSt
Lipophilicity (Partition Coefficient in Octanol)	2 min[4]	1.1	1.4	1.4	1.4
	30 min[4]	0.9	1.0	1.0	1.1
Enantiomeric Excess		1.1%	1.2%	0.7%	0.8%

Note 4: Post-reconstitution time

Table 3. pH Measurement on the Proposed Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4) and the Reference Drug, Ceretec™

Post-reconstitution time	Proposed Product (Lot # 4L263)	Proposed Product (Lot # 5B142)	Proposed Product (Lot # 5F648)	Reference Drug, Ceretec™ from GE Healthcare
Normal Saline				
2 minutes	9.4	9.4	9.4	-
30 minutes	9.3	9.4	9.4	-
Sodium Tc 99m Pertechnetate				
2 minutes	9.4	9.4	9.4	9.0-9.8*
30 minutes	9.4	9.4	9.3	
* From Ceretec™ Drug Labeling[3]				
Note. The drug product pH specification for the proposed drug product is (b) (4) for both batch release and stability[15] (b) (4)				

[15] Global Submit – N208870 – 0001(1) dated 07/20/2016. Module 3.2.P.5.1. Specification(s). (Accessed on March 27, 2017)

3. *IN VITRO* BIOEQUIVALENCE STUDY:

An *in vitro* bioequivalence study assessing WBC radiolabeling efficiency was submitted as additional evidence of demonstration of equivalence between the proposed product and the reference drug, Ceretec™. The kit of the preparation of Tc 99m exametazime (b) (4) has been developed for *ex-vivo* radiolabeling of autologous WBC to detect sites of infection. The radiolabeled WBC when reinjected to the patient, is localized to the intra-abdominal infection and inflammatory bowel disease sites. The radiolabeling of WBC occurs due to the uptake of the lipophilic complex Tc 99m – exametazime when added to leukocyte rich plasma prepared from the patient blood samples. The active lipophilic complex Tc 99m – exametazime is formed on reconstitution of lyophilized powder of the kit with normal saline containing Tc 99m obtained on elution of Tc 99m from generator with 0.9% NaCl for injection, USP. In order to capture the sameness in the above labeling mechanism of WBC, the Applicant proposed under PIND 123604 (Meeting dated Sep 24, 2014) to submit *in vitro* bioequivalence (BE) study to support the biowaiver request in addition to meeting the requirements under the provision of 21 CFR 320.22(b)(1).[16] In the meeting package dated Sept 28, 2015 and Oct 15, 2015, the Applicant submitted the detailed *in vitro* BE protocol and proposed % labeling efficiency (%LE) and % cell efflux radioactivity [%CER] as the metrics to address bioequivalence. The Agency advised the Applicant by written responses:[17] (1) to collect %CER data over multiple time points to calculate and use area under the curve (AUC) as the endpoint for *in vitro* equivalence assessment; (2) to use two one-sided t-test (TOST) procedure with 90% confidence interval (CI) around the geometric mean ratio of products for each endpoint to conclude BE instead of the proposed paired t-test with null and alternative hypotheses to support the claim of bioequivalence; and (3) to provide power calculations (80% to 90%) and relevant sample sizes based on varied estimates of the variability in %LE and %CER. The Applicant provided responses to some of the above comments in the response letter dated May 16, 2016.[18] In the NDA submission, the Applicant refined the *in vitro* equivalence study protocol and made the following minor technical adjustments to the original protocol proposed in the PIND meeting package: (1) sample size changed from 16 to 30 blood samples; (2) use of heparin as anticoagulant instead of acid citrate dextrose (ACD); and (3) addition of Hespan® or hetastarch [6% Hydroxyethyl starch (HES)] in the blood collection tube as a sedimentation agent. The following briefly describes the steps/protocol for *in vitro* BE study. Details of the protocol/steps (RES.MNT.SDY.025, Version 02) can be accessed at the cited reference.[10]

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[16] Global Submit – N208870 – 0001(1) dated 07/20/2016. **Module 1.12.1. Type B Meeting Dated Sep. 24, 2014 – Meeting Minutes.** (Accessed on March 28, 2017)

[17] Global Submit – N208870 – 0001(1) dated 07/20/2016. **Module 1.12.1. Type C Meeting – Guidance Response Dated Dec 4, 2015.** (Accessed on March 28, 2017)

[18] Global Submit – N208870 – 0001(1) dated 07/20/2016. **Module 1.12.1. Response to the Written Responses Letter Dated May 16, 2016.** (Accessed on March 28, 2017)

***In Vitro* BE Study Steps/Protocol:**

(1) Blood samples from thirty (n=30) healthy adult donors (male or female; 21-45 years of age) in well hydrated fasted state (n=15) and fed state (n=15 donors on standardized meal) were aseptically withdrawn to isolate WBCs (Note. Three blood samples were excluded in the evaluation, since the blood draw occurred prior to sign-off of the final study protocol; Therefore n=27 donors considered for *in vitro* BE analysis as this sample size was considered adequate to obtain statistically meaningful equivalence data; n=27 provided power of >0.8[7]).

(2) Blood sample (40mL) from each healthy adult donor was added to 60 mL syringe containing 2mL of Heparin and 8mL of Hespan and gently mixed for 2 minutes. This step was repeated three times for each donor to obtain four samples to perform 4 labeling studies using **two lots of the proposed product (Lot #s 5B142, and 5F648) and two lots of the reference drug or two reference drug samples of the same lot (Lot #s 13053380, and 12880163)**. Blood samples were transported to the labeling facility where the number of WBC in each sample was determined using a hemocytometer and radiolabeling was performed.

(3) On sedimentation of red blood cells (RBCs), leukocyte rich plasma (LRP) was collected in a centrifuge test tube (WBC tube) and centrifuged at 400-450g for 5 minutes. Leukocyte poor plasma (LPP, supernatant) was transferred to another centrifuge tube without disturbing the white cell button.

(4) The white cell button in WBC tubes was gently suspended in 1 mL of NaCl for injection USP (0.9%). The following were added to the WBC button in succession (a) 9mL sterile water, (b) 2mL of 5% NaCl, and (c) 10 mL of 0.9% NaCl, and swirled the tube for 5-30 seconds. The WBC tubes were centrifuged at 400g for 5-7 minutes and the supernatant lysis wash was transferred to the waste tube and the WBC button was gently resuspended in 1.5mL of 0.9% NaCl. It was ensured button is broken up.

(5) The lyophilized (b) (4) of the proposed drug product and the reference drug was reconstituted with approximately 30 mCi of Tc 99m pertechnetate in 5mL of sodium chloride injection (0.9% NaCl). **Radiochemical purity** (RCP) test of the reconstituted drug products was performed and recorded to ensure at least 80% of the radiochemical purity.

(6) A 10µL of the sample from the WBC tube (final product of step 4) was withdrawn to which was added 657 µL of 0.9% NaCl and cells were uniformly suspended for WBC counting in a hemocytometer. The **WBC counts** available for radiolabeling for each

donor (4 tubes/donor) were recorded [Total WBCs available for radiolabeling = (total number of cells counted/4) × 66.7 × 10,000 = WBC/mL × 1.49].

(7) The prepared radiopharmaceutical (product of step 5) was added to the WBC tube (final product of step 4) and WBCs were incubated at room temperature for 15 min with swirling every 5 minutes. The supernatant was separated and collected in wash tube [LPP wash tube] and the labeled WBCs were retained in the WBC tubes. Radioactivity associated with WBC tube (A) and LPP wash tube (B) was measured by energy calibrated radioactivity detector for each donor (4 measurements for both A and B per donor; one measurement for each lot/sample of the test and reference drug) and **percent labeling efficiency (%LE)** was calculated by %LE = [A/(A+B)]×100. The %LE data for the test and reference drug were subjected to equivalency test using one-tailed paired t-test at α of 0.05.

(8) The labeled WBC sample was tested for cell viability using trypan blue dye method. The number of cells with blue color (C) and those which have excluded the dye (D) are counted in hemocytometer. The **percent cell viability** was calculated by % cell viability = (D×100)/(C+D).

(9) For measurement of the % cell efflux radioactivity, the labeled WBC is resuspended in 3 mL of LPP obtained from step 3 and the button is broken up. Five hundred microliter aliquot from the above suspension is withdrawn and placed into four labeled test tubes (Table 4). One mL of LPP is added to each of the four labeled test tubes and the mixture incubated at 37˚C for the predefined time (Table 4). At the end of each incubation time, the respective tube was centrifuged at 450g for 5 minutes to separate supernatant. Supernatant was transferred to corresponding supernatant test tubes. Radioactivity was measured for both the tubes containing WBC (E) and supernatant (F) for each time point and both the test and reference drug. The **percent cell efflux radioactivity (%CER)** was calculated by %CER = (F×100)/(E+F). Based on the %CER vs time profile, C_{max} and AUC (trapezoidal method) were calculated and used for statistical *in vitro* BE analysis comparing the test and the reference drug.

Table 4. Experiment Design on the Measurement of Efflux of Radioactivity from Labeled WBC

Test Tube No.	1	2	3	4
Tc-99m Labeled Cells (µL)	500	500	500	500
LPP (mL)	1	1	1	1
37°C Incubation (minutes)	15	90	180	240

Biopharmaceutics Information Requests (IRs):

During the review cycle, three rounds of biopharmaceutics information request were made and are briefly described below.

Biopharmaceutics Information Request # 1:[19]

During filing review, the lack of some relevant information was identified and the Applicant was requested the following information in the filing communication letter to continue reviewing the submission:

(a) Submit the complete set of data and results (i.e., Appendices containing individual results referenced in the study result document) on radiochemical purity, WBC counts, %LE, %cell viability, and %CER generated from the in *vitro BE* study protocol;

Applicant's Response and Reviewer's Evaluation: The Applicant submitted Appendices containing individual results; however, all of the Appendices provided were scan copies of the hand written results which were considered not convenient for exporting the data into software for confirming the Applicant's statistical BE analysis. ***The Applicant's response is not adequate.***

(b) Rationale on the use of expired reference drug lot # 12966581 (Expiry date – March 28, 2016, In Vitro testing dates – April 17, 2016 to April 25, 2016 for blood samples # 22 to 27);

Applicant's Response and Reviewer's Evaluation: The Applicant clarified that the expiry date of 2016MA28 refers to May 28, 2016 and not March 28, 2016 which indicates unexpired reference drug lot was used for in vitro study. ***The Applicant's response is adequate.***

[19] Global Submit – N208870 – 0007(7) dated 10/31/2016. Module 1.11.4. Response to Filing Review Issues Identified Communication dated Sep 15, 2016. (Accessed on March 28, 2017)

(c) Rationale of not using both reference drug lots [13053380 (n=21 donors); 12966581 (n=4 donors); and both lots (n=2 donors)] for blood samples from all donors for *in vitro* equivalence study;

Applicant's Response and Reviewer's Evaluation: The Applicant stated that the reference drug product was available in very limited quantities and 1-2 batches available on the market. Due to this it was not possible to procure large quantities of different batches and was not feasible to conduct study with equal number of lots. However, both batches are released as per the manufacturer's testing specifications, both reference drug lots are the same pharmaceutical products and therefore were considered to be adequate for the in vitro equivalence study purpose. ***The Applicant's response is adequate.***

(d) Submit *in vitro* equivalence analysis by batch (i.e., comparing each test lot to each reference drug lot) or comparing each test lot with reference drug lot # 13053380;

Applicant's Response and Reviewer's Evaluation: The Applicant performed in vitro equivalence analysis by batch i.e., comparing each test and reference drug lot using two sample t-test (at α=0.05) and none of the comparison were significantly different. ***The response is not adequate*** *since the test was performed only for %LE. Additionally, the traditional BE analysis approach was not employed for comparison (i.e., two one-sided t-test statistical analyses on geometric mean ratios of product averages and application of 90% CI approach to conclude bioequivalence)*

(e) Rationale of using blood samples from both groups of subjects for *in vitro* equivalence study and identifying the blood samples from fasted or fed state subjects. The detailed information request and the Applicant responses are available at the cited reference.[19]

Applicant's Response and Reviewer's Evaluation: The Applicant identified the blood samples from fasted or fed state donors. Further, it was stated that inclusion of blood samples from fasted and fed groups of subjects allows demonstration of non-variability of results as function of the fasted/fed state and also represents the usual expected clinical condition of use. ***The Applicant's response is adequate.***

Biopharmaceutics Information Request # 2:[20]

Since responses to biopharmaceutics information request 1(a) and (d) were not adequate as described above, the following information request was sent to the Applicant to continue reviewing the submission:

[20] Global Submit – N208870 – 0008(8) dated 12/19/2016. Module 1.11.4. Response to Information Request dated December 05, 2016. (Accessed on March 28, 2017)

(1) Submit %LE and %CER data in an appropriate format (Table below) and as SAS transport files (.xpt files) for review purpose and provide definition files for the dataset.

% Labeling Efficiency (Reference and Test Product)

Date	Subject/blood sample	Gender	Age	Fast/Fed state	Typenex Desc.	Product	Vial Lot Number	Radioactivity associated with WBC (A) (units)	Radioactivity associated with LPP Wash (B) (units)	% Labelling Efficiency [(A/(A+B))×100]
	1			Fast	WSF9826	Reference	13055380			
	1			Fast	WTT9680	Test	5B142			
	1			Fast	WPN4676	Reference	13055380			
	1			Fast	WTW0315	Test	5F648			
	2									
	2									
	2									
	2									

% Cell Efflux Radioactivity (Reference and Test Product)

Date	Subject/blood sample	Gender	Age	Fast/Fed state	Typenex Desc.	Product	Vial Lot Number	Time (min)	Radioactivity in cells (mCi) (E)	Radioactivity in supernatant (mCi) (F)	% Cell efflux radioactivity [(F×100)/(E+F)]	C_{max}	AUC_{0-t}
	1			Fast	WSF9826	Reference	13055380	15					
	1			Fast	WSF9826	Reference	13055380	90					
	1			Fast	WSF9826	Reference	13055380	180					
	1			Fast	WSF9826	Reference	13055380	240					
	1			Fast	WTT9680	Test	5B142	15					
	1			Fast	WTT9680	Test	5B142	90					
	1			Fast	WTT9680	Test	5B142	180					
	1			Fast	WTT9680	Test	5B142	240					

Applicant's Response and Reviewer's Evaluation: The Applicant provided %LE and %CER dataset in the requested format along with definition files. ***The Applicant's response is adequate.***

(2) Submit radiochemical purity, WBC count, and cell viability data in the above similar format.

Applicant's Response and Reviewer's Evaluation: The Applicant submitted RCP, WBC, cell viability data in the requested format. ***The Applicant's response is adequate.***

(3) Provide the radioactivity measurement units of the labeling data [WBC (A) and LPP (B)] provided in Table 3A(1) and 3A(2) of submitted Appendices [0007(7) dated 10/31/2016, 3.2.P.2].

Applicant's Response and Reviewer's Evaluation: The Applicant stated that the radioactivity measurement unit is millicurie (mCi). ***The Applicant's response is adequate.***

(4) It is noted that, though %labeling efficiency data were analyzed using two one-sided t-test, the absolute differences between test and reference were used instead of the test and reference ratio for *in vitro* BE analysis. Therefore, provide the two one-sided t-test statistical analyses for % labeling efficiency and apply 90% confidence interval approach. The acceptance criteria for the ratio of the product averages to conclude bioequivalence should be between 80-125%. Conduct the statistical analysis comparing each test lot to each reference drug lot by the above recommended approach.

Applicant's Response and Reviewer's Evaluation: The Applicant performed in vitro BE analysis as requested comparing each test lot with each reference drug lot. ***The evaluation of this analysis is made later in the review.***

Biopharmaceutics Information Request # 3:[21]

During review, it was noted that %CER data in Table 2 of the response to information request dated Dec 05, 2016 [0008(8); 12/19/2016, Module 1.11.4] did not match with the data in .xpt file titled 'cer – Cell Efflux Radioactivity' [0008(8); 12/19/2016; Module 3.2.P.2]. Specifically, the Cmax and AUC values in Table 2 did not represent the %CER reported for a specific subject. For example, Cmax and AUC values for Typenex Desc. WSF9826, WTT9680, and WPN4676 (First 12 rows of Table 2), appear to be switched. Such as, Cmax and AUC values of WSF9826 presented in Table 2 (first 4 rows of Table 2) were actually the values for WPN4676 (Rows # 9-12 of Table 2). This error was also noted in several places of Table 2 (e.g., including but not limited to WSF9881 and WPN5311). The Applicant was requested to correct these error and Table 2. The Applicant responded to the request and updated Table.[21] ***The response is adequate.***

Evaluation of *In Vitro* Bioequivalence (BE) Analysis:

The below portion of the review focuses on the evaluation of the *in vitro* BE data on % labeling efficiency (%LE) and % cell efflux radioactivity (%CER) and confirming the Applicant's conclusion on bioequivalence between the proposed product (test) and the reference drug, Ceretec™ (reference). Table 5 presents radiochemical purity (RCP) results for the proposed product and reference drug lots used in the *in vitro* BE study. The results indicate that all batches meet proposed RCP acceptance criterion of greater than or equal to 80% supporting the appropriateness of the use of radiopharmaceutical prepared from proposed test and reference drug batches for WBC radiolabeling.

Table 5. Radiochemical Purity (RCP) for the Proposed Product and Reference Drug, Ceretec™ Lots used in *In Vitro* BE Study

Product	Lot #	# of Samples	Minimum RCP	Maximum RCP	Average RCP	%RSD
Proposed Test	5F648	27	82.6	97.6	92.2	3.26
	5B142	27	81.1	98.9	91.2	4.42
Reference Drug, Ceretec™	13053380	44	81.1	99.7	92.5	4.29
	12966581	10	90.4	93.6	91.3	1.16

[21] Global Submit – N208870 – 0010(10) dated 01/19/2017. Module 1.11.4. Response to Information Request dated December 05, 2016 Updated for Request dated Jan. 13, 2017. (Accessed on March 28, 2017)

Percent Labeling Efficiency (%LE):

In the initial submission dated 07/20/2016, although the Applicant performed BE evaluation on %CER using the geometric mean ratio of test and reference for both ln-transformed C_{max} and AUC and applied 90% confidence interval approach (80%-125%) for both of these %CER endpoints in conclusion of bioequivalence, the same was not performed for %LE. Instead, absolute differences between test and reference were used for %LE evaluation. In response to the information request (Biopharm IR # 2) mentioned above, the Applicant conducted BE analysis on %LE based on the ratio approach using geometric mean of ln-transformed data and 90% CI interval (80%-125%)[21] which is evaluated below. Table 6 provides the bioequivalence analysis performed by the Applicant for the endpoint %LE comparing each test lot with each of the reference drug lots as requested in biopharmaceutics IR # 2 and since the 90% CI is within the BE acceptance criterion of 80%-125% for each of the comparisons, *in vitro* bioequivalence between the proposed product and the reference drug was concluded by the Applicant.

Table 6. *In Vitro* Bioequivalence Analysis for %LE Endpoint Comparing Each Proposed Test Lot to Each Reference Drug Lot (By Applicant)[21]

	Sample Size	Geometric Mean Test Product	Geometric Mean RLD	Ratio (Test Product /RLD)	Acceptance criteria (80% - 125%)	90% CI (Lower)	90% CI (Upper)
Sample 1 RLD Batch 12966581 & Test Product 5B142	6	57.508	56.824	1.012	Pass	0.990	1.031
Sample 2 RLD Batch 12966581 & Test Product 5F648	4	57.078	58.956	0.968	Pass	0.927	1.008
Sample 3 RLD Batch 13053380 & Test Product 5B142	21	48.660	54.198	0.898	Pass	0.823	0.978
Sample 4 RLD Batch 13053380 & Test Product 5F648	23	51.766	50.451	1.026	Pass	0.981	1.132

To confirm the Applicant's conclusion on bioequivalence between the proposed and reference drug products with respect to %LE and %CER (C_{max} and AUC), the reviewer pooled the data across reference drug and proposed product batches i.e., pooled %LE data across reference drug batches (Lot #s 12966581 and 130533800) and test batches (Lot #s 5B142 and 5F648) to perform the BE analysis in Phoenix software (Build 7.0.0.2535). Initially, the Applicant was requested (Biopharm IR # 2) to perform BE analysis by batch due to the observed variability across reference drug batches. However, during the review cycle, it was decided to pool %LE and %CER data for bioequivalence analysis due to the following reasons and justifications:

(1) The *in vitro* study is unbalanced i.e., unequal sample size when samples separated by the reference drug lot used (Table 7). However, when data of two reference drug lots pooled, the sample size is equal cross both the test and reference drug.

Table 7. Sample Size Information on the Proposed Test and Reference Drug Lots Used for *In Vitro* Bioequivalence Study

Lot #s	Sample Size for # of Blood Samples Radiolabeled with Respective Lots	Comments*	Total Sample Size for Test and Reference Drug
Test Lot # 5B142	27	• Blood sample from n=27 donors radiolabelled once with this lot (n=27)	54
Test Lot # 5F648	27	• Blood sample from n=27 donors radiolabelled once with this lot (n=27)	
Reference Drug Lot # 13053380	44	• Blood sample from n=21 donors radiolabelled twice separately with this lot (n =21×2 = 42) • Blood sample from n=2 donors radiolabelled once with this lot (n=2) • Total n = 42 + 2 = 44	54
Reference Drug Lot # 129665810	10	• Blood sample from n=4 donors radiolabelled twice separately with this lot (n = 4×2 = 8) • Blood sample from n=2 donors radiolabelled once with this lot (n=2) • Total n = 8 + 2 = 10	
* Note. As mentioned before, blood sample from each donor was divided in four tubes and each tube blood sample treated to harvest leukocytes. Leukocytes in two tubes radiolabeled with each lot of the test product and in two tubes radiolabeled with either same lot of reference drug or two different lots of reference drug			

(2) Considering the example of first raw in Table 6, the sample size used by the Applicant for comparison of the reference drug batch 12966581 and test batch 5B142 is n=6. However, the actual sample size is as provided in Table 8. Therefore, there may be a bias in the selection of the data specifically when two leukocytes samples from the same donor was radiolabelled with the same reference drug lot (e.g., selection of data from n=1 out of n=2 samples for the same blood donor) for the comparison and statistical test (Details in Table 8). Similar was the observation with respect to comparison of the reference drug lot 12966581 with test lot 5F648, reference drug lot 13053380 with test lot 5B142, and reference drug lot 13053380 with test lot 5F648.

Table 8. Sample Size for Comparing %LE Across Test Lot 5B142 and the Reference Drug lot 12966581 (Refer Raw 1 of Table 6)

Lot #	Total Sample Size (n)	Sample size (n) considering this reference drug and test lot used for the blood sample from the same donor*	Sample size for comparison by Applicant
Reference Drug Lot # 12966581	10	10 (8+2) Donor 22 to 25: n=8; Donor 26 to 27: n=2	6 (4+2) Donor 22 to 25: n=4 Donor 26 to 27: n=2
Test Lot # 5B142	27	6 (4+2) Donor 22 to 25: n=4; Donor 26 to 27: n=2	6 (4+2) Donor 22 to 25: n=4 Donor 26 to 27: n=2
* Two leukocyte samples from **blood donor # 22 to 25** were radiolabelled with **reference drug lot 12966581 (n = 4×2 = 8)**, the other two leukocyte samples from these donors radiolabeled with each **test lot 5B142 (n = 4×1 = 4)** and 5F648 (n = 4×1 = 4) Each of the four leukocyte sample from **blood donor # 26 to 27** was radiolabeled with **reference drug lot 12966581 (n = 2×1 = 2)**, reference drug lot 13053380 (n = 2×1 = 2), **test lot 5B142 (n = 2×1 = 2)**, and test lot 5F648 (n = 2×1 = 2)			

(3) Based on Figure 2(b), variability in %LE observed as function of reference drug lot 12966581 and 13053380 cannot be attributed to the effect of lot as variability in radiolabeling efficiency is expected due to the following:

a. Subject specific leukocyte/WBC counts at the time of blood sampling from the donor (supported by 46% variability observed in WBC count; Table 9)
b. Sensitive nature of the labeling technique and use of low centrifugal force to prevent damage to leukocytes that may lead to WBC loss in leukocyte poor plasma and subsequently cause variability in the number of WBCs available for labeling after extracting leukocytes from blood plasma (supported by 46% variability observed in WBCs available for radiolabeling; Table 9)

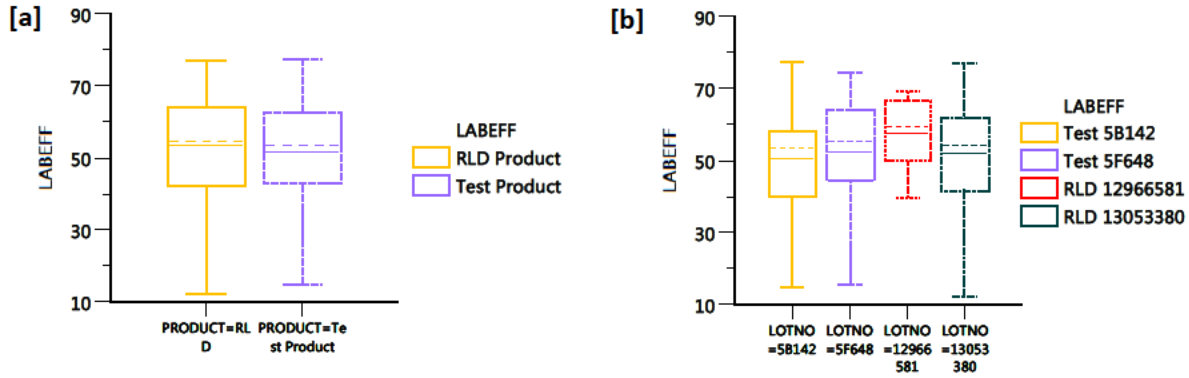

Figure 2. Box Plot for %LE (LABEFF) by (a) Product (Reference Drug and Test); and (b) Reference Drug and Test Lots [Plotted by Biopharmaceutics Reviewer in Phoenix]

Table 9. Observed Variability in WBC Count and WBCs Available for Radiolabeling

Statistics	WBCN (Total Number of WBC Counted)	CELLN (Total WBCs available for Radiolabeling)
N	108	108
Mean	359.60	89345777
Std Dev	165.18	41039729
%CV	45.93	45.93

Further, two reference drug lots are released on the market based on the manufacturer's meeting all batch release requirements and variability due to lot # is therefore not expected supporting the pooling of data across two reference drug batches. This along with the above information and statistical justification discussed below (Point # 5) supports pooling of %LE data across two reference drug batches. When data pooled across two reference drug batches, variability is very similar to two test batches [Figure 2(a); when data pooled for two test lots]

(4) The pooling of data for the proposed test batches (Lot # 5B142 and 5F648) is also justified based on similar variability observed across these batches [Figure 2(b)] and statistical justification discussed below (Point # 5).

(5) Statistical test indicating the absence of the significant effect of lot # on %LE as well as the absence of significant effect of lot # on %LE for labeling performed using samples from blood donors on fasted and fed state.

To justify the data pooling for both %LE and %CER (C_{max} and AUC) across both reference drug and test lots, Dr. Satish Misra (a statistician from DB1\OB\OTS\CDER) who is part of the review team, was consulted. The detailed results are provided in the statistical report[22] as Attachment 1 under the section "Attachments". According to the statistical report [Analysis of Variance (ANOVA) in SAS software)], the %LE and %CER (C_{max} and AUC) can be pooled as there is not significant effect of the reference drug lot # and test lot # on %LE and %CER data. However, the effect test on fast/fed in the statistical report analyzes whether there is effect of fast or fed condition but does not address whether two reference drug lots and two test lots used for blood samples collected from donors in fasted state can be pooled. Similarly, the same is not addressed for the fed state. However, this reviewer was able to address the above question by ANOVA test in JMP 11 statistical software (Detailed results provided in Attachment from Table A1 to A3) which supports the pooling of %LE and %CER (C_{max} and AUC) data across two reference drug batches and two test batches for

[22] DARRTS – NDA 208870 – REV-BIOMETRICS-21(Primary Review) dated 03/31/2017 by Misra, Satish C. (Accessed on March 31, 2017)

both fasted and fed states (Figure 3). According to the statistician, there is no significant interaction between the Lot # and Fast/Fed Condition for the test and reference drugproducts (Attachment A1) which was the same conclusion when statistically tested by this reviewer in JMP 11.

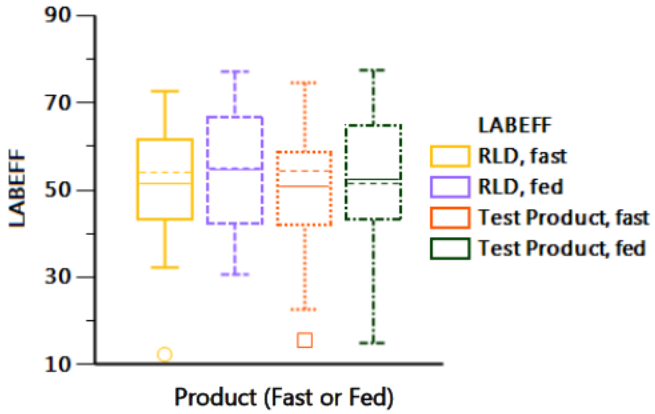

Figure 3. Box Plot for %LE by Product Lot and Fast/Fed Condition [Plotted by Biopharmaceutics Reviewer in Phoenix]

Based on analysis in Phoenix (Build 7.0.0.2535; two one-sided t-test, geometric mean ratio and 90% confidence interval approach) performed by this reviewer, the proposed test product is bioequivalent to the reference drug with respect to %LE (Table 10) and confirms the Applicant's bioequivalence conclusion. Additionally, the BE analysis was performed separately for the fasted and fed state, the proposed test and reference drug are bioequivalent under these conditions as well (i.e., blood sample collected from donors under fasted state and fed state for ex-vivo WBC radiolabeling).

Table 10. *In Vitro* Bioequivalence Analysis for %Labeling Efficiency (%LE) Endpoint Comparing Proposed Test and Reference Drug in Phoenix 7 (By Biopharmaceutics Reviewer)

Sample Size by Lot #	Sample Size of Test & Refrrence Drug	Geometric Mean Reference Drug	Geometric Mean Test	Geometric Mean Ratio (Test/Reference Drug)	90% Confidence Interval	Acceptance criteria (80% -125%)
Reference Drug (13053380) = 44 Reference Drug (12966581) = 10 Test (5F648) = 27 Test (5B142) = 27	54	51.16	49.12	96.02	(88.30, 104.42)	Pass
Fasted State						
Reference Drug (13053380) = 17 Reference Drug (12966581) = 7 Test (5F648) = 12 Test (5B142) = 12	24	49.03	48.23	98.38	(84.99, 113.88)	Pass
Fed State						
Reference Drug (13053380) = 27 Reference Drug (12966581) = 3 Test (5F648) = 15 Test (5B142) = 15	30	52.93	49.85	94.17	(85.22, 104.06)	Pass

Percent Cell Efflux Radioactivity (%CER)

Percent cell efflux radioactivity (%CER) is the measurement of efflux of radioactivity from leukocytes. "After radiolabeling, Tc 99m-HMPAO lipophilic complex is converted inside the cells mainly to a hydrophilic complex by reducing agents such as glutathione, thus preventing its free passage through the cell membrane. However, with time this conversion is reversible and some Tc 99m-HPMACO as well as some free Tc 99m, can be released by leucocytes. Damaged leukocytes may release more radioactivity and more quickly than intact cells."[23] A question whether %CER is clinically relevant and meaningful endpoint was discussed with the OND review team during internal OPQ-OND meeting. Based on the discussion, cell metabolism along with mechanism described above can cause dissociation or efflux of radioactivity from WBC and may lead to different distribution pattern when compared to the radiolabeled cells that are intact. The distribution pattern may differ between the test and reference products as function of differences in drug product attributes. %CER measurement can be considered a surrogate for cell viability and represents the property of the whole labeled cell (would represent both the cell and

[23] Global Submit – N208870 – 0001(1) dated 07/20/2016. Module 3.3. Literature References – de Vries 2010. Guidelines for the labeling of leucocytes with 99mTc-HMPAO. (Accessed on March 29, 2017)

drug product) rather than of a cell or a drug itself. Hence, %CER is also a meaningful and clinical relevant parameter for *in vitro* BE analysis comparing the proposed test and reference drug.

As communicated during IND, the Applicant included analysis on %CER endpoint that included two parameters – C_{max} (measurement of peak radioactivity) and area under the curve (AUC, measurement of extent of radioactivity associated with the radiolabeled leukocytes). The duration of radioactivity measurements (15min, 90min, 180min, and 240 min) was appropriately justified by the Applicant in response to the FDA comments during IND.[18] According to the Applicant, efflux tends to be more rapid immediately after labeling and hence an earlier time point of 15 min was included. Whereas, the product is typically infused within 4 hrs of labeling, this justified the selection of upper bound of 240 min. The collection of data beyond 240 min was not considered since cells begin to die and hence is irrelevant to look efflux past 240 min. Two additional time points of 90 min and 180 min were included in the protocol to better define AUC. The Applicant's approach is adequate.

In the initial submission dated 07/20/2016, the Applicant performed BE evaluation on %CER using the geometric mean ratio of test and reference for both ln-transformed C_{max} and AUC and applied 90% confidence interval (CI) approach (80%-125%) for both of these %CER endpoints (Table 11). According to the Applicant, for both C_{max} and AUC, 90% CI for test to reference drug ratio met the acceptance criteria of 80%-125% and hence bioequivalence was concluded between the test and reference drug for %CER endpoint. The analysis was performed by batch or lot # of test i.e., N=27; and the same sample size was chosen for the reference drug (Table 11). However, with respect to reference drug, this cannot be considered appropriate as there may be a bias in selection of N=27 radiolabeling results out of N=44 for the reference drug lot # 13053380, and N =10 of reference drug lot # 12966581 due to the observed variability in %CER across reference drug and test lots [Figure 4(a) and 4(b)]. The same can be stated on variability for C_{max} and AUC across lots especially for reference drug lots as well as for the reference drug lots when separated by fasted and fed state due to few outliers [Figures 5(b), 5(c), 6(b), and 6(c)]. However, similar to the concern raised for %LE, an argument can be made for %CER that variability is due to subject specific WBC count, the sensitive nature of the technique for labeling and efflux measurement, and use of low centrifugal force to prevent damage to leukocytes that may lead to WBC loss in supernatant which leads to variable %CER-time profiles across samples. Therefore, similar to %LE, %CER data across test lots (5B142 and 5F648) and reference drug lots (12966581 and 13053380) were pooled for BE analysis by this reviewer due to the reasons discussed above as well as statistical justification on the absence of the significant effect of lot# on %CER as well as the absence of the significant effect of lot# on %CER for samples from blood donors on fasted and fed state. (Refer Attachment A1 for statistical report from DB1\OB\OTS\CDER; and statistical analysis performed by this reviewer detailed in Table A2 and A3 of the Attachment for C_{max} and AUC respectively). According to the statistical report

by statistician, for %CER, there is no significant interaction between the Lot # and Fast/Fed Condition for the test and reference drug products (Attachment A1) which was the same conclusion when statistically tested by this reviewer using JMP 11. However, based on the statistical report (refer to Appendix), a significant effect of fast/fed condition is present for both C_{max} (**Reference**: Fast - 33.71, Fed – 38.52 , p-value < 0.05; **Test**: Fast - 33.01, Fed – 39.39, p-value < 0.05) and AUC (**Reference**: Fast – 5915.68, Fed – 6767.01, p-value < 0.05; **Test**: Fast – 5840.38, Fed – 6772.95, p-value < 0.05); however, this comparison is not relevant, since the objective of the analysis is to perform BE evaluation between the proposed test and reference drug separately in fasted and fed state. In addition, as discussed before, in clinical settings, patient can be either on fasted or fed state for diagnosis with the radiolabeled WBC.

Table 11. *In Vitro* Bioequivalence Analysis for %CER Endpoint (C_{max} and AUC) Comparing Each Proposed Test Lot to Each Reference Drug Lot (By Applicant)[10]

%Efflux Radioactivity – JDI Product (Test Lot 1) vs Ceretec (N = 27)

Dependent Variable	Geometric Mean JDI Lot 5F648	Geometric Mean Ceretec	Ratio (JDI Product/Ceretec)	90% CI Lower	90% CI Upper
ln(C_{max})	35.78	36.23	0.988	0.897	1.087
ln(AUC_{last})	6395.44	6462.19	0.990	0.892	1.098

%Efflux Radioactivity – JDI Product (Test Lot 2) vs **Ceretec** (N = 27)

Dependent Variable	Geometric Mean JDI Lot 5B142	Geometric Mean Ceretec	Ratio (JDI Product/Ceretec)	90% CI Lower	90% CI Upper
ln(C_{max})	36.03	35.38	1.018	0.925	1.121
ln(AUC_{last})	6171.11	6184.70	0.998	0.917	1.086

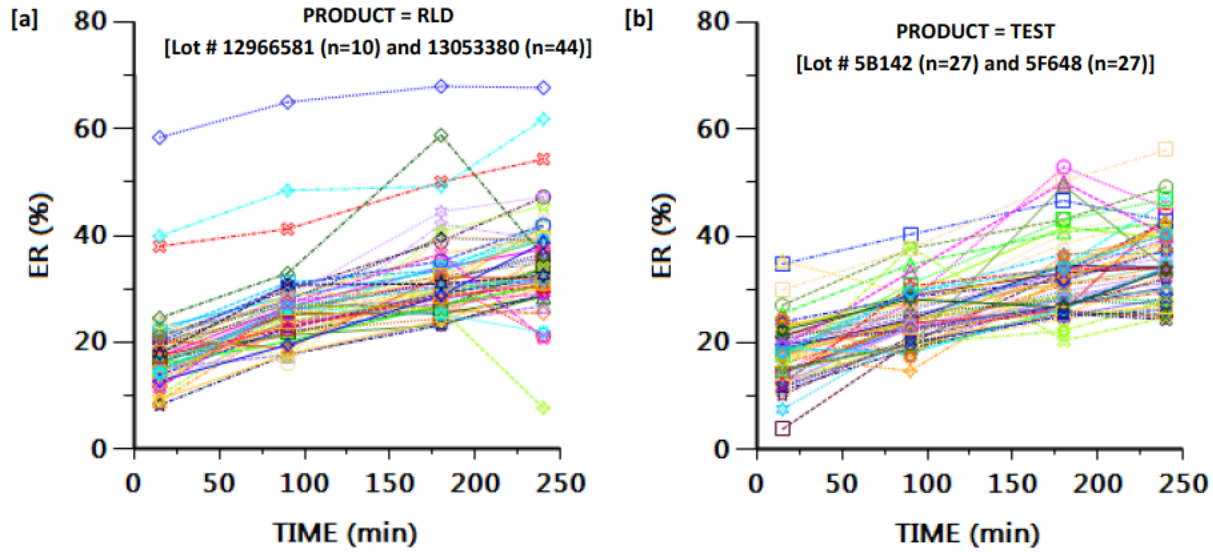

Figure 4. %CER vs Time Curve (a) Reference Drug; and (b) Test [Plotted by Biopharmaceutics Reviewer in Phoenix]

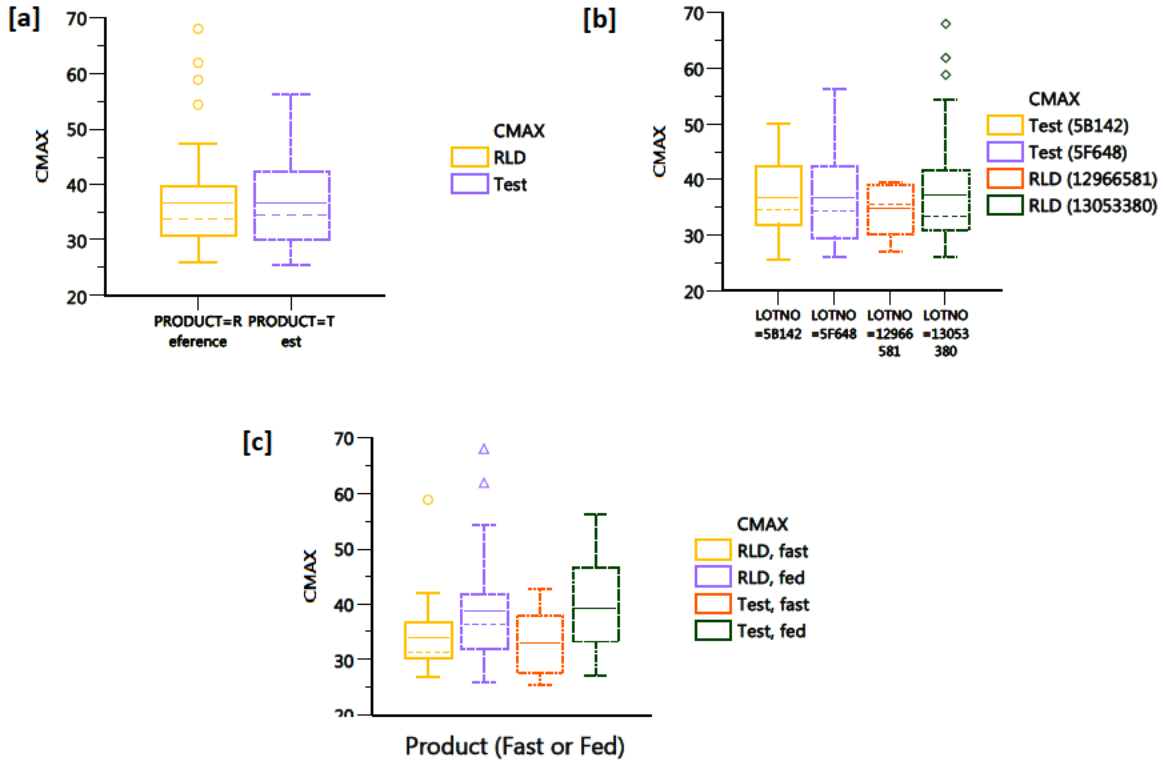

Figure 5. Box Plot for %CER (C_{max}) by (a) Product (Reference Drug and Test); (b) Reference Drug and Test Lots; and (c) Product Lot and Fast/Fed Condition [Plotted by Biopharmaceutics Reviewer in Phoenix]

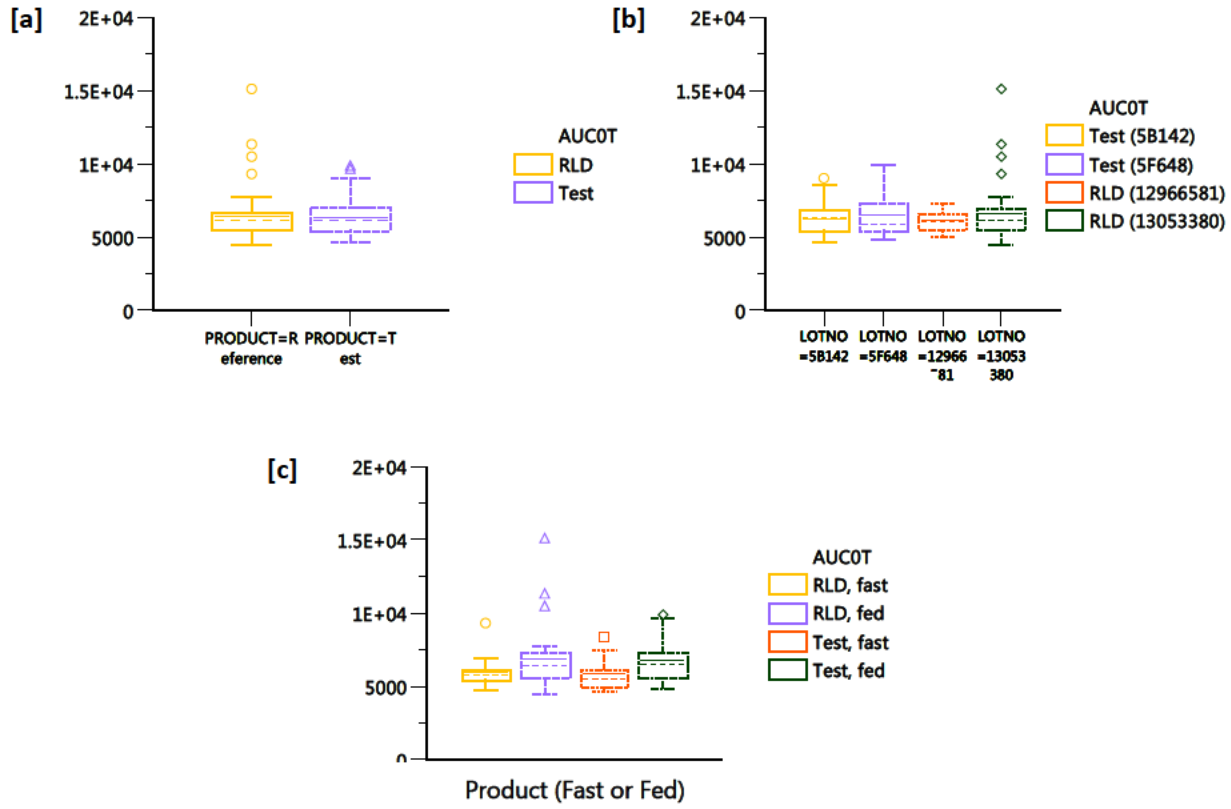

Figure 6. Box Plot for %CER (AUC) by (a) Product (Reference Drug and Test); (b) Reference Drug and Test Lots; and (c) Product Lot and Fast/Fed Condition [Plotted by Biopharmaceutics Reviewer in Phoenix]

To confirm the Applicant's conclusion on equivalence between the proposed and reference drug products for %CER (C_{max} and AUC), the reviewer pooled the data across reference drug and proposed product batches i.e., pooled %CER data across reference drug batches (Lot #s 12966581 and 130533800) and test batches (Lot #s 5B142 and 5F648) due to reasons discussed above to perform BE analysis in Phoenix software (Build 7.0.0.2535, two one-sided t-test, geometric mean ratio and 90% confidence interval approach). According to the analysis in Phoenix, the proposed test product is bioequivalent to the reference drug with respect to %CER (C_{max} and AUC; Table 12) and confirms the Applicant's bioequivalence conclusion. Additionally, the BE analysis was performed separately for the fasted and fed state, the proposed test and reference drug are bioequivalent under these conditions as well (i.e., blood sample collected from donors under fasted state and fed state for ex-vivo WBC radiolabeling; Table 12).

Table 12. *In Vitro* Bioequivalence Analysis for %Cell Efflux Radioactivity (%CER, C_{max} and AUC) Endpoint Comparing Proposed Test and Reference in Phoenix 7 (By Biopharmaceutics Reviewer)

Sample Size by Lot #	Sample Size of Test and Reference Drug	Parameter	Geometric Mean Reference Drug	Geometric Mean Test	Geometric Mean Ratio (Test/Reference Drug)	90% Confidence Interval	Acceptance criteria (80% -125%)
Reference Drug (13053380) = 44 **Reference Drug** (12966581) = 10 Test (5F648) = 27 Test (5B142) = 27	54	C_{max}	35.80	35.91	100.29	(95.28, 105.56)	Pass
		AUC_{0-t}	6305.83	6261.82	99.30	(94.76, 104.06)	Pass
Fasted State							
Reference Drug (13053380) = 16 **Reference Drug** (12966581) = 7 Test (5F648) = 11 Test (5B142) = 12	23	C_{max}	33.41	32.53	97.38	(91.05, 104.15)	Pass
		AUC_{0-t}	5898.23	5762.63	97.70	(92.49, 103.20)	Pass
Fed State							
Reference Drug (13053380) = 28 **Reference Drug** (12966581) = 3 Test (5F648) = 16 Test (5B142) = 15	31	C_{max}	38.12	38.88	102.00	(94.66, 109.92)	Pass
		AUC_{0-t}	6764.48	6744.60	99.71	(93.08, 106.81)	Pass

Reviewer's Assessment: *Adequate*

The demonstration of bioequivalence for the proposed Kit for the Preparation of Technetium (Tc 99m) Exametazime (b) (4) is supported by the following:

(1) The proposed drug product and reference drug, Ceretec™, are chemically and pharmaceutically equivalent and both have the same formulation, strength, dosage form, and route of administration. The proposed drug product contains the same active and inactive ingredients in the same concentration as the reference drug, Ceretec™. This supports the qualitative and quantitative sameness of active and inactive ingredients between the proposed and reference drug product.

(2) Both the proposed product and reference drug, Ceretec™, are similar in physicochemical properties (pH, osmolality, density, specific gravity, viscosity, lipophilicity, and enantiomeric excess).

(3) The proposed product is bioequivalent to the reference drug, Ceretec™, with respect to two clinically relevant *in vitro* endpoints, % labeling efficiency (%LE) and % cell efflux radioactivity (%CER – C_{max} and AUC).

R Regional Information

4. Comparability Protocols

Reviewer's Assessment: *Not Applicable.*

5. Post-Approval Commitments

Reviewer's Assessment: *None.*

6. Lifecycle Management Considerations

None.

List of Deficiencies

Deficiencies – None. All deficiencies or the IRs were addressed during the review cycle and are described in detail in the main body of the review under section "***Demonstration of Bioequivalence Based on In Vitro Studies***".

ONDP-Division of Biopharmaceutics reviewed NDA 208870 and responses to biopharmaceutics information requests. The NDA 208870 is recommended for Approval from a Biopharmaceutics perspective.

Primary Biopharmaceutics Reviewer Name and Date
Poonam Delvadia, Ph.D. (Branch 3\DB\ONDP\OPQ), May 05, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed)
Sandra Suarez Sharp, Ph.D., Acting Team Lead (Branch 3\DB\ONDP\OPQ), May 05, 2017

Appendix

Attachment A1: Statistical Report to Biopharmaceutics Consult Request to DB1\OB\OTS\CDER[22]

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Memorandum to Consult Request from Biopharmaceutics

FROM:	Satish Misra, Ph. D., Primary Statistical Reviewer, DB1
THROUGH:	Jyoti Zalkikar, Ph. D., Secondary Statistical Reviewer, DB1
THROUGH:	Peiling Yang, Ph. D., Tertiary Statistical Reviewer, DB1
APPLICATION #:	NDA 208870
REQUESTED BY:	Poonam R. Delvadia, Ph.D., Biopharmaceutics Reviewer, Branch 3\ONDP\OPQ\CDER\FDA
PRODUCT:	Tc99m Exametazime (b) (4)
SPONSOR:	Jubilant Draximage, Inc.
DATE OF SUBMISSION:	July 19, 2016
PDUFA DATE:	May 19, 2017
EDR LOCATION:	\\CDSESUB1\evsprod\NDA208870\208870.enx

Jubilant DraxImage Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4) is diagnostic radiopharmaceutical for intravenous use. It is indicated (b) (4) for leukocytes labeled scintigraphy as an adjunct in the localization of (b) (4) intra-abdominal infection, inflammatory bowel disease (b) (4) (b) (4)

According to the sponsor, the proposed drug product and the listed drug are chemically and pharmaceutically equivalent. They both have the same formulation, strength, dosage form, and route of administration. The reference listed drug for this application is Ceretec™ manufactured by GE Healthcare and approved under NDA 019829. Ceretec™ is a radiopharmaceutical product used as a radiodiagnostic agent in nuclear medicine, indicated for brain imaging and leukocytes labeled scintigraphy for almost 30 years. Therefore, the active pharmaceutical ingredient in the formulation is not a new chemical entity. No new clinical data were submitted for review.

Branch 3 of the Division of Biopharmaceutics\ONDP\OPQ\CDER\FDA interacted with the reviewer and requested a consult review. The sponsor had submitted analyses which were not considered standard for establishing bioequivalence (BE). An Information Request to the sponsor on 5 December 2015 resulted in the submission of proper data in xpt format and proper analyses. These datasets in requested xpt format and analyses are located in the submission no. 0008 dated 19 December 2016.

Biopharmaceutics Division requested to confirm analyses for % labeling efficiency ((i.e., comparing each test lot with each RLD lot) and % cell efflux radioactivity data by batch (i.e., comparing each test lot with each Reference lot) and by fasted/fed state; and perform two one sided

t-test using geometric mean ratio approach and computing 90% CI. The 90% CI should be within the acceptable range of 80-125%.

These analyses were performed using SAS version 9.4. Analyses for % labeling efficiency and % % cell efflux radioactivity by batch (i.e., comparing each test lot with each RLD/Reference lot) and by fasted/fed state were performed. The results are given in the appendix below. Statistical analyses show that the proposed product and the listed drug are sufficiently similar across batch and food Intake (fast/fed). The data can be pooled.

The data for labelling efficiency (LE) and % cell efflux radioactivity data were analyzed using the approach for the Bioequivalence (BE) data. The ratio of LE for Test Product and the RLD/Reference was compared. A 90% confidence interval was applied, with an acceptance criterion of 80-125%. The results were similar to the sponsor provided results for the 4 tested samples, Test Lot to each RLD/Reference lot. Minor differences in the confidence intervals were noted, however for each comparison, the 90% Confidence Interval is between the acceptance criterion of 80% and 125%. The same was repeated for % cell efflux radioactivity data (CMAX & AUS0t), and the results were similar. The Test Product and the Reference Listed Drug can be considered to be equivalent in terms of labeling efficiency and % cell efflux radioactivity.

The two products demonstrate sufficient similarity between the proposed product and the listed drug. The results support biowaiver.

Appendix

Analysis 1: %labeff -Effect of Product and Food Intake (fast/fed) and interaction RLD product

The GLM Procedure

Class	Levels	Values
LOTNO	2	12966581 13053380
FASTFED	2	fast fed

Number of observations = 54
Dependent Variable: nloglabeff

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.29997829	0.09999276	1.04	0.3830
Error	50	4.80669386	0.09613388		
Corrected Total	53	5.10667215			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.13821243	0.13821243	1.44	0.2362
FASTFED	1	0.14664624	0.14664624	1.53	0.2226
LOTNO*FASTFED	1	0.01511963	0.01511963	0.16	0.6934

Analysis 2: %labeff -Effect of Product and Food Intake (fast/fed) with no interaction for RLD product

Number of observations = 54
Dependent Variable: nloglabeff

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.28485866	0.14242933	1.51	0.2314
Error	51	4.82181348	0.09454536		
Corrected Total	53	5.10667215			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.13821243	0.13821243	1.46	0.2322
FASTFED	1	0.14664624	0.14664624	1.55	0.2187

Analysis 3: %labeff - Effect of Product and Food Intake (fast/fed) and interaction
Test product

The GLM Procedure
Number of observations = 54

Class Level Information

Class	Levels	Values
LOTNO	2	5B142 5F648
FASTFED	2	fast fed

Dependent Variable: nloglabeff

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.10451950	0.03483983	0.28	0.8371
Error	50	6.14579451	0.12291589		
Corrected Total	53	6.25031401			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.02802900	0.02802900	0.23	0.6351
FASTFED	1	0.01447111	0.01447111	0.12	0.7329
LOTNO*FASTFED	1	0.06201939	0.06201939	0.50	0.4808

Analysis 4: %labeff - Effect of Product and Food Intake (fast/fed) with no interaction
Test product

Number of observations = 54
Dependent Variable: nloglabeff

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.04250011	0.02125005	0.17	0.8403
Error	51	6.20781390	0.12172184		
Corrected Total	53	6.25031401			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.02802900	0.02802900	0.23	0.6334
FASTFED	1	0.01447111	0.01447111	0.12	0.7317

Analysis 5: Cmax -Effect of Product and Food Intake (fast/fed) and interaction Reference product

The GLM Procedure
Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	12966581 13053380
FASTFED	2	fast fed

Dependent Variable: nlogcmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.77970545	0.25990182	6.29	0.0004
Error	212	8.75347033	0.04128995		
Corrected Total	215	9.53317577			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.08156990	0.08156990	1.98	0.1613
FASTFED	1	0.68502006	0.68502006	16.59	<.0001
LOTNO*FASTFED	1	0.01311549	0.01311549	0.32	0.5736

Analysis 6: Cmax -Effect of Product and Food Intake (fast/fed) with no interaction for Reference product

Number of observations = 216

Dependent Variable: nlogcmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.76658996	0.38329498	9.31	0.0001
Error	213	8.76658581	0.04115768		
Corrected Total	215	9.53317577			

Analysis 7: Cmax -Effect of Product and Food Intake (fast/fed) and interaction

Reference product

The GLM Procedure - Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	5B142 5F648
FASTFED	2	fast fed

Dependent Variable: nlogcmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	1.57613759	0.52537920	15.18	<.0001
Error	212	7.33819699	0.03461414		
Corrected Total	215	8.91433459			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.00256188	0.00256188	0.07	0.7858
FASTFED	1	1.55794183	1.55794183	45.01	<.0001
LOTNO*FASTFED	1	0.01563388	0.01563388	0.45	0.5023

Analysis 8: Cmax - Effect of Product and Food Intake (fast/fed) -no interaction

Test product

The GLM Procedure - Number of observations = 216

Class Level Information

Source	DF	Sum of Squares
Model	2	1.56050371
Error	213	7.35383087
Corrected Total	215	8.91433459

Dependent Variable: nlogcmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.56050371	0.78025186	22.60	<.0001
Error	213	7.35383087	0.03452503		
Corrected Total	215	8.91433459			

Source	DF	Type I SS	Mean Square	F Value	Pr > F
LOTNO	1	0.00256188	0.00256188	0.07	0.7856
FASTFED	1	1.55794183	1.55794183	45.12	<.0001

Analysis 9: AUC -Effect of Product and Food Intake (fast/fed) and interaction Reference product

The GLM Procedure – Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	12966581 13053380
FASTFED	2	fast fed

Dependent Variable: nlogauc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.73455495	0.24485165	5.76	0.0008
Error	212	9.01493486	0.04252328		
Corrected Total	215	9.74948981			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.08153549	0.08153549	1.92	0.1676
FASTFED	1	0.64197183	0.64197183	15.10	0.0001
LOTNO*FASTFED	1	0.01104764	0.01104764	0.26	0.6108

Analysis 10: AUC -Effect of Product and Food Intake (fast/fed) with no interaction for Reference product

The GLM Procedure - Number of observations = 216

Dependent Variable: nlogauc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.72350731	0.36175366	8.54	0.0003
Error	213	9.02598250	0.04237550		
Corrected Total	215	9.74948981			

Source	DF	Sum of Squares SS	Mean Square	F Value	Pr > F
LOTNO	1	0.08153549	0.08153549	1.92	0.1669
FASTFED	1	0.64197183	0.64197183	15.15	0.0001

Analysis 11: AUC -Effect of Product and Food Intake (fast/fed) and interaction Test product

The GLM Procedure
Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	5B142 5F648
FASTFED	2	fast fed

Dependent Variable: nlogauc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	1.23280956	0.41093652	14.42	<.0001
Error	212	6.04333769	0.02850631		
Corrected Total	215	7.27614725			

Source	DF	Type I SS	Mean Square	F Value	Pr > F
LOTNO	1	0.04598153	0.04598153	1.61	0.2055
FASTFED	1	1.09735735	1.09735735	38.50	<.0001
LOTNO*FASTFED	1	0.08947068	0.08947068	3.14	0.0779

Analysis 12: AUC -Effect of Product and Food Intake (fast/fed) with no interaction for Test product

The GLM Procedure Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	5B142 5F648
FASTFED	2	fast fed

Dependent Variable: nlogauc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.14333889	0.57166944	19.85	<.0001
Error	213	6.13280836	0.02879253		
Corrected Total	215	7.27614725			

Source	DF	Type I SS	Mean Square	F Value	Pr > F
LOTNO	1	0.04598153	0.04598153	1.60	0.2077
FASTFED	1	1.09735735	1.09735735	38.11	<.0001

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/s/

SATISH C MISRA
03/30/2017

JYOTI ZALKIKAR
03/31/2017

PEILING YANG
03/31/2017
Signed for Dr. Hsien-Ming J Hung

Table A1. Effect of Lot # on %Labeling Efficiency (%LE) for both the Proposed Test and Reference Drug Ceretec™ (ANOVA in JMP 11, $\alpha = 0.05$)

Product	Total Sample Size (N)	Fast/Fed	Lot #	Lot # Sample Size ($N_{Lot\#}$)	F Ratio	Prob>F	Conclusion*
%LE (By Product)							
Reference Drug, Ceretec™	54	Fast and Fed	13053380	44	1.3322	0.2537	Not significant
			12966581	10			
Proposed Test	54	Fast and Fed	5B142	27	0.2410	0.6255	Not significant
			5F648	27			
% LE (By Product, and By Fast and Fed)							
Reference Drug, Ceretec™	24	Fast	13053380	17	0.4846	0.4936	Not significant
			12966581	7			
	30	Fed	13053380	27	2.0141	0.1669	Not significant
			12966581	3			
Proposed Test	24	Fast	5B142	12	0	0.9996	Not significant
			5F648	12			
	30	Fed	5B142	15	0.4086	0.5279	Not significant
			5F648	15			
* Prob> F when greater than 0.05 – No significant effect of lot							

Table A2. Effect of Lot # on C_{max} [%Cell Efflux Radioactivity (%CER)] for both the Proposed Test and Reference Drug Ceretec™ (ANOVA in JMP 11, $\alpha = 0.05$)

Product	Total Sample Size (N)	Fast/Fed	Lot #	Lot # Sample Size ($N_{Lot\#}$)	F Ratio	Prob>F	Conclusion*
C_{max} (%CER, By Product)							
Reference Drug, Ceretec™	54	Fast and Fed	13053380	44	0.6497	0.4239	Not significant
			12966581	10			
Proposed Test	54	Fast and Fed	5B142	27	0.0026	0.9592	Not significant
			5F648	27			
C_{max} (%CER) (By Product, and By Fast and Fed)							
Reference Drug, Ceretec™	23	Fast	13053380	16	0.1642	0.6894	Not significant
			12966581	7			
	31	Fed	13053380	28	0.0042	0.9488	Not significant
			12966581	3			
Proposed Test	23	Fast	5B142	12	0.0148	0.9044	Not significant
			5F648	11			
	31	Fed	5B142	15	0.0809	0.7781	Not significant
			5F648	16			
* Prob> F when greater than 0.05 – No significant effect of lot							

Table A3. Effect of Lot # on AUC [%Cell Efflux Radioactivity (%CER)] for both the Proposed Test and Reference Drug Ceretec™ (ANOVA in JMP 11, $\alpha = 0.05$)

Product	Total Sample Size (N)	Fast/Fed	Lot #	Lot # Sample Size ($N_{Lot\#}$)	F Ratio	Prob>F	Conclusion*
AUC (%CER, By Product)							
Reference Drug, Ceretec™	54	Fast and Fed	13053380	44	0.5837	0.4483	Not significant
			12966581	10			
Proposed Test	54	Fast and Fed	5B142	27	0.4483	0.5061	Not significant
			5F648	27			
AUC (%CER) (By Product, and By Fast and Fed)							
Reference Drug, Ceretec™	23	Fast	13053380	16	0.2162	0.6467	Not significant
			12966581	7			
	31	Fed	13053380	28	0.0123	0.9126	Not significant
			12966581	3			
Proposed Test	23	Fast	5B142	12	1.2679	0.2729	Not significant
			5F648	11			
	31	Fed	5B142	15	0.0001	0.9920	Not significant
			5F648	16			
* Prob> F when greater than 0.05 – No significant effect of lot							

Sandra Suarez

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Poonam Delvadia

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MICROBIOLOGY

Product Background:

Technetium Tc 99m Exametazime (b) (4) is indicated for leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection, and inflammatory bowel disease.

NDA: 208870

Drug Product Name/Strength: Technetium Tc 99m Exametazime (b) (4) each vial contains 0.5 mg/vial, packaged in a single dose

Route of Administration: Sterile lyophilized (b) (4)

Applicant Name: Jubilant DraxImage Inc.

Manufacturing Site:

Jubilant HollisterStier General Partnership (Formerly Draxis Pharma General Partnership)
16751 Route Trans-Canada Highway
Kirkland, QC H9H 4J4

Method of Sterilization: (b) (4)

Review Summary:

The submission is **recommended** for approval on the basis of sterility assurance.

The safety risk due to the microbiology deficiencies is considered moderate.

List Submissions being reviewed (table):

Submit	Received	Review Request	Assigned to Reviewer
07/20/2016	07/20/2016	N/A	08/05/2016
09/16/2016	09/16/2016	N/A	N/A
01/09/2017*	01/09/2017	N/A	N/A
02/21/2017*	02/21/2017	N/A	N/A
02/28/2017*	02/28/2017	N/A	N/A
03/02/2017*	03/02/2017	N/A	N/A
03/03/2017*	03/03/2017	N/A	N/A
03/14/2017*	03/14/2017	N/A	N/A

***IR responses**

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

Microbiology Information Requests were issued to the applicant on the following dates: December 07, 2016; February 16, 2017; March 01, 2017 and March 02, 1017.The applicant provided responses in submissions dated January 9, 2017; February 21, 2017; February 28, 2017; March 02, 2017; March 03, 2017 and March 14, 2017. The responses are reviewed here.

SUPPORTING/RELATED DOCUMENTS:

- DMF (b) (4) (Type V, (b) (4)) (reviewed in Microbiology reviews dated 10/29/2009 by Colleen Thomas (adequate) and D15343M02R01 dated 10/03/2016 by Wendy Tan (adequate).
- DMF (b) (4) (Type V, (b) (4) reviewed in Microbiology review 11648mic31.doc, dated 08/25/2015; Lisa S.G. Shelton (adequate).
- ANDA 078806 for (b) (4) validation studies, reviewed in Microbiology reviews 78-806a1.doc and 78-806a2.doc, dated 11/07/2008 and 01/09/2009, respectively by S. Donald (adequate).
- (b) (4) for (b) (4) validation studies, reviewed in Microbiology review (b) (4) .doc, dated (b) (4) by J. Wells (adequate).
- (b) (4) reviewed in Microbiology review a2 (b) (4) mr01.doc, dated (b) (4) by Y. Chen (adequate).
- (b) (4) , reviewed in Microbiology review a (b) (4) .doc dated (b) (4) by S. Tiwari (adequate).

REMARKS:

This is an electronic submission.
No CP was included in the application.

P.1 Description of the Composition of the Drug Product

Reviewer's Assessment:

(Section 3.2.P.1).
Technetium Tc 99m Exametazime (b) (4) is a sterile, non-pyrogenic lyophilized mixture which has to be reconstituted with 5 ml sterile eluate from a Technetium Tc 99m generator for use for the preparation of Technetium Tc 99m Exametazime (b) (4) It is supplied in a 10 ml clear glass vial stoppered with 13 mm grey (b) (4) stopper and capped with 20 mm Flip OFF dark blue capsules.

Composition of the Drug Product per unit (1mL).

Ingredients	Composition		Function	Quality Standard
	Amount per unit (mg per vial)	% w/w		
Active Substance(s)				
Exametazime (*d,l*-HMPAO)	0.5 mg	0.050 %	Active ingredient	House
Excipients				
Sodium Chloride	4.5 mg	0.446 %	(b) (4)	USP/EP/BP
Stannous Chloride Dihydrate	7.6 µg	0.001 %	Reducing agent	NF/EP
(b) (4)				
Nitrogen	Head Space Fill	Head Space Fill	(b) (4) Head Space Fill	NF/EP
Total Quantity	(b) (4)	100.000%		

* = (b) (4)

(b) (4)

Acceptable

P.2 Pharmaceutical Development

Reviewer's Assessment:

Please see section P.7 for a description of container closure system used to package the drug product.

P.2.5 Microbiological Attributes

Reviewer's Assessment:

Container/Closure and Package Integrity

(Section 3.2.P.7, container-closure-syestm.pdf).
Test method: Helium leak test
Test was performed by: (b) (4)
The CCIT test is stated to use the same vials and stoppers that are used for the production and were subjected to same (b) (4) as the commercial batches.

Brief description: testing was performed on twenty (20) vials from lots 4L263 and 5F648. The helium ingress test involves adding a known amount of helium to the headspace of the sealed vial, then measuring any helium leaking from the vial over a defined period of time by using Seal Integrity Monitoring System

(SIMS™) which is calibrated against a NIST-traceable standard leak and measures the rate of helium leak. The acceptance criterion for the helium leak rate is < 6 x 10^{-8} standard cc/sec as per the referenced article authored by Kirsch et. al. PDA Journal of Pharmaceutical Science and Technology, Volume 51, Number 5, Sept-Oct 1997 pp. 202. Applicant has provided the sensitivity of dye ingress method which has a leak rate of 10^{-3} cc/sec.

The following Table summarizes the results:

Table 3.2.P.7- 7 Helium Leak Test Results for Lot# 4L263 and Lot # 5F648

Lot	Specifications	Helium leak rate rang (std*mL/sec)
4L263	< 6 x 10^{-6} std*mL/sec	1.3 – 1.9 x 10^{-7}
5F648	< 6 x 10^{-6} std*mL/sec	1.5 – 2.1 x 10^{-7}

The above results from lots 4L263 and 5F648 show an actual helium leak rate range well below the 6 x 10^{-6} std*mL/sec. A COA of helium leak test from (b) (4) has been provided in the application.

Applicant has provided a LOA (Doc ID#10038) of the helium leak test from (b) (4) and referenced DMF (b) (4) (Type V, (b) (4) for information regarding the helium leak test. Applicant has referred Section 3.2.P.5.2, table 2-1, (b) (4) helium leak test method (Selblty-12) and associated validation reports.

Note to reviewer: DMF (b) (4) was reviewed for the (b) (4) helium leak test method (Selblty-12) in Microbiology reviews dated 10/20/09; Colleen Thomas (adequate) and D15343M02R01dated 01/03/2016 by Wendy Tan (adequate).

Reviewer's Assessment:
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

Antimicrobial Effectiveness Testing

Reviewer's Assessment:

The subject drug product is filled in a single-use vial; antimicrobial effectiveness testing is not required.

P.3 Manufacture

P.3.1 Manufacturers

Jubilant HollisterStier General Partnership (Formerly Draxis Pharma General Partnership)

16751 Route Trans-Canada Highway
Kirkland, QC H9H 4J4

Responsible for drug product manufacturing, packaging, sterility and stability testing.

P. 3.3 Description of the Manufacturing Process and Process Controls

Reviewer's Assessment:

(b) (4) ***Manufacturing Process***

Please see section P.3.5

Buildings and Facilities

(Section 3.2.P.3.3, Description of manufacturing process and process controls. pdf)

A brief description of the manufacturing building and facilities is provided. The drug product is manufactured at Jubilant HollisterStier General Partnership, Kirkland (Quebec), Canada.

(b) (4)

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

Reviewer's Assessment:

(section 1.14.1.3).
Storage temperature: Store at 15 – 25 °C (59 – 77 °F).
Route of administration: IV
Container: Single use vials

Reconstitution

The package insert instructs to adhere to strict aseptic procedures throughout during the preparation of the radiopharmaceutical and administration procedures.

The lyophilized mixture has to be reconstituted with a 5 ml sterile eluate from a Technetium Tc 99m generator for use for the preparation of Technetium Tc 99m Exametazime (b) (4) (not provided in the kit).
Before reconstitution the technetiumTc-99m generator eluate may be adjusted to the correct radioactive concentration to a volume of 5 mL by dilution with preservative-free, non-bacteriostatic Sodium Chloride Injection USP (0.9%).

The reconstituted product may be stored at room temperature, 20- 25 °C and used within 30 minutes. Use for WBC labeling within 30 minutes. Discard any unused material. Labeled autologous WBCs with Exametazime should be administered to the patients as soon as possible and preferably within two hours.

Acceptable

List of Deficiencies: **None**

Primary Microbiology Reviewer Name and Date:

Samata Tiwari

05.01.2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Nandini Bhattacharya, Ph.D.

05.01.2017

Samata Tiwari

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Nandini Bhattacharya

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Danae Christodoulou

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OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #:208870	**Submission Type:NDA**	**Established/Proper Name: Tc 99m Exametazime** (b) (4)
Applicant: Jubilant DraxImage Inc.	**Letter Date: 07/15/2016**	**Dosage Form: Lyophilized** (b) (4)
Chemical Type:	**Stamp Date: 7/20/16**	**Strength: 0.5 mg/vial**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Describe filing issues here or on additional sheets **Biopharmaceutics** - Fileable from biopharmaceutics perspective (with IR provided at the end of this document)
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			In Table 3.2.P.1-1 you provided the quantitative composition of the kit. In addition, Ppovide a quantitative composition table for the reconstituted Tc 99m Exametazime (b) (4) drug product.

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☒	☐	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☒	☐	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other_____	☐	☐	

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Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☒	☐	Pre-IND/pre-NDA
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other_____		☐	☐	
Quality Considerations					
26.	Drug Substance Overage		☒	☐	
27.	Design Space	Formulation	☐	☐	Exametazine excess is used in the kit
28.		Process	☐	☐	
29.		Analytical Methods	☐	☐	
30.		Other	☐	☐	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☐	☒	
36.		Excipients	☐	☒	
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☐	☒	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	
49.	New product design[1]		☐	☒	
50.	Other_____		☐	☐	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Categorical exclusion requested
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance	☒	☐	☐	

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C. FILING CONSIDERATIONS					
	❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols				
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? 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? For each site, does the application list: ❑ 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)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture	☒	☐	☐	

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C. FILING CONSIDERATIONS					
	○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ❑ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product ○ Includes production data on drug product	☒	☐	☐	

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C. FILING CONSIDERATIONS					
	manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
	BIOPHARMACEUTICS				
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	In accordance with the MOU between ONDP and OCP as of July 1, 2015, *in vivo* BA/BE studies will be reviewed by OCP. The proposed product is a lyophilized (b) (4) [505(b)(2)] and there are no *in vivo* BA/BE studies in the submission. A request of waiver from conducting *in vivo* BA/BE studies has been submitted by the applicant supported by comparative physicochemical properties and *in vitro* equivalence study. *In vitro* equivalence study will be evaluated by DB/ONDP according to e-mail and telephone communication with OCP representative for this NDA.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	Since, the proposed product is a lyophilized (b) (4) and it relies on FDA's previous findings on safety and efficacy [505(b)(2) application] for the listed drug Ceretec™ (NDA 019829), *in vivo* data (BA/BE and pivotal clinical studies) are not present in

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C. FILING CONSIDERATIONS					
					the submission. However, developmental formulations were tested for applicable release and stability specifications which do not require biopharmaceutics review.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☒	☐	☐	The application includes a biowaiver request based on 21 CFR 320.22 (b)(1)(i) and (ii) and supportive data are submitted. However, the information provided is not complete. Therefore, additional information necessary to evaluate the biowaiver request will be requested either with communication on filing determination (due 09/18/2016) or before 74 day letter is due (10/02/2016) or via 74 day letter. The Application is fileable from biopharmaceutics perspective (with IR). Please refer IR for biopharmaceutics information provided at the end of this document.
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☒	☐	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk	☐	☐	☒	

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C. FILING CONSIDERATIONS					
	○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples				

Notes:

The drug product is the reconstituted kit, Tc 99m exametazime. The application is a 505(b)(2) with referenced approved drug the Ceretec kit, NDA 19829 (approved). The applicant has not submitted a table with the quantitative composition of the reconstituted product and results from reconstitution runs.

Attachments: Kit composition, drug substance and drug product specifications

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Table 3.2.P.1-1 Composition of the Drug Product per unit (1mL)

Ingredients	Composition		Function	Quality Standard
	Amount per unit (mg per vial)	% w/w		
Active Substance(s)				
Exametazime (*d,l*-HMPAO)	0.5 mg	0.050 %	Active ingredient	House
Excipients				
Sodium Chloride	4.5 mg	0.446 %	(b) (4)	USP/EP/BP
Stannous Chloride Dihydrate	7.6 µg	0.001 %	Reducing agent	NF/EP
(b) (4)				
Nitrogen	Head Space Fill	Head Space Fill	(b) (4) Head Space Fill	NF/EP
Total Quantity	(b) (4)	100.000%		

(b) (4)

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Table 3.2.S.4.1 - Specification for Exametazime API (520251

Parameter	Acceptance Criteria	Test Method
Description	(b) (4)	Organoleptic
Appearance	Free from any visible contamination.	Organoleptic
Clarity of Solution	Solution in Saline is clear.	MTD-GEN-009 (Organoleptic, pH measurement)
Identification A	The absorption bands of the sample correspond to the absorption bands of the Reference.	MTD-IR-001 (Infrared spectroscopy)
Identification B	Retention time of main peak is within (b) (4)% of the Reference Standard retention time.	MTD-LC-001 (HPLC)
Melting Point	(b) (4)°C	USP <741>
Loss on Drying (3h/105°C)	NMT (b) (4)% w/w	USP <731>
pH (0.5 mg/ml in Saline)	(b) (4)	MTD-GEN-009 (Organoleptic, pH measurement)
Assay	(b) (4)%	MTD-LC-001 (HPLC)
Impurities and Degradation Products	Total: NMT (b) (4)% Individual Impurities: • (b) (4) NMT (b) (4)% • Any unspecified impurity: NMT (b) (4)% • Impurity A: NMT (b) (4)%	MTD-LC-002 (HPLC)
	• (b) (4) NMT (b) (4)%	MTD-LC-012 (HPLC)
Enantiomeric Excess	± (b) (4)%	MTD-LC-007 (HPLC)
Heavy Metals	NMT (b) (4)ppm	MTD-GEN-002 (Colorimetric test)
Residual Solvents	Meets USP <467> and Ph.Eur Requir. (5.4) • (b) (4) NMT (b) (4) ppm • (b) (4) NMT (b) (4) ppm • (b) (4) NMT (b) (4) ppm	MTD-GC-005 (Gas chromatography)
Bacterial Endotoxins	NMT (b) (4) Endotoxins Unit/ mg.	USP <85> / Ph.Eur (2.6.14)

Table 3.2.P.5.1-2 Drug Product Specifications for Stability Study

JDI Internal code	**506791**	
Standard	**House**	
Revision #	**6**	
Approval Date	**May 16, 2016**	
Test	**Method** **(Type of method)**	**Acceptance Criteria**
Tests applicable on the Lyophilized product		
Description	Organoleptic	(b) (4)
Appearance	Organoleptic	Free from visible contamination
Container	Organoleptic	No change in appearance of inner walls and stopper
Clarity of Solution & Completeness	MTD-GEN-005, (Visual)	Reconstituted solution must have the appearance of purified water Reconstitution Time: NMT (b) (4)
Exametazime Assay	MTD-LC-001, (HPLC)	(b) (4) mg/vial
Impurities and Degradation Products	MTD-LC-002, (HPLC)	Total: NMT (b) (4) % Individual impurities: - (b) (4) NMT (b) (4) % - Any unspecified impurity: NMT (b) (4) % - Impurity A: NMT (b) (4) %
	MTD-LC-012 (HPLC)	(b) (4) NMT (b) (4) %
Stannous Chloride Content	MTD-GEN-006, (Polarography)	NLT (b) (4) µg/vial (expressed as Sn)
Water Content	MTD-KF-001, (Karl Fischer)	NMT (b) (4) %
(b) (4)		

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JDI Internal code	506791	
Standard	House	
Revision #	6	
Approval Date	May 16, 2016	
Test	**Method** **(Type of method)**	**Acceptance Criteria**
	(GC)	
Bacterial Endotoxins	USP <85> and SOP 1684	NMT [redacted] EU/mL
Sterility	USP <71>	Sterile
Tests applicable on the Reconstituted Product: Technetium Tc 99m Exametazime [redacted]		
pH	MTD-GEN-005 (USP <791>)	[redacted]
Radiochemical Purity (within 30 min post reconstitution)	MTD-RCP-001 USP Product Monograph, (TLC)	NLT [redacted] % of Total Radioactivity as primary Tc-Exametazime [redacted]
		NMT [redacted] % of Total Radioactivity as [redacted]
Biological distribution	MTD-BIO-001 USP Product Monograph	NLT [redacted] % of Radioactivity in brain
		NMT [redacted] % of Radioactivity in intestines
		NMT [redacted] % of Radioactivity in liver
		In Not Less Than [redacted] animals

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JDI Internal code	506791	
Standard	House	
Revision #	6	
Approval Date	May 16, 2016	
Test	**Method** **(Type of method)**	**Acceptance Criteria**
	(GC)	
Bacterial Endotoxins	USP <85> and SOP 1684	NMT (b)(4) EU/mL
Sterility	USP <71>	Sterile
Tests applicable on the Reconstituted Product: Technetium Tc 99m Exametazime (b) (4)		
pH	MTD-GEN-005 (USP <791>)	(b) (4)
Radiochemical Purity (within 30 min post reconstitution)	MTD-RCP-001 USP Product Monograph, (TLC)	NLT (b)(4) % of Total Radioactivity as primary Tc-Exametazime (b) (4)
		NMT (b)(4) % of Total Radioactivity as (b) (4) (b) (4)
Biological distribution	MTD-BIO-001 USP Product Monograph	NLT (b)(4) % of Radioactivity in brain
		NMT % of Radioactivity in intestines
		NMT % of Radioactivity in liver
		In Not Less Than (b) (4) animals

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Biopharmaceutics Information Request (IR)

We acknowledge that a formal biowaiver request for the proposed Kit for Preparation of Technetium Tc 99m Exametazime (b) (4) has been submitted referencing 21 CFR320.22 (b)(1)(i) and (ii) and is further supported by quality comparability and in vitro equivalence study comparing the test and reference drug product (Ceretec™). We have identified the lack of some relevant information. In order to continue reviewing your submission, provide the following information/data.

a. Reference is made in the In Vitro Equivalence Study report [0001(1), Module 3.2.P.2] to the following:

   i. Appendix C (Raw Data in Appendix M, pg 16) for WBC counts,
   ii. Appendix D (Raw Data in Appendix L, pg 17), for radiochemical purity for each vial,
   iii. Appendix E (Raw Data in Appendix N, pg 18) for labeling efficiency,
   iv. Appendix F (Raw Data in Appendix O, Pg 23) for cell viability, and
   v. Appendix G (Raw Data in Appendix P, Pg 23) for cell efflux.

   However, these Appendices are not presented in the report. Submit the referenced Appendices and related individual sample data for the above attributes.

b. We note that RLD lot # 12966581 (expiry date – March 28, 2016) was tested in the in vitro equivalence study past its expiry (testing dates – April 17, 2016 to April 24, 2016 for blood samples # 22 to 27). Provide justification on the use of the expired RLD lot in the in vitro equivalence study.

c. Provide rationale for not using both RLD lots for blood samples from all subjects for in vitro equivalence study. For example, RLD lot # 12966581 is used for blood sample # 22 to 25; whereas, for blood sample # 1 to 21, RLD lot # 13053380 is used. Two blood samples (# 26 and 27) used both RLD lots for the in vitro equivalence study.

d. Provide in vitro equivalence data analysis by batch (i.e., comparing each test lot to each RLD lot). Alternatively, provide in vitro equivalence data analysis considering the comparison of each test lot with RLD lot # 13053380.

e. We note that blood samples were collected from two groups of healthy adult donors that – (1) were in well hydrated fasted state; and (2) were on a standardized meal. Provide a rationale for using blood samples from both groups of subjects for in vitro equivalence

study. Identify the blood samples from fasted or fed state subject(s) in Table 2 of in vitro equivalence study report [0001(1), Module 3.2.P.2, Pg 18 of the report]. Consider including fasted and fed state as a covariate for in vitro equivalence data analysis or provide justification for pooling data from both groups for equivalence analysis.

CMC Information Request:

1. In Table 3.2.P.1-1 you provided the quantitative composition of the kit. In addition, provide a quantitative composition table for the reconstituted Tc 99m Exametazime (b) (4) drug product.
2. Your release specification for the reconstituted drug product includes only the attributes of pH, and radiochemical purity by TLC. Include radionuclidic identity, purity and radio chemical purity as part of your release specification. We recommend that you validate your TLC method for radiochemical purity against an HPLC method.
3. Provide information about the Tc99m generator(s) used to radiolabel the kit from your exhibit batches along with batch record and batch analysis data for the reconstituted solution.
4. Submit three drug product samples from each lot of your exhibit batches (Lot 4L263, Lot 5B142 and Lot 5F648).

Danae D. Christodoulou -S

Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.09.26 10:30:07 -04'00'

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 9/26/2016 11:05:37AM
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