

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 203263

Name: Doxorubicin Hydrochloride Liposome
Injection USP, 2 mg/mL

Sponsor: Sun Pharma Global FZE

Approval Date: February 4, 2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203263

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203263

APPROVAL LETTER



ANDA 203263

Caraco Pharmaceutical Laboratories Ltd.
U.S. Agent for: Sun Pharma Global FZE
Attention: Robert Kurkiewicz
Director, Regulatory Affairs
1150 Elijah McCoy Drive
Detroit, MI 48202

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 16, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Doxorubicin Hydrochloride Liposome Injection USP, 2 mg/mL, packaged in 20 mg/10 mL and 50 mg/25 mL Single-use Vials.

Reference is also made to your amendments dated November 3, 2011; March 7, March 20, April 9, May 10, June 29, July 4, July 5, July 27, August 4, September 26, October 5, and December 20, 2012; and January 21, 2013.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Doxorubicin Hydrochloride Liposome Injection USP, 2 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Doxil[®] Liposome Injection, 2 mg/mL, of Janssen Research and Development, LLC. Your drug release testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

02/04/2013

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 203263

LABELING

10 mL Single Use Vial

NDC 47335 048 40

**DOXOrubicin Hydrochloride
Liposome Injection**

20 mg/10 mL (2 mg/mL)

Cytotoxic Agent Must be diluted

**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

FOR INTRAVENOUS INFUSION ONLY
Store in a refrigerator, 2°C to 8°C (36°F to 46°F)
Avoid freezing

Manufactured by
Sun Pharmaceutical Ind. Ltd., Ind a

PJLB1860 PJLB1860 PJLB1860
ISS 07/2012
GUJ/DRUGS/28/396

Batch No.

Exp.

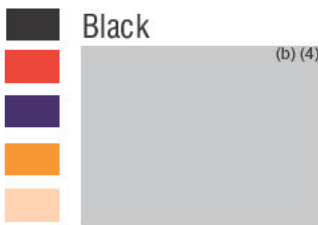
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(b) (4)

Size: 70x25 mm
ANDA-US

Unvarnish area: 15 x 9 mm



Size: 42x35x60 mm
ANDA-US

25 mL Single Use Vial

NDC 47335-050-40

**DOXOrubicin Hydrochloride
Liposome Injection**

50 mg/25 mL (2 mg/mL)

Cytotoxic Agent Must be diluted

**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

FOR INTRAVENOUS INFUSION ONLY

Store in a refrigerator, 2°C to 8°C (36°F to 46°F).
Avoid freezing.

Manufactured by:
Sun Pharmaceutical Ind. Ltd.
India.

PJLB1861 PJLB1861 PJLB1861 ISS 07/2012
GUJ/DRUGS/28/396

Batch No.

Exp.

47335-05040

100 mm

 Black

 (b) (4)



Unvarnish area: 20 x 8 mm

**Size: 100x35 mm
ANDA-US**

FOR INTRAVENOUS INFUSION ONLY
MUST BE DILUTED PRIOR TO ADMINISTRATION

50 mg/25 mL
(2 mg/mL)

DOXOrubicin Hydrochloride Liposome Injection

NDC 47335-050-40

PJSB0684 PJSB0684
PJSB0684 PJSB0684

Each mL contains doxorubicin hydrochloride, 2 mg; N-(carboxyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt, 3.19 mg; fully hydrogenated soy phosphatidylcholine, 9.58 mg; cholesterol, 3.19 mg; ammonium sulfate, approximately 2 mg; sucrose; histidine; and hydrochloric acid and/or sodium hydroxide.

Note: Liposomal formulation.

USUAL DOSAGE: See package insert for dosage information.

Discard unused portion.

Retain vial in carton until time of use.



Distributed by:
Caraco Pharmaceutical Laboratories, Ltd
1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured by:
Sun Pharmaceutical Ind. Ltd.
Halol Baroda Highway,
Halol 389 350, Gujarat, India.

NDC 47335 050 40
DOXOrubicin Hydrochloride Liposome Injection

50 mg/25 mL
(2 mg/mL)

Sterile Cytotoxic Agent
MUST BE DILUTED PRIOR TO ADMINISTRATION

LIPOSOMAL FORMULATION DO NOT SUBSTITUTE

FOR INTRAVENOUS INFUSION ONLY

PJSB0684 ISS. 07/2012

GUJ/DRUGS/28/396

Batch No.:

Exp.:

NDC 47335 050 40
DOXOrubicin Hydrochloride Liposome Injection

50 mg/25 mL
(2 mg/mL)

Sterile Cytotoxic Agent
MUST BE DILUTED PRIOR TO ADMINISTRATION

LIPOSOMAL FORMULATION DO NOT SUBSTITUTE

FOR INTRAVENOUS INFUSION ONLY

Rx only
25 mL Single Use Vial



NDC 47335 050 40
DOXOrubicin Hydrochloride Liposome Injection

50 mg/25 mL
(2 mg/mL)

Store in a refrigerator, 2°C to 8°C
(36°F to 46°F). Avoid freezing.

LIPOSOMAL FORMULATION DO NOT SUBSTITUTE

FOR INTRAVENOUS INFUSION ONLY



NDC 47335-050-40
DOXOrubicin Hydrochloride Liposome Injection

50 mg/25 mL
(2 mg/mL)

MUST BE DILUTED PRIOR TO ADMINISTRATION
FOR INTRAVENOUS INFUSION ONLY

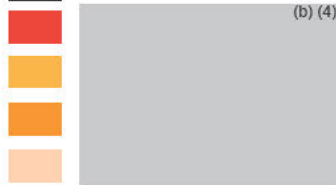
75 mm

42 mm

44 mm

Size: 44x42x75mm

Black



Unvarnish area: 29 x 13 mm



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use doxorubicin hydrochloride safely and effectively. See full prescribing information for doxorubicin hydrochloride liposome injection.

Doxorubicin Hydrochloride Liposome Injection for intravenous infusion

Initial U.S. Approval: 1995

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, SUBSTITUTION

See full prescribing information for complete boxed warning.

- Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin hydrochloride approaches 550 mg/m². Cardiac toxicity may also occur at lower cumulative doses with mediastinal irradiation or concurrent cardiotoxic agents (5.1).
- Acute infusion-related reactions, sometimes reversible upon terminating or slowing infusion, occurred in up to 10% of patients. Serious and sometimes fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications/emergency equipment to treat such reactions should be available for immediate use (5.2).
- Severe myelosuppression may occur (5.3).
- Reduce dosage in patients with impaired hepatic function (2.6).
- Accidental substitution of doxorubicin hydrochloride liposome injection resulted in severe side effects. Do not substitute on mg per mg basis with doxorubicin hydrochloride (2.1).

RECENT MAJOR CHANGES

Contraindications, Nursing Mother (4) Removed 9/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION

1 INDICATIONS AND USAGE

- Ovarian Cancer
- AIDS-Related Kaposi's Sarcoma

2 DOSAGE AND ADMINISTRATION

- Usage and Administration Precautions
- Patients With Ovarian Cancer
- Patients With AIDS-Related Kaposi's Sarcoma
- Dose Modification Guidelines
- Patients With Impaired Hepatic Function
- Preparation for Intravenous Administration
- Procedure for Proper Handling and Disposal

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- Cardiac Toxicity
- Infusion Reactions
- Myelosuppression
- Hand-Foot Syndrome (HFS)
- Radiation Recall Reaction
- Fetal Mortality
- Toxicity Potential
- Monitoring: Laboratory Tests

FULL PRESCRIBING INFORMATION

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION

- The use of doxorubicin hydrochloride liposome injection may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin hydrochloride approaches 550 mg/m². In a clinical study in patients with advanced breast cancer, 250 patients received doxorubicin hydrochloride liposome injection at a starting dose of 50 mg/m² every 4 weeks. At all cumulative anthracycline doses between 450 to 500 mg/m² or between 500 to 550 mg/m², the risk of cardiac toxicity for patients treated with doxorubicin hydrochloride liposome injection was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy [see Warnings and Precautions (5.1)].
- Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, lightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with doxorubicin hydrochloride liposome injection. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Doxorubicin hydrochloride liposome injection should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions [see Warnings and Precautions (5.2)].
- Severe myelosuppression may occur [see Warnings and Precautions (5.3)].
- Dosage should be reduced in patients with impaired hepatic function [see Dosage and Administration (2.6) and Use in Specific Populations (8.6)].
- Accidental substitution of doxorubicin hydrochloride liposome injection for doxorubicin hydrochloride has resulted in severe side effects. Doxorubicin hydrochloride liposome injection should not be substituted for doxorubicin hydrochloride on a mg per mg basis [see Dosage and Administration (2.1)].

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer
Doxorubicin hydrochloride liposome injection is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

1.2 AIDS-Related Kaposi's Sarcoma

Doxorubicin hydrochloride liposome injection is indicated for the treatment of AIDS-related Kaposi's sarcoma in patients after failure of prior systemic chemotherapy or intolerance to such therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Usage and Administration Precautions

Liposomal encapsulation can substantially affect a drug's functional properties relative to those of the unencapsulated drug. Therefore DO NOT SUBSTITUTE one drug for the other.

Do not administer as a bolus injection or an undiluted solution. Rapid infusion may increase the risk of infusion-related reactions [see Warnings and Precautions (5.2)]. Doxorubicin hydrochloride liposome injection should not be given by the intramuscular or subcutaneous route.

Unit specific compatibility data are available. It is not recommended that doxorubicin hydrochloride liposome injection be mixed with other drugs.

Doxorubicin hydrochloride liposome injection should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of doxorubicin hydrochloride liposome injection, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction.

2.2 Patients With Ovarian Cancer

Doxorubicin hydrochloride liposome injection should be administered intravenously at a dose of 50 mg/m² (doxorubicin hydrochloride equivalent) at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related adverse reactions are observed, the rate of infusion can be increased to complete administration of the drug over one hour. The patient should be dosed once every 4 weeks, for as long as the patient does not progress, shows no evidence of cardiotoxicity [see Warnings and Precautions (5.1)], and continues to tolerate treatment. A minimum of 4 courses is recommended because median time to response in clinical trials was 4 months. To manage adverse reactions such as hand-foot syndrome (HFS), stomatitis, or hematologic toxicity the doses may be delayed or reduced [see Dosage and Administration (2.5)]. Pretreatment with or concomitant use of antiemetics should be considered.

2.3 Patients With AIDS-Related Kaposi's Sarcoma

Doxorubicin hydrochloride liposome injection should be administered intravenously at a dose of 20 mg/m² (doxorubicin hydrochloride equivalent). An initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over one hour. The dose should be repeated once every three weeks, for as long as patients respond satisfactorily and tolerate treatment.

2.5 Dose Modification Guidelines

Doxorubicin hydrochloride liposome injection exhibits nonlinear pharmacokinetics at 50 mg/m²; therefore, dose adjustments may result in a non-proportional greater change in plasma concentration and exposure to the drug [see Clinical Pharmacology (12.3)].

INDICATIONS AND USAGE

Doxorubicin hydrochloride is an anthracycline topoisomerase inhibitor indicated for:

- **Ovarian cancer (1.1)**
After failure of platinum-based chemotherapy.
- **AIDS-related Kaposi's Sarcoma (1.2)**
After failure of prior systemic chemotherapy or intolerance to such therapy.

DOSAGE AND ADMINISTRATION

Administer doxorubicin hydrochloride liposome injection at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion related reactions occur, increase rate of infusion to complete administration over 1 hour. Do not administer as bolus injection or undiluted solution (2.1).

- **Ovarian cancer:** 50 mg/m² IV every 4 weeks for 4 courses minimum (2.2)
- **AIDS-related Kaposi's Sarcoma:** 20 mg/m² IV every 3 weeks (2.3)

DOSAGE FORMS AND STRENGTHS

Single use vial: 20 mg/10 mL and 50 mg/25 mL (3)

CONTRAINDICATIONS

- Hypersensitivity reactions to a conventional formulation of doxorubicin hydrochloride or the components of doxorubicin hydrochloride liposome injection (4, 5, 2)

WARNINGS AND PRECAUTIONS

- Hand-Foot Syndrome may occur. Dose modification or discontinuation may be required (5.4)
- Radiation recall reaction may occur (5.5)

ADVERSE REACTIONS

Most common adverse reactions (>20%) are asthenia, fatigue, fever, anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, hand and foot syndrome, rash, neutropenia, thrombocytopenia and anemia (6).

To report SUSPECTED ADVERSE REACTIONS contact CARACO Pharmaceutical Laboratories Ltd. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Doxorubicin hydrochloride may interact with drugs known to interact with conventional formulations of Doxorubicin hydrochloride. (7)

USE IN SPECIFIC POPULATIONS

- Doxorubicin hydrochloride liposome injection can cause fetal harm when used during pregnancy. (5.6, 8.1)
- Discontinue nursing during treatment with doxorubicin hydrochloride liposome injection (8.3).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2012

6 ADVERSE REACTIONS

- Overall Adverse Reactions Profile
- Adverse Reactions in Clinical Trials
- Post Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Nursing Mothers
- Pediatric Use
- Geriatric Use
- Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacokinetics

13 NON-CLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, and Impairment of Fertility

14 CLINICAL STUDIES

- Ovarian Cancer
- AIDS-Related Kaposi's Sarcoma

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

Patients should be carefully monitored for toxicity. Adverse reactions, such as HFS, hematologic toxicities, and stomatitis may be managed by dose delays and adjustments. Following the first appearance of a Grade 2 or higher adverse reactions, the dosing should be adjusted or delayed as described in the following tables. Once the dose has been reduced, it should not be increased at a later time.

Recommended Dose Modification Guidelines

Table 1: Hand-Foot Syndrome (HFS)

Toxicity Grade	Dose Adjustment
1 (mild erythema, swelling, or desquamation not interfering with daily activities)	Redose unless patient has experienced previous Grade 3 or 4 HFS. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there are no prior Grade 3-4 HFS, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.
3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued.
4 (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued.

Table 2: Hematological Toxicity

Grade	ANC	Platelets	Modification
1	1,500 to 1,900	75,000 to 150,000	Resume treatment with no dose reduction
2	1,000 to < 1,500	50,000 to < 75,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction
3	500 to 999	25,000 to < 50,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction
4	<500	<25,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose at 25% dose reduction or continue full dose with cytokine support

Table 3: Stomatitis

Toxicity Grade	Dose Adjustment
1 (painless ulcers, erythema, or mild soreness)	Redose unless patient has experienced previous Grade 3 or 4 toxicity. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval
2 (painful erythema, edema, or ulcers, but can eat)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued. If resolved to Grade 0-1 within 2 weeks and there was no prior Grade 3-4 stomatitis, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval
3 (painful erythema, edema, or ulcers, and cannot eat)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued.
4 (requires parenteral or enteral support)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to doxorubicin hydrochloride liposome injection original dose interval. If after 2 weeks there is no resolution, doxorubicin hydrochloride liposome injection should be discontinued.

2.6 Patients With Impaired Hepatic Function

Limited clinical experience exists in treating patients with hepatic impairment with doxorubicin hydrochloride liposome injection. Based on experience with doxorubicin hydrochloride, it is recommended that the doxorubicin hydrochloride liposome injection dosage be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3 mg/dL - give ½ normal dose; serum bilirubin > 3 mg/dL - give ¼ normal dose.

2.7 Preparation for Intravenous Administration

Each 10 mL vial contains 20 mg doxorubicin hydrochloride at a concentration of 2 mg/mL. Each 25 mL vial contains 50 mg doxorubicin hydrochloride at a concentration of 2 mg/mL.

Doxorubicin hydrochloride liposome injection doses up to 90 mg must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in doxorubicin hydrochloride liposome injection. Diluted doxorubicin hydrochloride liposome injection should be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours.

Do not use with in-line filters.

Do not mix with other drugs.
Do not use with any diluent other than 5% Dextrose Injection.
Do not use any bacteriostatic agent, such as benzyl alcohol.

Doxorubicin hydrochloride liposome injection is not a clear solution but a translucent, red liposomal dispersion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

Rapid flushing of the infusion line should be avoided.

2.8 Procedure for Proper Handling and Disposal

Caution should be exercised in the handling and preparation of doxorubicin hydrochloride liposome injection.

The use of gloves is required.

If doxorubicin hydrochloride liposome injection comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

Doxorubicin hydrochloride liposome injection should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of doxorubicin hydrochloride liposome injection, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. **Doxorubicin hydrochloride liposome injection must not be given by the intramuscular or subcutaneous route.**

Doxorubicin hydrochloride liposome injection should be handled and disposed of in a manner consistent with other anticancer drugs. Several guidelines on this subject exist [see References (15)].

3 DOSAGE FORMS AND STRENGTHS

- Single use vial: 20 mg/10 mL
- Single use vial: 50 mg/25 mL

4 CONTRAINDICATIONS

Doxorubicin hydrochloride liposome injection is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin hydrochloride or the components of doxorubicin hydrochloride liposome injection [see Warnings and Precautions (5.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Toxicity

Special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin hydrochloride. Acute left ventricular failure may occur with doxorubicin, particularly in patients who have received a total cumulative dose of doxorubicin exceeding the currently recommended limit of 550 mg/m². Lower (400 mg/m²) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide.

Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Congestive heart failure or cardiomyopathy may be encountered after discontinuation of anthracycline therapy. Patients with a history of cardiovascular disease should be administered doxorubicin hydrochloride liposome injection only when the potential benefit of treatment outweighs the risk.

Cardiac function should be carefully monitored in patients treated with doxorubicin hydrochloride liposome injection. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or multigated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity in patients treated with doxorubicin hydrochloride liposome injection. If these test results indicate possible cardiac injury associated with doxorubicin hydrochloride liposome injection therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

In a clinical study in patients with advanced breast cancer, 250 patients received doxorubicin hydrochloride liposome injection at starting dose of 50 mg/m² every 4 weeks. At all cumulative anthracycline doses between 450 to 500 mg/m², or between 500 to 550 mg/m², the risk of cardiac toxicity for patients treated with doxorubicin hydrochloride liposome injection was 11%. In this study, cardiotoxicity was defined as a decrease of >20% from baseline if the resting left ventricular ejection fraction (LVEF) remained in the normal range, or a decrease of >10% if the resting LVEF became abnormal (less than the institutional lower limit of normal). The data on left ventricular ejection fraction (LVEF) defined cardiotoxicity and congestive heart failure (CHF) are in the table below.

Table 5: Number of Patients With Advanced Breast Cancer

	Doxorubicin Hydrochloride Liposome Injection (n=250)
Patients who Developed Cardiotoxicity (LVEF Defined)	10
Cardiotoxicity (With Signs & Symptoms of CHF)	0
Cardiotoxicity (No Signs & Symptoms of CHF)	10
Patients With Signs and Symptoms of CHF Only	2

5.2 Infusion Reactions

Acute infusion-related reactions were reported in 7.1% of patients treated with doxorubicin hydrochloride liposome injection in the randomized ovarian cancer study. These reactions were characterized by one or more of the following symptoms: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction resolved when the rate of infusion was slowed. In this study, two patients treated with doxorubicin hydrochloride liposome injection (0.8%) discontinued due to infusion-related reactions. In clinical studies, six patients with AIDS-related Kaposi's sarcoma (0.9%) and 13 (1.7%) solid tumor patients discontinued doxorubicin hydrochloride liposome injection therapy because of infusion-related reactions.

Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

The majority of infusion-related events occurred during the first infusion. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the doxorubicin hydrochloride liposomes or one of its surface components.

The initial rate of infusion should be 1 mg/min to help minimize the risk of infusion reactions [see Dosage and Administration (2)].

5.3 Myelosuppression

Because of the potential for bone marrow suppression, careful hematologic monitoring is required during use of doxorubicin hydrochloride liposome injection, including white blood cell, neutrophil, platelet counts, and Hgb/Hct. With the recommended dosage schedule, leukopenia is usually transient. Hematologic toxicity may require dose reduction or delay or suspension of doxorubicin hydrochloride liposome injection therapy. Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage. Development of sepsis in the setting of neutropenia has resulted in discontinuation of treatment and, in rare cases, death.

Doxorubicin hydrochloride liposome injection may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when doxorubicin hydrochloride liposome injection is administered in combination with other agents that cause bone marrow suppression.

In patients with relapsed ovarian cancer, myelosuppression was generally moderate and reversible. In the three single-arm studies, anemia was the most common hematologic adverse reaction (52.6%), followed by leukopenia (WBC < 4,000/mm³; 42.2%), thrombocytopenia (24.2%), and neutropenia (ANC < 1,000; 19%). In the randomized study, anemia was the most common hematologic adverse reaction (40.2%), followed by leukopenia (WBC < 4,000/mm³; 36.8%), neutropenia (ANC < 1,000; 35.1%), and thrombocytopenia (13%) [see Adverse Reactions (6.2)].

In patients with relapsed ovarian cancer, 4.6% received G-CSF (or GM-CSF) to support their blood counts [see Dosage and Administration (2.5)].

For patients with AIDS-related Kaposi's sarcoma who often present with baseline myelosuppression due to such factors as their HIV disease or concomitant medications, myelosuppression appears to be the dose-limiting adverse reaction at the recommended dose of 20 mg/m² [see Adverse Reactions (6.2)]. Leukopenia is the most common adverse reaction experienced in this population; anemia and thrombocytopenia can also be expected. Sepsis occurred in 5% of patients; for 0.7% of patients the event was considered possibly or probably related to doxorubicin hydrochloride liposome injection. Eleven patients (1.6%) discontinued study because of bone marrow suppression or neutropenia.

5.4 Hand-Foot Syndrome (HFS)

In the randomized ovarian cancer study, 50.6% of patients treated with doxorubicin hydrochloride liposome injection at 50 mg/m² every 4 weeks experienced HFS (developed palmar-plantar skin eruptions characterized by swelling, pain, erythema and, for some patients, desquamation of the skin on the hands and the feet), with 23.8% of the patients reporting HFS Grade 3 or 4 events. Ten subjects (4.2%) discontinued treatment due to HFS or other skin toxicity. HFS toxicity grades are described above [see Definitions of HFS Grades in Dosage and Administration (2.5)].

Among 705 patients with AIDS-related Kaposi's sarcoma treated with doxorubicin hydrochloride liposome injection at 20 mg/m² every 2 weeks, 24 (3.4%) developed HFS, with 3 (0.9%) discontinuing.

HFS was generally observed after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in one to two weeks so that prolonged delay of therapy need not occur. However, dose modification may be required to manage HFS [see Dosage and Administration (2.5)]. The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

5.5 Radiation Recall Reaction

Recall reaction has occurred with doxorubicin hydrochloride liposome injection administration after radiotherapy.

5.6 Fetal Mortality

Pregnancy Category D
Doxorubicin hydrochloride liposome injection can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If doxorubicin hydrochloride liposome injection is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. If pregnancy occurs in the first few months following treatment with doxorubicin hydrochloride liposome injection, the prolonged half-life of the drug must be considered. Women of child

patients were receiving antifungal medications, primarily fluconazole (75.8%). Seventy-two percent of patients were receiving antivirals, 56.3% acyclovir, 29% ganciclovir, and 16% foscarnet. In addition, 47.8% patients received colony-stimulating factors (sargramostim/filgrastim) sometime during their course of treatment.

Adverse reactions led to discontinuation of treatment in 5% of patients with AIDS-related Kaposi's sarcoma. Those that did so included bone marrow suppression, cardiac adverse reactions, infusion-related reactions, toxoplasmosis, HFS, pneumonia, cough/dyspnea, fatigue, optic neuritis, progression of a non-KS tumor, or allergy to penicillin, and unspecified reasons.

Table 8: Hematology Data Reported in Patients With AIDS-Related Kaposi's Sarcoma

	Patients With Refractory or Intolerant AIDS-Related Kaposi's Sarcoma (n = 74)	Total Patients With AIDS-Related Kaposi's Sarcoma (n = 720)
Neutropenia		
< 1000/mm ³	34 (45.9%)	352 (48.9%)
< 500/mm ³	8 (10.8%)	96 (13.3%)
Anemia		
< 10 g/dL	43 (58.1%)	399 (55.4%)
< 8 g/dL	12 (16.2%)	131 (18.2%)
Thrombocytopenia		
< 150,000/mm ³	45 (60.8%)	439 (60.9%)
< 25,000/mm ³	1 (1.4%)	30 (4.2%)

Table 9: Probably and Possibly Drug-Related Non-Hematologic Adverse Reactions Reported in ≥ 5% of Patients With AIDS-Related Kaposi's Sarcoma

Adverse Reactions	Patients With Refractory or Intolerant AIDS-Related Kaposi's Sarcoma (n = 77)	Total Patients With AIDS-Related Kaposi's Sarcoma (n = 705)
Nausea	14 (18.2%)	119 (16.9%)
Asthenia	5 (6.5%)	70 (9.9%)
Fever	6 (7.8%)	64 (9.1%)
Alpecia	7 (9.1%)	63 (8.9%)
Alkaline Phosphatase Increase	1 (1.3%)	55 (7.8%)
Vomiting	6 (7.8%)	55 (7.8%)
Diarrhea	4 (5.2%)	55 (7.8%)
Stomatitis	4 (5.2%)	48 (6.8%)
Oral Moniliasis	1 (1.3%)	39 (5.5%)

The following additional (not in table) adverse reactions were observed in patients with AIDS-related Kaposi's sarcoma:

- Incidence 1% to 5%**
- Body as a Whole:** headache, back pain, infection, allergic reaction, chills.
- Cardiovascular:** chest pain, hypotension, tachycardia.
- Cutaneous:** herpes simplex, rash, itching.
- Digestive:** mouthulceration, anorexia, dysphagia.
- Metabolic and Nutritional:** SGPT increase, weight loss, hyperbilirubinemia.
- Other:** dyspnea, pneumonia, dizziness, somnolence.
- Incidence Less Than 1%**
- Body as a Whole:** sepsis, moniliasis, cryptococcosis.
- Cardiovascular:** thrombophlebitis, cardiomyopathy, palpitation, bundle branch block, congestive heart failure, heart arrest, thrombosis, ventricular arrhythmia.
- Digestive:** hepatitis.
- Metabolic and Nutritional Disorders:** dehydration.
- Respiratory:** cough increase, pharyngitis.
- Skin and Appendages:** maculopapular rash, herpes zoster.
- Special Senses:** taste perversion, conjunctivitis.

6.3 Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of doxorubicin hydrochloride liposome injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Musculoskeletal and Connective Tissue Disorders:** rare cases of muscle spasms.
- Respiratory, Thoracic and Mediastinal Disorders:** rare cases of pulmonary embolism (in some cases fatal).
- Hematologic disorders:** Secondary acute myelogenous leukemia with and without fatal outcome has been reported in patients whose treatment included doxorubicin hydrochloride liposome injection.
- Skin and subcutaneous tissue disorders:** rare cases of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with doxorubicin hydrochloride liposome injection. Doxorubicin hydrochloride liposome injection may interact with drugs known to interact with the conventional formulation of doxorubicin hydrochloride.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (6.6)].

Doxorubicin hydrochloride liposome injection is embryotoxic at doses of 1 mg/kg/day in rats and is embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about one-eighth the 50 mg/m² human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from doxorubicin hydrochloride liposome injection, discontinue nursing during treatment with doxorubicin hydrochloride liposome injection.

8.4 Pediatric Use

The safety and effectiveness of doxorubicin hydrochloride liposome injection in pediatric patients have not been established.

8.5 Geriatric Use

Of the patients treated with doxorubicin hydrochloride liposome injection in the randomized ovarian cancer study, 34.7% (n=53) were 65 years of age or older while 7.9% (n=19) were 75 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Hepatic Impairment

The pharmacokinetics of doxorubicin hydrochloride liposome injection has not been adequately evaluated in patients with hepatic impairment. Doxorubicin is eliminated in large part by the liver. Thus, doxorubicin hydrochloride dosage should be reduced in patients with impaired hepatic function [see Dosage and Administration (2.6)].

Prior to doxorubicin hydrochloride liposome injection administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase, and bilirubin [see Dosage and Administration (2.6)].

10 OVERDOSAGE

Acute overdosage with doxorubicin hydrochloride causes increases in mucositis, leucopenia, and thrombocytopenia.

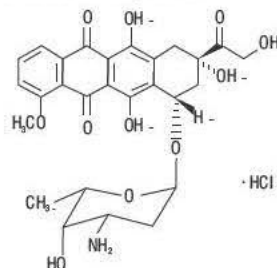
Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions, and symptomatic treatment of mucositis.

11 DESCRIPTION

Doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride encapsulated in pegylated liposomes for intravenous administration.

Doxorubicin is an anthracycline topoisomerase II inhibitor isolated from *Streptomyces peucetius* var. *caesius*.

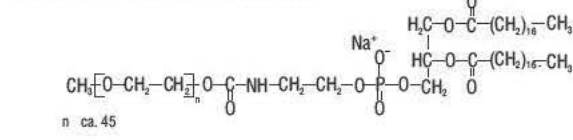
Doxorubicin hydrochloride, which is the established name for (8S,10S)-10-((3-amino-2,3,6-trideoxy-α-L-lyxo-heptopyranosyl)oxy)-9-β-D-glucopyranosyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthoquinone hydrochloride, has the following structure:



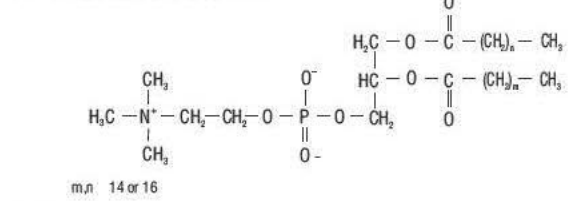
The molecular formula of the drug is C₂₇H₃₉NO₁₁·HCl; its molecular weight is 579.99.

Doxorubicin hydrochloride liposome injection is provided as a sterile, translucent, red liposomal dispersion in 10 mL or 25 mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin hydrochloride, USP at a concentration of 2 mg/mL and a pH of 6.5. The pegylated liposome carriers are composed of cholesterol, 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and N-(carboxymethyl)polyethylene glycol 2000-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the pegylated liposomes.

MPEG-DSPE has the following structural formula:



HSPC has the following structural formula:

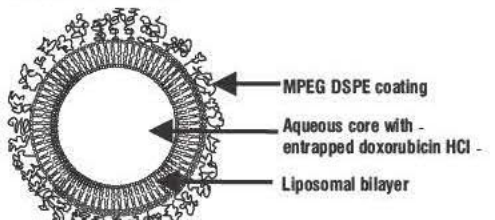


12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
The active ingredient of doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride. The mechanism of action of doxorubicin hydrochloride is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and nuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

Doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride encapsulated in long-circulating pegylated liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that is capable of encapsulating active drugs. The pegylated liposomes of doxorubicin hydrochloride liposome injection are formulated with surface-bound tetrahydrophosphorylethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the monoclonal phagocyte system (MPS) and to increase blood circulation time.

Representation of a pegylated liposome:



Pegylated liposomes have a half-life of approximately 55 hours in humans. They are stable in blood, and direct measurement of liposomal doxorubicin shows that at least 90% of the drug (the assay used cannot quantify less than 5 to 10% free doxorubicin) remains liposome-encapsulated during circulation.

It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated doxorubicin liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing pegylated liposomes, which can be visualized microscopically. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors and in transgenic mice with Kaposi's sarcoma-like lesions. Once the pegylated liposomes distribute to the tissue compartment, the encapsulated doxorubicin hydrochloride becomes available. The exact mechanism of release is not understood.

12.3 Pharmacokinetics

The plasma pharmacokinetics of doxorubicin hydrochloride liposome injection were evaluated in 42 patients with AIDS-related Kaposi's sarcoma (KS) who received single doses of 10 or 20 mg/m² administered by 30-minute infusion. Twenty-three of these patients received single doses of both 10 and 20 mg/m² with a 3-week wash-out period between doses. The pharmacokinetic parameter values of doxorubicin hydrochloride liposome injection, given for total doxorubicin (mostly liposomally bound), are presented in Table 11.

Table 11: Pharmacokinetic Parameters of Doxorubicin Hydrochloride Liposome Injection in Patients With AIDS-Related Kaposi's Sarcoma

Parameter (units)	10 mg/m ²	20 mg/m ²
Peak Plasma Concentration (mcg/mL)	4.12 ± 0.215	8.34 ± 0.49
Plasma Clearance (L/h/m ²)	0.056 ± 0.01	0.041 ± 0.004
Steady State Volume of Distribution (L/m ²)	2.83 ± 0.145	2.72 ± 0.12
AUC (mcg·h/mL)	277 ± 32.9	590 ± 58.7
First Phase (λ ₁) Half-Life (h)	4.7 ± 1.1	5.2 ± 1.4
Second Phase (λ ₂) Half-Life (h)	52.3 ± 5.6	55 ± 4.8

n = 23
Mean ± Standard Error

Doxorubicin hydrochloride liposome injection displayed linear pharmacokinetics over the range of 10 to 20 mg/m². Disposition occurred in two phases after doxorubicin hydrochloride liposome injection administration, with a relatively short first phase (~5 hours) and a prolonged second phase (~55 hours) that accounted for the majority of the area under the curve (AUC).

The pharmacokinetics of doxorubicin hydrochloride liposome injection at a 50 mg/m² dose is reported to be nonlinear. At this dose, the elimination half-life of doxorubicin hydrochloride liposome injection is expected to be longer and the clearance lower compared to a 20 mg/m² dose. The exposure (AUC) is thus expected to be more than proportional to a 50 mg/m² dose when compared with the lower doses.

Distribution:
In contrast to the pharmacokinetics of doxorubicin, which displays a large volume of distribution, ranging from 700 to 1100 L/m², the small steady state volume of distribution of doxorubicin hydrochloride liposome injection shows that doxorubicin hydrochloride liposome injection is confined mostly to the vascular fluid volume. Plasma protein binding of doxorubicin hydrochloride liposome injection has not been determined; the plasma protein binding of doxorubicin is approximately 70%.

Metabolism:

Doxorubicin, the major metabolite of doxorubicin, was detected at very low levels (range: of 0.8 to 28.2 ng/mL) in the plasma of patients who received 10 or 20 mg/m² doxorubicin hydrochloride liposome injection.

Excretion:

The plasma clearance of doxorubicin hydrochloride liposome injection was slow, with a mean clearance value of 0.041 L/h/m² at a dose of 20 mg/m². This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24 to 35 L/h/m².

Because of its slower clearance, the AUC of doxorubicin hydrochloride liposome injection, primarily representing the circulation of liposome-encapsulated doxorubicin, is approximately two to three orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin hydrochloride as reported in the literature.

Special Populations:

The pharmacokinetics of doxorubicin hydrochloride liposome injection have not been separately evaluated in women, in members of different ethnic groups, or in individuals with renal or hepatic insufficiency.

Drug-Drug Interactions:
Drug-drug interactions between doxorubicin hydrochloride liposome injection and other drugs, including antiviral agents, have not been adequately evaluated in patients with ovarian cancer or AIDS-related Kaposi's sarcoma.

Tissue Distribution in Patients with Kaposi's Sarcoma:

Kaposi's sarcoma lesions and normal skin biopsies were obtained at 48 and 96 hours post infusion of 20 mg/m² doxorubicin hydrochloride liposome injection in 11 patients. The concentration of doxorubicin hydrochloride liposome injection in KS lesions was a median of 19 (range, 3 to 53) times higher than in normal skin at 48 hours post treatment; however, this was not corrected for likely differences in blood content between KS lesions and normal skin. The corrected ratio may lie between 1 and 22 times. Thus, higher concentrations of doxorubicin hydrochloride liposome injection are delivered to KS lesions than to normal skin.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Although no studies have been conducted with doxorubicin hydrochloride liposome injection, doxorubicin hydrochloride and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Pegylated liposomes without drug were negative when tested in Ames, mouse lymphoma and chromosomal aberration assays *in vitro*, and mammalian micronucleus assay *in vivo*.

The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated. However, doxorubicin hydrochloride liposome injection resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kg (about twice the 50 mg/m² human dose on a mg/m² basis). Decreased testicular weights and hypospemia were present in rats after repeat doses ≥ 0.25 mg/kg/day (about one-third the 50 mg/m² human dose on a mg/m² basis), and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day (about one-half the 50 mg/m² human dose on a mg/m² basis).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

Doxorubicin hydrochloride liposome injection was studied in three open-label, single-arm, clinical studies of 176 patients with metastatic ovarian cancer. One hundred forty-five (145) of these patients were refractory to both paclitaxel- and platinum-based chemotherapy regimens.

Refractory ovarian cancer is defined as disease progression while on treatment, or relapse within 6 months of completing treatment. Patients in these studies received doxorubicin hydrochloride liposome injection at 50 mg/m² infused over one hour every 3 or 4 weeks for 3 to 4 cycles or longer in the absence of dose-limiting toxicity or progression of disease.

The baseline demographics and clinical characteristics of the patients with refractory ovarian cancer are provided in Table 12 below.

Table 12: Patient Demographics for Patients With Refractory Ovarian Cancer From Single Arm Ovarian Cancer Studies

	Study 1 (U.S.) (n = 27)	Study 2 (U.S.) (n = 82)	Study 3 (non-U.S.) (n = 36)
Age at Diagnosis (Years)			
Median	64	61.5	51.5
Range	46 to 75	34 to 85	22 to 80
Drug-Free Interval (Months)			
Median	1.8	1.7	2.6
Range	0.5 to 15.6	0.6 to 7	0.7 to 15.2
Sum of Lesions at Baseline (cm ³)			
Median	25	18.3	32.4
Range	1.2 to 230	1.3 to 285	0.3 to 114
FIGO Staging			
I	1 (3.7%)	3 (3.7%)	4 (11.1%)
II	3 (11.1%)	3 (3.7%)	1 (2.8%)
III	15 (55.6%)	60 (73.2%)	24 (66.7%)
IV	8 (29.6%)	16 (19.5%)	6 (16.7%)
Not Specified	—	—	1 (2.8%)
CA-125 at Baseline			
Median	123.5	199	1004.5
Range	20 to 14,012	7 to 46,594	20 to 12,089
Number of Prior Chemotherapy Regimens			
1	7 (25.9%)	13 (15.9%)	9 (25%)
2	11 (40.7%)	44 (53.7%)	19 (52.8%)
3	6 (22.2%)	25 (30.5%)	8 (22.8%)
4	3 (11.1%)	—	—

The primary efficacy parameter was response rate for the population of patients refractory to both paclitaxel- and a platinum-containing regimen. Assessment of response was based on Southwest Oncology Group (SWOG) criteria, and required confirmation four weeks after the initial observation. Secondary efficacy parameters were time to response, duration of response, and time to progression.

The response rates for the individual single arm studies are given in Table 13 below.

Table 13: Response Rates in Patients With Refractory Ovarian Cancer From Single Arm Ovarian Cancer Studies

	Study 1 (U.S.)	Study 2 (U.S.)	Study 3 (non-U.S.)
Response Rate	22.2% (6/27)	17.1% (14/82)	0% (0/36)
95% Confidence Interval	8.6% to 42.3%	9.7% to 27%	0% to 9.7%

When the data from the single arm studies are combined, the response rate for all patients refractory to paclitaxel and platinum agents was 13.8% (20/145) (95% CI 8.1% to 19.3%). The median time to progression was 15.9 weeks, the median time to response was 17.6 weeks, and the duration of response was 39.4 weeks.

Doxorubicin hydrochloride liposome injection was also studied in a randomized, multicenter, open-label, study in 474 patients with epithelial ovarian cancer after platinum-based chemotherapy. Patients in this study received an initial dose of either doxorubicin hydrochloride liposome injection 50 mg/m² infused over one hour every 4 weeks or topotecan 1.5 mg/m² infused daily for 5 consecutive days every 3 weeks. Patients were stratified according to platinum sensitivity and the presence of bulky disease (presence of tumor mass greater than 5 cm in size). Platinum sensitivity is defined by response to initial platinum-based therapy and a progression-free interval of greater than 6 months off treatment. The primary efficacy endpoint for this study was time to progression (TTP). Other efficacy endpoints included overall survival and objective response rate.

The baseline patient demographic and clinical characteristics are provided in Table 14 below.

Table 14: Ovarian Cancer Randomized Study Baseline Demographic and Clinical Characteristics

	Doxorubicin Hydrochloride Liposome Injection (n = 239)	Topotecan (n = 235)
Age at Diagnosis (Years)		
Median	60	60
Range	27 to 87	25 to 85
Drug-Free Interval (Months)		
Median	7	6.7
Range	0.9 to 82.1	0.5 to 109.6
FIGO Staging		
I	11 (4.6%)	15 (6.4%)
II	13 (5.4%)	8 (3.4%)
III	175 (73.2%)	164 (69.8%)
IV	40 (16.7%)	48 (20.4%)
Platinum Sensitivity		
Sensitive	109 (45.6%)	110 (46.8%)
Refractory	130 (54.4%)	125 (53.2%)
Bulky Disease		
Present	108 (45.2%)	105 (44.7%)
Absent	131 (54.8%)	130 (55.3%)

Study results are provided in Table 15.

There was no statistically significant difference in TTP between the two treatment arms.

Table 15: Results of Efficacy Analyses*

TTP (Protocol Specified Primary Endpoint)	Protocol Defined ITT Population	
	Doxorubicin Hydrochloride Liposome Injection (n = 239)	Topotecan (n = 235)
Median (Months) [†]	4.1	4.2
p-value	0.617	
Hazard Ratio [‡]	0.955	
95% CI for Hazard Ratio	(0.762, 1.196)	
Overall Survival		
Median (Months) [‡]	14.4	13.7
p-value [‡]	0.05	
Hazard Ratio [‡]	0.822	
95% CI for Hazard Ratio	(0.676, 1)	
Response Rate		
Overall Response n (%)	47 (19.7)	40 (17)
Complete Response n (%)	9 (3.8)	11 (4.7)
Partial Response n (%)	38 (15.9)	29 (12.3)
Median Duration of Response (Months) [‡]	6.9	5.9

* Analysis based on investigators' stratification for protocol defined ITT population.

[†] Kaplan-Meier estimates.

[‡] p-value is based on the stratified log-rank test.

[§] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for doxorubicin hydrochloride liposome injection.

[¶] p-value not adjusted for multiple comparisons.

14.2 AIDS-Related Kaposi's Sarcoma

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203263

LABELING REVIEWS

APPROVAL SUMMARY #2
LABELING REVIEW BRANCH

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes ☐ No
Communication plan (505-1(e))	☐ Yes ☐ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes ☐ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes ☐ No
Timetable for assessment (505-1(d))	☐ Yes ☐ No

ANDA REMS acceptable?

Yes No n/a

1. APPLICANT INFORMATION:

ANDA Number	203263
Date of Submission	26 SEP 2012
Applicant	Sun Pharma
Drug Name	Doxorubicin HCl Liposome Injection USP- 2 mg/mL
Strength(s)	20 mg/ 10 mL, 50 mg/ 25 mL- SDV

Labels and Labeling Summary	
Container	
10 mL and 25 mL- SDV	FPL satisfactory in the July 27, 2012 submission.
Cartons (1s)	FPL satisfactory in the July 27, 2012 submission.
PLR Insert	FPL satisfactory in the September 26, 2012 submission.

2. NOTE TO THE CHEMIST: None.

3. MODEL LABELING: NDA

NDA-Doxil® (doxorubicin HCl liposome injection), 2 mg/mL, 10 mL and 25 mL
NDA# 050718/ S-043, Approved 9.19.2012.
Manufactured by: Ben Venue Laboratories, Inc., Bedford, OH 44146
Distributed by: Ortho Biotech Products, LP Raritan, NJ 08869-0670

4. MEDWATCH: (Checked on 7/12/2012) - None

5. PATENT AND EXCLUSIVITY: (Checked on 7/12/2012) - Applicant 6.16.2011 submission-
No patents listed in the OB. Exclusivity: **ODE expire May 17,2014. Carved out of the generic labeling.**

Patent and Exclusivity

1.3.5.2 **Patent Certification Patent Certification** (§ 314.94(a)(12) Pursuant to 21 U.S.C. 355U(2)(A)(vii), Sun Pharma Global FZE's Statement of Certification, for all patents which claim the listed drug, Doxil® (doxorubicin HCl Liposome injection) referred to in this application or which claim a use of the listed drug have been provided in this section.

Statement of Exclusivity (§ 314.94(a)(3)) Pursuant to 21 CFR § 314.94(a)(3)(ii), Sun Pharma Global FZE hereby certifies that according to the information published in the list, the reference listed drug Doxil® (doxorubicin HCl liposome injection) referred to in this application is entitled for marketing exclusivity under section 505(b)(4)(D) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act. Details of marketing exclusivity are given below.

Exclusivity Code Exclusivity Expiration : ODE May 17, 2014

Sun Pharma Global FZE is not seeking approval for the indication covered by the above mentioned exclusivity.

Mr. Vishwanath Kenkare
Manager,
Sun Pharma Global FZE

FDA Application-

Results for Orphan Drug Product Designations Search

[Return to Orphan Designation Search Page](#)

Result Number:	1
Generic Name:	Doxorubicin Hcl Liposome Injection
Trade Name:	Doxil
Date Designated:	12-29-2004
Orphan Designation:	Treatment of multiple myeloma
Orphan Designation Status:	Designated/Approved
FDA Orphan Approval Status:	Approved for Orphan Indication
Approved Orphan Indication:	For use in combination with bortezomib for the treatment of patients with multiple myeloma who have not previously received bortezomib and have at least one prior therapy.
Exclusivity Start Date:	05-17-2007
Sponsor:	Johnson & Johnson Pharmaceutical Research & Dev. 920 US Highway 202, P. O. Box 300 Raritan, NJ 08869

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM:
Manufactured by: Sun Pharmaceutical Ind. Ltd., Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

(b) (4)

Final print 7/27/2012 has:
Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

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Halol-389 350, Gujarat, India.

ISS. 07/2012
PJPI0355

7. USP: No (Checked on 7/12/2012)

8. Not PF – 8/30/2012

9. INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section.

- The inactive ingredients in the ANDA appear to be consistent with the inactive ingredients in the RLD. The generic uses pegylate liposome carrier with the same molecular formula as the RLD with the RLD using Stealth (trade marked).

ANDA - 203263- Doxorubicin hydrochloride liposome injection is provided as a sterile, translucent, red liposomal dispersion in 10 mL or **30 mL (vial size- requested change)** glass, single use vials.

Each vial contains 20 mg or 50 mg doxorubicin hydrochloride at a concentration of 2 mg/mL and a pH of 6.5. The pegylated liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the **pegylated** liposomes.

ANDA MECHANISM OF ACTION- Doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride encapsulated in longcirculating pegylated liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The pegylated liposomes of doxorubicin hydrochloride liposome injection are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time. Representation of a pegylated liposome:

NDA 50718- Description DOXIL is provided as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The STEALTH® liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the STEALTH® liposomes.

Rld Mechanism of Action are the same

DOXIL is doxorubicin HCl encapsulated in long circulating STEALTH® liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH® liposomes of DOXIL are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

RLD Manufactured by: Ben Venue Laboratories, Inc., Bedford, OH 44146
Distributed by: Ortho Biotech Products, LP Raritan, NJ 08869-0670
{Package Eng.: To Add OBI Logo Here}
An ALZA STEALTH® Technology Product
STEALTH® and DOXIL® are registered trademarks of
ALZA Corporation.

10. PACKAGING CONFIGURATIONS/PRODUCT LINE:

INNOVATOR: Samples attached.

RLD 16 HOW SUPPLIED/STORAGE AND HANDLING

DOXIL (doxorubicin HCl liposome injection) is supplied as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials.

Each 10-mL vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/mL.

Each 30-mL vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/mL.

Refrigerate unopened vials of DOXIL at 2°-8°C (36°- 46°F). Avoid freezing.

Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on DOXIL.

The following packages of six individually cartoned vials are available:

mg in vial - fill vol -vial size - NDC #s

20 mg vial -10-mL- 10-mL- 17314-9600-1 from blue to purple label color with new company.

50 mg vial - 25-mL- 30-mL 17314-9600-2 gold color.

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

20 mg in 10 mL (2 mg/mL)
sterile, single use vial

**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

FOR INTRAVENOUS INFUSION ONLY
Refrigerate, 2°-8°C (36°-46°F). Avoid freezing.
Keep out of reach of children.
See package insert for dosage information.

Rx ONLY

Cardiac Care Medical Products, L.P.

ALZA STEALTH® TECHNOLOGY PRODUCT

© CORPLP 2001
Rev November 2010 1021892

LOT: EXP:

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

Each mL contains doxorubicin HCl, 2 mg. STEALTH® liposome carriers are composed of cholesterol, 3.19 mg; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg; and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycerol-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg. Each mL also contains ammonium sulfate, 2 mg; histidine; hydrochloric acid and/or sodium hydroxide; and sucrose.

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

20 mg in 10 mL (2 mg/mL)
sterile, single use vial

**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

**FOR INTRAVENOUS
INFUSION ONLY**

Refrigerate, 2°-8°C (36°-46°F). Avoid freezing.

janssen

ALZA STEALTH® TECHNOLOGY PRODUCT

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

Note: Liposomal formulation. See package insert for dosage information.

59676-960-01 0

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

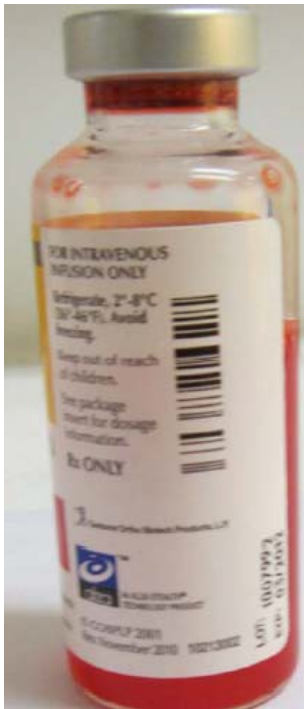
Keep out of reach of children.
Rx only
Product of Japan
Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146
Manufactured for:
Janssen Products, LP
Horsham, PA 19044

© Janssen 2001
Revised February 2012

010174

LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE

50 mg/25 mL product below carton same color as vial



PACKAGING CONFIGURATIONS/PRODUCT LINE: **ANDA: Information**
section 16 HOW SUPPLIED/STORAGE AND HANDLING

Doxorubicin hydrochloride liposome injection is supplied as a sterile, translucent, red liposomal dispersion in 10 mL or 30 mL glass, single use vials. Each 10 mL vial contains 20 mg doxorubicin hydrochloride at a concentration of 2 mg/mL. Each 30 mL vial contains 50 mg doxorubicin hydrochloride at a concentration of 2 mg/mL.

Refrigerate unopened vials of doxorubicin hydrochloride liposome injection at 2° to 8°C (36° to 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on doxorubicin hydrochloride liposome injection.

The following packages of individually cartoned vials are available:

mg in vial, fill vol, vial size, NDC #s
20 mg vial, 10 mL, 10 mL 47335-049-40
50 mg vial, 25 mL, 30 mL 47335-050-40

20 mg/10 mL – 10 mL vial size (1 vial)- SDV; **label color is dark purple**
50 mg/25 mL – 25 mL vial size (1 vial) - SDV; **label color is gold color**

11. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISON –
RLD: Store refrigerated, 2° to 8°C (36° to 46°F). Protect from light. (b) (4)
(b) (4) Discard unused portion
ANDA: Store refrigerated, 2° to 8°C (36° to 46°F). **Protect from light.** Retain in carton until time of use. Discard unused portion.
12. CONTAINER CLOSURE: Sun Pharma Global FZE- **VIALS ARE COLOURLESS.**
ANDA for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL 3.2.P.7 Container Closure System 3.2.P.7.1 Summary of Container Closure System:
To maintain the integrity of the drug product and to ensure its stability, Injection, 2 mg/mL, 10 mL is filled in, Type-I tubular glass vial, stoppered with 20 mm grey (b) (4) rubber stopper and sealed with 20 mm light blue flip off aluminium seal. Duly overprinted vial label is affixed on each vial, labeled vial is placed in one show box along with the package insert containing physician information. Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 25 mL is filled in, Type-I moulded glass vial, stoppered with 20 mm grey (b) (4) rubber stopper and sealed with 20 mm light blue flip off aluminium seal. Duly overprinted vial label is affixed on each vial,
13. FINISHED PRODUCT DESCRIPTION: Sun Pharma Global FZE
ANDA for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL
3.2.P Drug Product, 3.2.P.1 Description & Composition of the drug Product
Description:

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL. A translucent red colored liposomal dispersion filled in colourless 10 mL USP Type-I tubular glass vial with 20 mm grey (b) (4) rubber stopper, sealed with 20 mm light blue color flip off aluminium seal.

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 25 mL
A translucent red colored liposomal dispersion filled in colourless 30 mL USP Type-I moulded glass vial with 20 mm grey (b) (4) rubber stopper, sealed with 20 mm light blue color flip off aluminium seal.

Unit composition

In the finished dosage form, Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL contains the following. DMF access letter for MPEG-Distearoyl Phosphatidylethanolamine [N-(carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine, sodium salt] and Hydrogenated Soya Phosphatidyl Choline has been provided in Module 1, Section 1.4.1.1.

Statement of Composition

Strength	2 mg/mL (10 mL and 25 mL)	
	mg/mL	%w/v
Components		
Doxorubicin Hydrochloride, USP	2.00	0.20
Hydrogenated Soya Phosphatidyl Choline	9.58	0.95
MPEG-Distearoyl Phosphatidylethanolamine	3.19	0.31
Cholesterol (b) (4) NF	3.19	0.31
Ammonium Sulphate, NF		(b) (4)
Histidine USP		(b) (4)
Sucrose, NF		
Sodium Hydroxide, NF		
Hydrochloric Acid NF		(b) (4)

*1 Ammonium Sulphate is (b) (4), approximately 2 mg per mL.

*2 Used for pH adjustment (b) (4)

Sun Pharma Global FZE

ANDA for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL

3.2.P.1 Description & Composition of the drug Product

Functionality of Excipients in the formulation and IIG levels for this route of administration

Sr. #	Ingredient	Function	IIG levels for Intraveno	Concentrati on in proposed	Concentration in Referen
1	Hydrogenated Soya Phosphatidyl Choline				
2	MPEG-Distearoyl Phosphatidylethanol				
3	Cholesterol (b) (4) NF				
4	Ammonium Sulphate, NF				
5	Histidine USP				
6	Sucrose, NF				
7	Sodium Hydroxide,				
8	Hydrochloric Acid, NF				
9					
10					
11					

(b) (4)

Composition of proposed formulation of Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL is same as that of the reference listed drug. Quantity of all the excipients used in the formulation are in accordance with the reference listed drug and/or the amount specified in the IIG database.

APPEARS THIS WAY ON ORIGINAL

DOSAGE AND ADMINISTRATION:

DILUENT COMPATIBILITY: [Acceptable]

(b) (4)

From Chemistry Review:

- Storage and Stability [Acceptable]
- From Chemistry Review:

14. Labeling differences due to the following data sections modified by the carve out of the protected indication:

Reference to the brand name "DOXIL" has been replaced by the drug product name "doxorubicin Hydrochloride liposome injection" in Sun's labeling
Highlight section- dosage forms and strengths "30 mL" has been replaced by "25 mL" in Sun's labeling.

I&D- Section 1.3 Section 5 Multiple Myeloma (1.3)- omitted in recent major changes

In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.

D&A Omitted section 2.4 - Multiple Myeloma: 30 mg/m² IV on day 4 following bortezomib which is administered at 1.3 mg/m² bolus on days 1, 4, 8 and 11, every 3 weeks (2.4)

Text below table 3. omitted MM.

Section 5.1- text following table 5 and 5.3 text referring to table 10 (see 6.2). 5.4 penultimate paragraph.

Section 6.1- Adverse reactions "1310 patients" has been replaced by "992 patients"; and "318 patients with multiple myeloma" has been omitted in Sun's labeling. And Section 6.2 patients with MM & table 10 omitted

Section 8.5 Geriatrics - "Of the 318 patients treated with DOXIL in combination with bortezomib for multiple myeloma, 37% were 65 years of age or older and 8% were 75 years of age or older." has been omitted from Sun's labeling

Section 11- Description- "STEALTH liposomes" has been replaced by "pegylated liposomes" in Sun's labeling.

Section 14.3 & tables omitted Multiple myeloma

15. PLR format is acceptable. 6pt. No med guide.
16. This is a cytotoxic drug. The applicant was asked to add "cytotoxic agent".

Date of Review: 10/16/2012

Date of Submission: 9/26/2012

Primary Reviewer: Angela Payne

Team Leader: John Grace

V:\FIRMSNZ\SUN\LTRS&REV\203263ap2labdrtsreview.doc

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

/s/

ANGELA M PAYNE
10/18/2012

JOHN F GRACE
10/18/2012

APPROVAL SUMMARY #1
LABELING REVIEW BRANCH

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes ☐ No
Communication plan (505-1(e))	☐ Yes ☐ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes ☐ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes ☐ No
Timetable for assessment (505-1(d))	☐ Yes ☐ No

ANDA REMS acceptable?

Yes No n/a

1. APPLICANT INFORMATION:

ANDA Number	203263
Date of Submission	July 27, 2012
Applicant	Sun Pharma
Drug Name	Doxorubicin HCl Liposome Injection USP- 2 mg/mL
Strength(s)	20 mg/ 10 mL, 50 mg/ 25 mL- SDV

Labels and Labeling Summary	
Container	
10 mL and 25 mL- SDV	FPL satisfactory in the July 27, 2012 submission.
Cartons (1s)	FPL satisfactory in the July 27, 2012 submission.
PLR Insert	FPL satisfactory in the July 27, 2012 submission.

NOTE TO THE CHEMIST: None.

FOR THE RECORD:

1. MODEL LABELING: NDA

NDA-Doxil® (doxorubicin HCl liposome injection), 2 mg/mL, 10 mL and 25 mL
NDA# 050718/ S-033. There is one RLD supplement pending in DARRTS.
Manufactured by: Ben Venue Laboratories, Inc., Bedford, OH 44146
Distributed by: Ortho Biotech Products, LP Raritan, NJ 08869-0670

2. MEDWATCH: (Checked on 7/12/2012) - None

3. PATENT AND EXCLUSIVITY: (Checked on 7/12/2012) - Applicant 6.16.2011 submission- No patents listed in the OB. Exclusivity: **ODE expire May 17,2014. Carved out of the generic labeling.**

Patent and Exclusivity

1.3.5.2 **Patent Certification Patent Certification** (§ 314.94(a)(12) Pursuant to 21 U.S.C. 355U(2)(A)(vii), Sun Pharma Global FZE's Statement of Certification, for all patents which claim the listed drug, Doxil® (doxorubicin HCl Liposome injection) referred to in this application or which claim a use of the listed drug have been provided in this section.

Statement of Exclusivity (§ 314.94(a)(3)) Pursuant to 21 CFR § 314.94(a)(3)(ii), Sun Pharma Global FZE hereby certifies that according to the information published in the list, the reference listed drug Doxil® (doxorubicin HCl liposome injection) referred to in this application is entitled for marketing exclusivity under section 5050)(4)(D) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act. Details of marketing exclusivity are given below.

Exclusivity Code Exclusivity Expiration : ODE May 17, 2014

Sun Pharma Global FZE is not seeking approval for the indication covered by the above mentioned exclusivity.

Mr. Vishwanath Kenkare
Manager,
Sun Pharma Global FZE

FDA Application-

Results for Orphan Drug Product Designations Search

[Return to Orphan Designation Search Page](#)

Result Number:	1
Generic Name:	Doxorubicin Hcl Liposome Injection
Trade Name:	Doxil
Date Designated:	12-29-2004
Orphan Designation:	Treatment of multiple myeloma
Orphan Designation Status:	Designated/Approved
FDA Orphan Approval Status:	Approved for Orphan Indication
Approved Orphan Indication:	For use in combination with bortezomib for the treatment of patients with multiple myeloma who have not previously received bortezomib and have at least one prior therapy.
Exclusivity Start Date:	05-17-2007
Sponsor:	Johnson & Johnson Pharmaceutical Research & Dev. 920 US Highway 202, P. O. Box 300 Raritan, NJ 08869

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM:

Manufactured by: Sun Pharmaceutical Ind. Ltd., Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

(b) (4)

Final print 7/27/2012 has:

Distributed by:

Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured by:

Sun Pharmaceutical Ind. Ltd.
Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

ISS. 07/2012

PJPI0355

5. USP: No (Checked on 7/12/2012)
6. Not PF – 8/30/2012
7. INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section.

- The inactive ingredients in the ANDA appear to be consistent with the inactive ingredients in the RLD. The generic uses pegylate liposome carrier with the same molecular formula as the RLD with the RLD using Stealth (trade marked).

ANDA - 203263- Doxorubicin hydrochloride liposome injection is provided as a sterile, translucent, red liposomal dispersion in 10 mL or **30 mL (vial size- requested change)** glass, single use vials.

Each vial contains 20 mg or 50 mg doxorubicin hydrochloride at a concentration of 2 mg/mL and a pH of 6.5. The pegylated liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the **pegylated** liposomes.

ANDA MECHANISM OF ACTION- Doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride encapsulated in longcirculating pegylated liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The pegylated liposomes of doxorubicin hydrochloride liposome injection are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to

protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time. Representation of a pegylated liposome:

NDA 50718- Description DOXIL is provided as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The STEALTH® liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the STEALTH® liposomes.

Rld Mechanism of Action are the same

DOXIL is doxorubicin HCl encapsulated in long circulating STEALTH® liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH® liposomes of DOXIL are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

RLD Manufactured by: Ben Venue Laboratories, Inc., Bedford, OH 44146
Distributed by: Ortho Biotech Products, LP Raritan, NJ 08869-0670
{Package Eng.: To Add OBI Logo Here}
An ALZA STEALTH® Technology Product
STEALTH® and DOXIL® are registered trademarks of
ALZA Corporation.

8. PACKAGING CONFIGURATIONS/PRODUCT LINE:

INNOVATOR: Samples attached.

RLD 16 HOW SUPPLIED/STORAGE AND HANDLING

DOXIL (doxorubicin HCl liposome injection) is supplied as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each 10-mL vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/mL. Each 30-mL vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/mL. Refrigerate unopened vials of DOXIL at 2°-8°C (36°- 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on DOXIL.

The following packages of six individually cartoned vials are available:

mg in vial - fill vol -vial size - NDC #s

20 mg vial -10-mL- 10-mL- 17314-9600-1 from blue to purple label color with new company.

50 mg vial - 25-mL- 30-mL 17314-9600-2 gold color.

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

20 mg in 10 mL (2 mg/mL)
sterile, single use vial

**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

FOR INTRAVENOUS INFUSION ONLY
Refrigerate, 2°-8°C (36°-46°F). Avoid freezing.
Keep out of reach of children.
See package insert for dosage information.

Rx ONLY

Conductor Clinical Biotech Products, L.P.

ALZA STEALTH® TECHNOLOGY PRODUCT

Manufactured by: Ben Venue Laboratories, Inc. Bedford, OH 44146

Manufactured for: Conductor Clinical Biotech Products, L.P. Kailton, NJ 08869-0670

© CCRPLP 2001
Rev. November 2010 10212902

LOT:
EXP:

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

Each mL contains doxorubicin HCl, 2 mg. STEALTH® liposome carriers are composed of cholesterol, 3.19 mg; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg; and N-(carboxyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg. Each mL also contains ammonium sulfate, 2 mg; histidine; hydrochloric acid and/or sodium hydroxide; and sucrose.

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

20 mg in 10 mL (2 mg/mL)
sterile, single use vial

**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

**FOR INTRAVENOUS
INFUSION ONLY**
Refrigerate, 2°-8°C (36°-46°F). Avoid freezing.

janssen

ALZA

An ALZA STEALTH® Technology Product

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

Note: Liposomal formulation. See package insert for dosage information.

59676-960-01 0

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

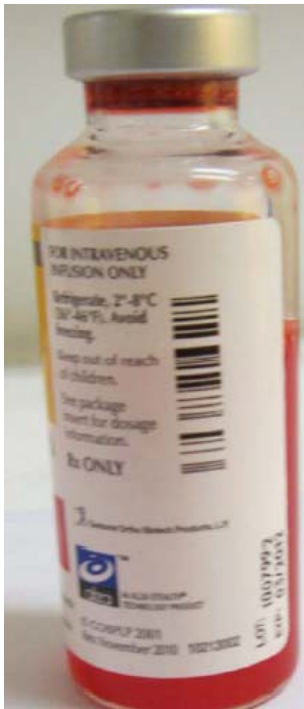
**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

Keep out of reach of children.
Rx only
Product of Japan
Manufactured by: Ben Venue Laboratories, Inc. Bedford, OH 44146
Manufactured for: Janssen Products, LP Horsham, PA 19044

© Janssen 2001
Revised February 2012

010174

50 mg/25 mL product below carton same color as vial



PACKAGING CONFIGURATIONS/PRODUCT LINE: **ANDA: Information**
section 16 HOW SUPPLIED/STORAGE AND HANDLING

Doxorubicin hydrochloride liposome injection is supplied as a sterile, translucent, red liposomal dispersion in 10 mL or 30 mL glass, single use vials. Each 10 mL vial contains 20 mg doxorubicin hydrochloride at a concentration of 2 mg/mL. Each 30 mL vial contains 50 mg doxorubicin hydrochloride at a concentration of 2 mg/mL.

Refrigerate unopened vials of doxorubicin hydrochloride liposome injection at 2° to 8°C (36° to 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on doxorubicin hydrochloride liposome injection.

The following packages of individually cartoned vials are available:

mg in vial, fill vol, vial size, NDC #s
20 mg vial, 10 mL, 10 mL 47335-049-40
50 mg vial, 25 mL, 30 mL 47335-050-40

20 mg/10 mL – 10 mL vial size (1 vial)- SDV; **label color is dark purple**
50 mg/25 mL – 25 mL vial size (1 vial) - SDV; **label color is gold color**

9. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISON –
RLD: Store refrigerated, 2° to 8°C (36° to 46°F). Protect from light. (b) (4)
(b) (4) Discard unused portion
ANDA: Store refrigerated, 2° to 8°C (36° to 46°F). **Protect from light.** Retain in carton until time of use. Discard unused portion.
10. CONTAINER CLOSURE: Sun Pharma Global FZE- **VIALS ARE COLOURLESS.**
ANDA for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL 3.2.P.7 Container Closure System 3.2.P.7.1 Summary of Container Closure System:
To maintain the integrity of the drug product and to ensure its stability, Injection, 2 mg/mL, 10 mL is filled in, Type-I tubular glass vial, stoppered with 20 mm grey (b) (4) rubber stopper and sealed with 20 mm light blue flip off aluminium seal. Duly overprinted vial label is affixed on each vial, labeled vial is placed in one show box along with the package insert containing physician information. Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 25 mL is filled in, Type-I moulded glass vial, stoppered with 20 mm grey (b) (4) rubber stopper and sealed with 20 mm light blue flip off aluminium seal. Duly overprinted vial label is affixed on each vial,
11. FINISHED PRODUCT DESCRIPTION: Sun Pharma Global FZE
ANDA for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL
3.2.P Drug Product, 3.2.P.1 Description & Composition of the drug Product
Description:

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL. A translucent red colored liposomal dispersion filled in colourless 10 mL USP Type-I tubular glass vial with 20 mm grey (b) (4) rubber stopper, sealed with 20 mm light blue color flip off aluminium seal.

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 25 mL
A translucent red colored liposomal dispersion filled in colourless 30 mL USP Type-I moulded glass vial with 20 mm grey (b) (4) rubber stopper, sealed with 20 mm light blue color flip off aluminium seal.

Unit composition

In the finished dosage form, Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL contains the following. DMF access letter for MPEG-Distearoyl Phosphatidylethanolamine [N-(carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine, sodium salt] and Hydrogenated Soya Phosphatidyl Choline has been provided in Module 1, Section 1.4.1.1.

Statement of Composition

Strength	2 mg/mL (10 mL and 25 mL)	
	mg/mL	%w/v
Components		
Doxorubicin Hydrochloride, USP	2.00	0.20
Hydrogenated Soya Phosphatidyl Choline	9.58	0.95
MPEG-Distearoyl Phosphatidylethanolamine	3.19	0.31
Cholesterol (b) (4) NF	3.19	0.31
Ammonium Sulphate, NF		(b) (4)
Histidine USP		(b) (4)
Sucrose, NF		
Sodium Hydroxide, NF		
Hydrochloric Acid NF		(b) (4)

*1 Ammonium Sulphate is (b) (4) approximately 2 mg per mL.

*2 Used for pH adjustment (b) (4)

Sun Pharma Global FZE

ANDA for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL

3.2.P.1 Description & Composition of the drug Product

Functionality of Excipients in the formulation and IIG levels for this route of administration

Sr. #	Ingredient	Function	IIG levels for Intraveno	Concentration in proposed	Concentration in Referen
1	Hydrogenated Soya Phosphatidyl Choline				
2	MPEG-Distearoyl Phosphatidylethanol				
3	Cholesterol (b) (4) NF				
4	Ammonium Sulphate, NF				
5	Histidine USP				
6	Sucrose, NF				
7	Sodium Hydroxide,				
8	Hydrochloric Acid, NF				
9	(b) (4)				
10					
11					

Composition of proposed formulation of Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL is same as that of the reference listed drug. Quantity of all the excipients used in the formulation are in accordance with the reference listed drug and/or the amount specified in the IIG database.

DOSAGE AND ADMINISTRATION:

DILUENT COMPATIBILITY: [Acceptable]

APPEARS THIS WAY ON ORIGINAL

From Chemistry Review:

- Storage and Stability [Acceptable]
- From Chemistry Review:

12. Labeling differences due to the following data sections modified by the carve out of the protected indication:

Reference to the brand name "DOXIL" has been replaced by the drug product name "doxorubicin Hydrochloride liposome injection" in Sun's labeling
Highlight section- dosage forms and strengths "30 mL" has been replaced by "25 mL" in Sun's labeling.

I&D- Section 1.3 Section 5 Multiple Myeloma (1.3)- omitted in recent major changes
In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.

D&A Omitted section 2.4 - Multiple Myeloma: 30 mg/m2 IV on day 4 following bortezomib which is administered at 1.3 mg/m2 bolus on days 1, 4, 8 and 11, every 3 weeks (2.4)

Text below table 3. omitted MM.

Section 5.1- text following table 5 and 5.3 text referring to table 10 (see 6.2). 5.4 penultimate paragraph.

Section 6.1- Adverse reactions "1310 patients" has been replaced by "992 patients"; and "318 patients with multiple myeloma" has been omitted in Sun's labeling. And Section 6.2 patients with MM & table 10 omitted

Section 8.5 Geriatrics - "Of the 318 patients treated with DOXIL in combination with bortezomib for multiple myeloma, 37% were 65 years of age or older and 8% were 75 years of age or older." has been omitted from Sun's labeling

Section 11- Description- "STEALTH liposomes" has been replaced by "pegylated liposomes" in Sun's labeling.

Section 14.3 & tables omitted Multiple myeloma

13. PLR format is acceptable. 6pt. No med guide.
14. This is a cytotoxic drug. I ask the applicant to add cytotoxic agent

Date of Review: 8/30/2012

Date of Submission: 7/27/2012

Primary Reviewer: Angela Payne

Team Leader: John Grace

V:\FIRMSNZ\SUN\LTRS&REV\203263ap1labdrtsreview.doc

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

/s/

ANGELA M PAYNE
09/17/2012

JOHN F GRACE
09/18/2012

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 203263 Date of Submission: 6/16/2011

Applicant's Name: Sun Pharma Global FZE

Established Name: Doxorubicin Hydrochloride liposome Injection: 2 mg/mL, 20 mg/10 mL, and 50 mg/ 25 mL) single dose vials.

LABELING COMMENTS:

1. **CONTAINER:** (2 mg/mL: 10 mL and 25 mL)

- a. Add "Must be diluted" to the main panel prior to "for intravenous...."
- b. Please add "cytotoxic agent".
- c. This product is light sensitive, please add "Retain vial in carton until time of use"
- d. Relocate the refrigerate statement to the main panel as seen with the reference product.
- e. Place "LIPOSOMAL FORMULATION. DO NOT SUBSTITUE" in large red shaded box and place prior to the route of administration statement on the main panel.
- f. Please use color schemes that are similar to the reference listed drug's color scheme to differentiate your product strengths. We note this color scheme should be different than the non-liposomal (regular injection) product that is on the market.
- g. Please provide the reference product labels that properly depict the color scheme for comparison with your label.

| 2. **CARTON:** See comments under CONTAINER.

3. **PROFESSIONAL INSERT:**

- a. GENERAL COMMENTS- Please retain same table numbering system that appears in the reference listed drug's labeling. (example... your table 4 is numbered table 5 in the RLD labeling. Renumber your tables.
- b. DESCRIPTION, Section 11 - "...30 mL" should read "...25 mL". Do not include the size of the vial but rather the fill volume which is " 25 mL".
- c. HOW SUPPLIED section.... Revise the Each 30 mL vial contains 50 mg doxorubicin... to Each 25 mL vial containers.....[do not use the vial size]

Revise your labels and labeling, as instructed above, and submit final print electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

FOR THE RECORD

REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☐ No
Communication plan (505-1(e))	☐ Yes	☐ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☐ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☐ No
Timetable for assessment (505-1(d))	☐ Yes	☐ No
ANDA REMS acceptable?	☐ Yes	☐ No
		X n/a

NOTE TO THE CHEMIST: None.

:

1. MODEL LABELING: NDA

NDA-Doxil® (doxorubicin HCl liposome injection), 2 mg/mL, 10 mL and 25 mL

NDA# 050718/ S-033. There is one RLD supplement pending in DARRTS.

Manufactured by: Ben Venue Laboratories, Inc., Bedford, OH 44146

Distributed by: Ortho Biotech Products, LP Raritan, NJ 08869-0670

2. MEDWATCH: (Checked on 7/12/2012) - None

3. PATENT AND EXCLUSIVITY: (Checked on 7/12/2012) - Applicant 6.16.2011 submission- No patents listed in the OB. Exclusivity: ODE expires May 17, 2014. Carved out of the generic labeling.

Patent Certification Patent Certification

Pursuant to 21 U.S.C. 355U)(2)(A)(vii), Sun Pharma Global FZE's Statement of Certification, for all patents which claim the listed drug, Doxil® (doxorubicin HCl Liposome injection) referred to in this application or which claim a use of the listed drug have been provided in this section.

Statement of Exclusivity

Pursuant to 21 CFR § 314.94(a)(3)(ii), Sun Pharma Global FZE hereby certifies that according to the information published in the list, the reference listed drug Doxil® (doxorubicin HCl liposome injection) referred to in this application is entitled for marketing exclusivity under section 5050)(4)(D) and 505(c)(3)(D)(ii) of the Federal Food, Drug, and Cosmetic Act. Details of marketing exclusivity are given below.

Exclusivity Code Exclusivity Expiration: ODE May 17, 2014

Sun Pharma Global FZE is not seeking approval for the indication covered by the above mentioned exclusivity.

Generic Name: Doxorubicin HCl Liposome Injection
Trade Name: Doxil
Date Designated: 12-29-2004
Orphan Designation: Treatment of multiple myeloma
Orphan Designation Status: Designated/Approved
Approved Orphan Indication: For use in combination with bortezomib for the treatment of patients with multiple myeloma who have not previously received bortezomib and have at least one prior therapy.
Exclusivity Start Date: 05-17-2007

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM:

Manufactured by:
Sun Pharmaceutical Ind. Ltd.,
Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

(b) (4)

5. **USP:** No (Checked on 7/12/2012)

6. Not PF –

7. INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section.

The inactive ingredients in the ANDA appear to be consistent with the inactive ingredients in the RLD. The generic uses pegylated liposome carrier with the same molecular formula as the RLD with the RLD using Stealth (trade marked).

Doxorubicin hydrochloride liposome injection is provided as a sterile, translucent, red liposomal dispersion in 10 mL or 30 mL (vial size-requested change) glass, single use vials.

Each vial contains 20 mg or 50 mg doxorubicin hydrochloride at a concentration of 2 mg/mL and a pH of 6.5. The pegylated liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE),

3.19 mg/mL; fully hydrogenated soy phosphatidylcholine(HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the pegylated liposomes.

ANDA MECHANISM OF ACTION- Doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride encapsulated in long circulating pegylated liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The pegylated liposomes of doxorubicin hydrochloride liposome injection are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time. Representation of a pegylated liposome:

NDA 50718- Description DOXIL is provided as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The STEALTH® liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the STEALTH® liposomes.

RLD's Mechanism of Action is the same

DOXIL is doxorubicin HCl encapsulated in long circulating STEALTH® liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH® liposomes of DOXIL are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

RLD Manufactured by:
Ben Venue Laboratories, Inc.,
Bedford, OH 44146

Distributed by:
Ortho Biotech Products,
LP Raritan, NJ 08869-0670

{Package Eng.: To Add OBI Logo Here}
An ALZA STEALTH® Technology Product
STEALTH® and DOXIL® are registered trademarks of
ALZA Corporation.

8. PACKAGING CONFIGURATIONS/PRODUCT LINE:

INNOVATOR: Samples attached.

RLD: HOW SUPPLIED/STORAGE AND HANDLING

DOXIL (doxorubicin HCl liposome injection) is supplied as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials.

Each 10-mL vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/mL.

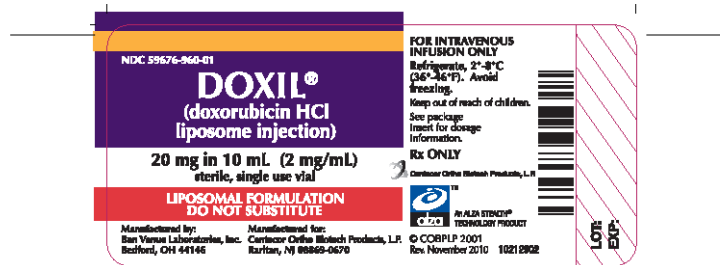
Each 30-mL vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/mL.

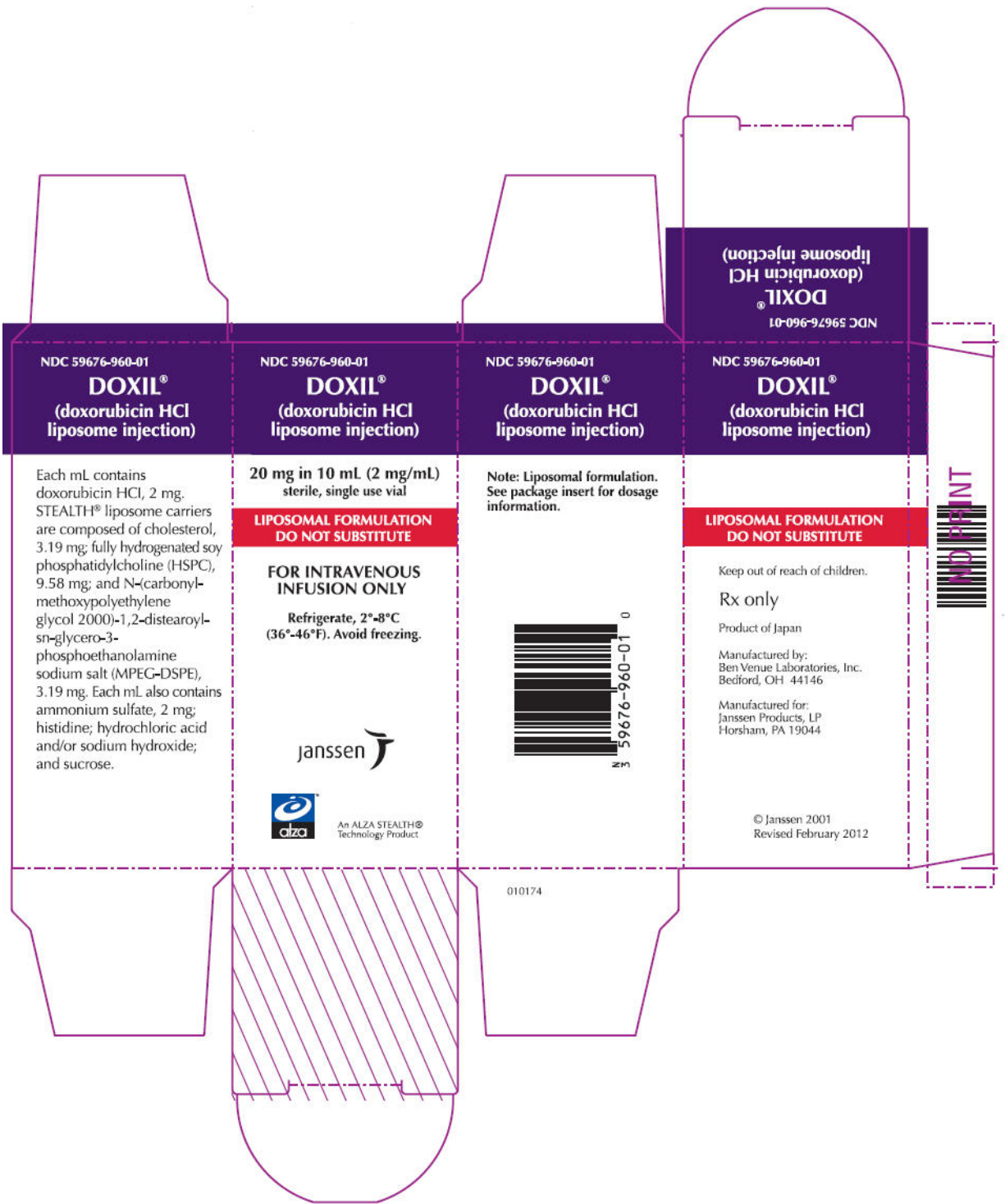
Refrigerate unopened vials of DOXIL at 2°-8°C (36°- 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on DOXIL.

The following packages of six individually cartoned vials are available:

20 mg vial -10-mL- 10-mL- 17314-9600-1

50 mg vial - 25-mL- 30-mL 17314-9600-2





NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

Each mL contains doxorubicin HCl, 2 mg. STEALTH® liposome carriers are composed of cholesterol, 3.19 mg; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg; and N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg. Each mL also contains ammonium sulfate, 2 mg; histidine; hydrochloric acid and/or sodium hydroxide; and sucrose.

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

20 mg in 10 mL (2 mg/mL)
sterile, single use vial

**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

**FOR INTRAVENOUS
INFUSION ONLY**

Refrigerate, 2°-8°C
(36°-46°F). Avoid freezing.

Janssen

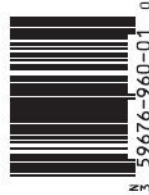


An ALZA STEALTH®
Technology Product

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

Note: Liposomal formulation.
See package insert for dosage
information.



010174

DOXIL®
(doxorubicin HCl liposome injection)
NDC 59676-960-01

NDC 59676-960-01

DOXIL®
(doxorubicin HCl liposome injection)

**LIPOSOMAL FORMULATION
DO NOT SUBSTITUTE**

Keep out of reach of children.

Rx only

Product of Japan

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

Manufactured for:
Janssen Products, LP
Horsham, PA 19044

© Janssen 2001
Revised February 2012



ANDA: HOW SUPPLIED/STORAGE AND HANDLING

Doxorubicin hydrochloride liposome injection is supplied as a sterile, translucent, red liposomal dispersion in 10 mL or 30 mL glass, single use vials.

Each 10 mL vial contains 20 mg doxorubicin hydrochloride at a concentration of 2 mg/mL.

Each 30 mL vial contains 50 mg doxorubicin hydrochloride at a concentration of 2 mg/mL.

Refrigerate unopened vials of doxorubicin hydrochloride liposome injection at 2° to 8°C (36° to 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on doxorubicin hydrochloride liposome injection.

The following packages of individually cartoned vials are available:

20 mg vial, 10 mL, 10 mL 47335-049-40

50 mg vial, 25 mL, 30 mL 47335-050-40

20 mg/10 mL – 10 mL vial size (1 vial)- SDV; label color is dark (b) (4)

50 mg/25 mL – 25 mL vial size (1 vial) - SDV; label color is (b) (4)

9. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISON –

RLD: Store refrigerated, 2° to 8°C (36° to 46°F). Protect from light.

(b) (4) Discard unused portion.

ANDA: Store refrigerated 2° to 8°C (36° to 46°F). Protect from light.
Retain in carton until time of use. Discard unused portion.

10. CONTAINER CLOSURE:

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, is filled in, Type-I tubular glass vial, stopper is 20 mm grey (b) (4) rubber stopper and sealed with 20 mm light blue flip off aluminum seal. Duly overprinted vial label is affixed on each vial; labeled vial is placed in one show box along with the package insert containing physician information.

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 25 mL is filled in, Type-I molded glass vial, stopper is 20 mm grey (b) (4) rubber stopper and sealed with 20 mm light blue flip off aluminum seal. Duly overprinted vial label is affixed on each vial,

11. FINISHED PRODUCT DESCRIPTION:

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL
A translucent red colored liposomal dispersion filled in colorless 10 mL USP Type-I tubular glass vial with 20 mm grey (b) (4) rubber stopper, sealed with 20 mm light blue color flip off aluminum seal.

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 25 mL

A translucent red colored liposomal dispersion filled in colorless 30 mL USP Type-I molded glass vial with 20 mm grey (b) (4) rubber stopper, sealed with 20 mm light blue color flip off aluminum seal.

Statement of Composition

Strength	2 mg/mL (10 mL and 25 mL)	
Components	mg/mL	%w/v
Doxorubicin Hydrochloride, USP	2.00	0.200
Hydrogenated Soya Phosphatidyl Choline	9.58	0.958
MPEG-Distearoyl Phosphatidylethanolamine	3.19	0.319
Cholesterol (b) (4) NF	3.19	0.319
Ammonium Sulfate, NF	*1	(b) (4)
Histidine USP		(b) (4)
Sucrose, NF		(b) (4)
Sodium Hydroxide, NF		(b) (4)
Hydrochloric Acid, NF		(b) (4)

*1 Ammonium Sulfate is (b) (4)

(b) (4) approximately 2 mg per mL.

*2 Used for pH adjustment

12. DOSAGE AND ADMINISTRATION:

From Chemistry Review

DILUENT COMPATABILITY: [Acceptable]

Firm demonstrated compatibility with 5% Glucose (b) (4)

Storage and Stability [Acceptable]

13. The following data sections were modified by the carve out of the protected indication:

Reference to the brand name "DOXIL has been replaced by the drug product name "doxorubicin hydrochloride liposome injection"

Highlight section- dosage forms and strengths "30 mL" has been replaced by "25 mL"

Section 6- Adverse reactions“1310 patients” has been replaced by “992 patients”; and “318 patients with multiple myeloma” has been omitted

Section 8.5 Geriatrics - “Of the 318 patients treated with DOXIL in combination with bortezomib for multiple myeloma, 37% were 65 years of age or older and 8% were 75 years of age or older.” has been omitted

Section 11- Description- “STEALTH liposomes” has been replaced by “pegylated liposomes”

Date of Review: 7/12/2012

Date of Submission: 6/16/2012

Primary Reviewer: Angela Payne

Team Leader: John Grace

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

/s/

ANGELA M PAYNE
07/18/2012

JOHN F GRACE
07/23/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203263

CHEMISTRY REVIEWS

ANDA 203-263

**Doxorubicin Hydrochloride Liposome
Injection, 2 mg/mL, 10 mL and 25 mL**

Sun Pharma Global FZE

**Xiaobin Zhao, Ph. D.
Office of Generic Drugs**

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Chemistry Review Data Sheet

1. ANDA #: 203,263

2. REVIEW #: 3

3. REVIEW DATE: January 22, 2013

4. REVIEWER: Xiaobin Zhao, Ph D

5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
Original	June 16, 2011
Response to information request	November 3, 2011
Amendment	March 20, 2012
Amendment	July 5, 2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	December 20, 2012
Amendment	January 22, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Sun Pharma Global FZE

US agent: Vincent Andolina

Address: Sun Pharmaceutical Industries, Inc., 270 Prospect
Plains Road Cranbury, NJ 08512

Telephone: 609-495-2808

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: NA

Non-Proprietary Name (USAN): Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL

Code Name/# (ONDC only): NA

Chem. Type/Submission Priority (ONDC only): NA

- Chem. Type: NA
- Submission Priority: NA

9. LEGAL BASIS FOR SUBMISSION:

The firm listed Doxil® (Doxorubicin HCl liposome injection), 2 mg/mL, 10 mL and 25 mL (NDA# 050718) as the RLD. A certification is provided that no patents are listed for the RLD in the electronic Orange Book, and the RLD is entitled for marketing exclusivity (ODE) which will expire on May 17, 2014. The firm is not seeking approval of the indication covered by the above mentioned exclusivity.

10. PHARMACOL. CATEGORY:

Antineoplastic

11. DOSAGE FORM:

Liposome Injection

12. STRENGTH/POTENCY:

2 mg/mL. Supplied in 20 mg/10 mL or 50 mg/25 mL of single dosage vial for IV injection.

13. ROUTE OF ADMINISTRATION:

i.v. infusion

14. Rx/OTC DISPENSED: Rx OTC

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

_____ SPOTS product – Form Completed

X Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

X NANO product – Form Completed (See Appendix A.4)

_____ Not a NANO product

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

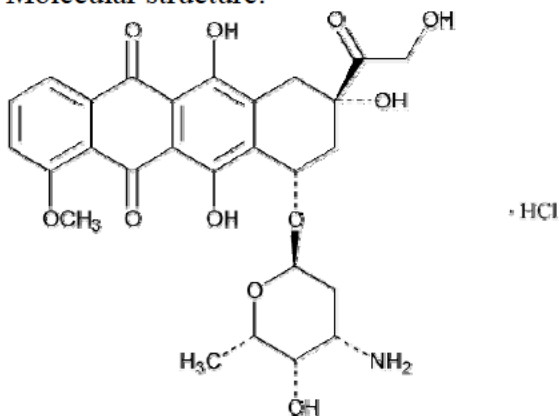
Chemical name: (8*S*,10*S*)-10-[3-Amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl]-oxy-8-glycoloyl]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride

Chemical formula: C₂₇H₂₉NO₁₁HCl

Formula weight: 580

CAS number: 25316-40-9

Molecular structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/8/2012	By Gloria Huang
(b) (4)	(b) (4)		4				
(b) (4)	III		4				
(b) (4)	III		4				
(b) (4)	IV		1	Adequate With info. request	1/17/2013	By B. Scott/DMF review team	
(b) (4)	IV		1	Adequate	1/14/2013	By X. Zhao	



CHEMISTRY REVIEW



Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	50718 by Centocor Ortho Biotech Products	Doxorubicin HCl Liposome Injection

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	5/4/2012	Jesse Wells
EES	Adequate	1/8/2013	
Methods Validation	NA		
Labeling	Adequate	10/18/2012	Angela Payne
Bioequivalence	Adequate	1/9/2013	Suman Dandamudi
EA	Categorical exclusion		
Radiopharmaceutical	NA		



19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes No If no, explain reason(s) below:

On 12/20/2011, expedited review was granted due to drug shortage.

Chemistry Review for ANDA 20-3263

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is approvable based on the product quality assessment.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance: Doxorubicin Hydrochloride is official in the current USP. The API is supplied by (b) (4). The firm referenced DMF (b) (4), which has been reviewed and found adequate. The control of drug substance is as per USP monograph and drug substance manufacturer's in-house specification. The certificate of analysis from the manufacturer is included for the drug substance material used in the exhibit batches # JK93496 (10 mL) and JK93743 (25 mL). The retesting period is assigned as (b) (4).

Drug product: Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, is a translucent red colored liposomal dispersion. The Unit composition contains Doxorubicin HCl, HSPC, MPEG-DSPE, cholesterol, histidine, ammonium sulfate, sucrose (b) (4) HCl, NaOH, (b) (4). The drug product is manufactured (b) (4). The intended commercial batch size and exhibit batch size are (b) (4). The drug loading is through ammonium sulfate gradient. The drug specification tests include description, identification, pH, (b) (4), and assay. The firm has submitted stability data from 6 month accelerated condition, 12 month intermediate condition, and 24 month long term condition from both upright and inverted orientations. Statistical analysis was conducted and the expiration dating is

Executive Summary Section

proposed as 18 months. Comparative analysis of impurities data from RLD and ANDA product also resulted in 18 months.

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

Doxorubicin hydrochloride liposome injection is indicated for the treatment of Ovarian cancer: 50 mg/m² IV every 4 weeks for 4 courses minimum, and AIDS-related Kaposi's Sarcoma: 20 mg/m² IV every 3 weeks.

Review Note: the firm does not propose Multiple Myeloma indication because the exclusivity of RLD has not expired yet.

Maximum daily dose (MDD) for this product is 50 mg/m² (total 90 mg). According to ICH Q3A, for a drug substance with 90 mg MDD, Identification threshold and Qualification threshold are 0.10% and 0.15%, respectively. According to ICH Q3B, for a drug product with 90 mg MDD, Identification threshold and Qualification threshold are 0.20 % and (b) (4) %, respectively. However, since this is a (b) (4) product, the limits may vary from the ICH guidances.

Doxorubicin hydrochloride liposome injection doses up to 90 mg must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in doxorubicin hydrochloride liposome injection. Diluted doxorubicin hydrochloride liposome injection should be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours.

Review Note: In-use dilution stability data has been reviewed to ensure the physicochemical properties are acceptable for infusion. There is no in-line filters used in the infusion. The study should be conducted at the lowest and highest possible concentrations during treatment.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA sponsor has adequately addressed all the deficiencies raised during the product quality review. The drug product shelf life is proposed as 18 months, based on the statistical evaluation of multiple batches, RLD shelf life, and levels of impurity at (b) (4)

The DMF (b) (4) for Doxorubicin HCl is adequate. The DMF (b) (4) is adequate. The DMF (b) (4) is adequate with information request. The manufacturing facility establishment recommendation is acceptable.

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

A. Labeling & Package Insert

Draft carton, container labels, annotated draft labeling text, draft labeling text, and comparison of labeling with the RLD are provided in 1.14.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The firm claimed a categorical exclusion from the requirement of an Environmental Assessment (EA) statement.

III. List Of Deficiencies To Be Communicated:

None. The ANDA is recommended for an approval.

Endorsements:

HFD-640 /Xiaobin Zhao/ 1/13/2013; 1/22/2013

HFD-640 /R. Rajagopalan/ 1/17/13 (t-con request); 1/23/2013

HFD-617/F.Nice/

TYPE OF LETTER: APPROVAL

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

/s/

XIAOBIN ZHAO
01/25/2013

FRANK J NICE
01/25/2013

RADHIKA RAJAGOPALAN
01/25/2013

GLEN J SMITH
01/25/2013

ANDA 203-263

**Doxorubicin Hydrochloride Liposome
Injection, 2 mg/mL, 10 mL and 25 mL**

Sun Pharma Global FZE

Xiaobin Zhao, Ph. D.

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Chemistry Review Data Sheet

1. ANDA #: 203,263

2. REVIEW #: 2

3. REVIEW DATE: Aug. 9, 2012

4. REVIEWER: Xiaobin Zhao, Ph D

5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
Original	June 16, 2011
Response to information request	November 3, 2011
Amendment	March 20, 2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	July 5, 2012

7. NAME & ADDRESS OF APPLICANT:

Name: Sun Pharma Global FZE
US agent: Vincent Andolina
Address: Sun Pharmaceutical Industries, Inc., 270 Prospect
Plains Road Cranbury, NJ 08512
Telephone: 609-495-2808

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: NA

Non-Proprietary Name (USAN): Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL

Code Name/# (ONDC only): NA

Chem. Type/Submission Priority (ONDC only): NA

- Chem. Type: NA
- Submission Priority: NA

9. LEGAL BASIS FOR SUBMISSION:

The firm listed Doxil® (Doxorubicin HCl liposome injection), 2 mg/mL, 10 mL and 25 mL (NDA# 050718) as the RLD. A certification is provided that no patents are listed for the RLD in the electronic Orange Book, and the RLD is entitled for marketing exclusivity (ODE) which will expire on May 17, 2014. The firm is not seeking approval of the indication covered by the above mentioned exclusivity.

10. PHARMACOL. CATEGORY:

Antineoplastic

11. DOSAGE FORM:

Liposome Injection

12. STRENGTH/POTENCY:

2 mg/mL. Supplied in 20 mg/10 mL or 50 mg/25 mL of single dosage vial for IV injection.

13. ROUTE OF ADMINISTRATION:

i.v. infusion

14. Rx/OTC DISPENSED: Rx OTC

Chemistry Review Data Sheet

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

_____ SPOTS product – Form Completed

X Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

X NANO product – Form Completed (See Appendix A.4)

_____ Not a NANO product

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

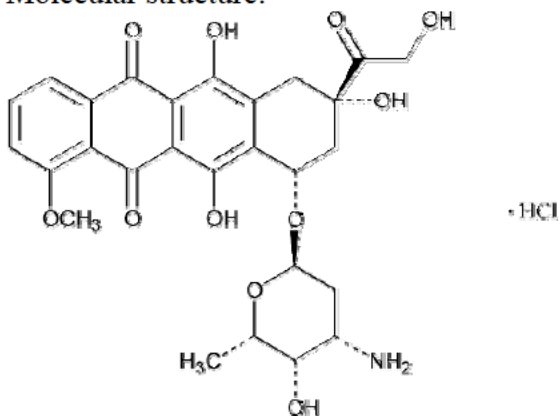
Chemical name: (8*S*,10*S*)-10-[3-Amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl]-oxy-8-glycoloyl]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride

Chemical formula: C₂₇H₂₉NO₁₁HCl

Formula weight: 580

CAS number: 25316-40-9

Molecular structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	9/19/2012	By Gloria Huang
(b) (4)	(b) (4)		4				
	III		4				
	III		4				
	IV		1	Inadequate	10/25/2012	B. Scott/DMF review team	
	IV		1	Inadequate	10/22/12	X. Zhao	

Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	50718 by Centocor Ortho Biotech Products	Doxorubicin HCl Liposome Injection

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	5/4/2012	Jesse Wells
EES	Pending	4/23/12	
Methods Validation	NA		
Labeling	Adequate	10/18/2012	Angela Payne
Bioequivalence	Inadequate	9/18/2012	Suman Dandamudi
EA	Categorical exclusion		
Radiopharmaceutical	NA		



19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes No If no, explain reason(s) below:

On 12/20/2011, expedited review was granted due to drug shortage.

Chemistry Review for ANDA 20-3263

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a quality perspective, the applicant still needs to address several minor quality deficiencies prior to an approval.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance: Doxorubicin Hydrochloride is official in the current USP. The API is supplied by (b) (4). The firm referenced DMF (b) (4), which has been reviewed and found adequate. The control of drug substance is as per USP monograph and drug substance manufacturer's in-house specification. The certificate of analysis from the manufacturer is included for the drug substance material used in the exhibit batches # JK93496 (10 mL) and JK93743 (25 mL). The retesting period is assigned as (b) (4).

Drug product: Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, is a translucent red colored liposomal dispersion. The Unit composition contains Doxorubicin HCl, HSPC, MPEG-DSPE, cholesterol, histidine, ammonium sulfate, sucrose (b) (4) HCl, NaOH, (b) (4).

(b) (4) The drug product is manufactured (b) (4)

The intended commercial batch size and exhibit batch size are (b) (4)

(b) (4) The drug loading is through ammonium sulfate gradient. The drug specification tests include Description, Identification, pH, (b) (4)

(b) (4) and Assay. The firm has submitted stability data from 6 month accelerated condition, 12 month intermediate condition, and 24 month long term condition from both upright and inverted

Executive Summary Section

orientations. Based on the submission, the stability data is insufficient to support the (b) (4) month expiration date proposed by the firm.

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

Doxorubicin hydrochloride liposome injection is indicated for the treatment of Ovarian cancer: 50 mg/m² IV every 4 weeks for 4 courses minimum, and AIDS-related Kaposi's Sarcoma: 20 mg/m² IV every 3 weeks.

Review Note: the firm does not propose Multiple Myeloma indication because the exclusivity of RLD has not expired yet.

Maximum daily dose (MDD) for this product is 50 mg/m² (total 90 mg). According to ICH Q3A, for a drug substance with 90 mg MDD, Identification threshold and Qualification threshold are 0.10% and 0.15%, respectively. According to ICH Q3B, for a drug product with 90 mg MDD, Identification threshold and Qualification threshold are 0.20 % and (b) (4) %, respectively. However, since this is a (b) (4) product, the limits may vary from the ICH guidances.

Doxorubicin hydrochloride liposome injection doses up to 90 mg must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in doxorubicin hydrochloride liposome injection. Diluted doxorubicin hydrochloride liposome injection should be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours.

Review Note: In-use dilution stability data should be reviewed to ensure the physicochemical properties are acceptable for infusion. There is no in-line filters used in the infusion. The study should be conducted at the lowest and highest possible concentrations during treatment.

C. Basis for Approvability or Not-Approval Recommendation

The firm needs to revise the drug product specification (b) (4) and implement better in-process controls. The submitted stability data is not supportive towards the proposed (b) (4) month expiration date. Minor issues are outlined in the draft deficiency letter at the end of this review document.

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

A. Labeling & Package Insert

Draft carton, container labels, annotated draft labeling text, draft labeling text, and comparison of labeling with the RLD are provided in 1.14.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The firm claimed a categorical exclusion from the requirement of an Environmental Assessment (EA) statement.

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203263

APPLICANT: Sun Pharma Global FZE

DRUG PRODUCT: Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL,
10 mL and 25 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

5.

6.

7.

(b) (4)

8.

(b) (4)

9.

10

11

12

13

14

Sincerely,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:

HFD-640 /Xiaobin Zhao/ 8/9/2012, 10/4/2012; 10/26/12

HFD-640 /R. Rajagopalan/ 8/27/12; 10/22/2012; 10/23/12; 10/26/12

HFD-617/F.Nice/10/31/12

TYPE OF LETTER: NOT APPROVABLE – MINOR

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

/s/

XIAOBIN ZHAO
10/31/2012

FRANK J NICE
11/01/2012

RADHIKA RAJAGOPALAN
11/01/2012

ANDA 203-263

**Doxorubicin Hydrochloride Liposome
Injection, 2 mg/mL, 10 mL and 25 mL**

Sun Pharma Global FZE

**Xiaobin Zhao
Chemistry Division II**

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2.3.P.3 Manufacture [Doxorubicin Hydrochloride Liposome Injection]	41
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2.3.P.5 Control of Drug Product [Doxorubicin Hydrochloride Liposome Injection].....	65
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2.3.P.8 Stability [Doxorubicin Hydrochloride Liposome Injection]	90

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Chemistry Review Data Sheet

1. ANDA #: 203,263

2. REVIEW #: 1

3. REVIEW DATE: January 31, and March 12, 2012

4. REVIEWER: Xiaobin Zhao, Ph D

5. PREVIOUS DOCUMENTS:

Previous Document(s)

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

June 16, 2011

Response to information request

November 3, 2011

Amendment

March 20, 2012

7. NAME & ADDRESS OF APPLICANT:

Name: Sun Pharma Global FZE

US agent: Vincent Andolina

Address: Sun Pharmaceutical Industries, Inc., 270 Prospect
Plains Road Cranbury, NJ 08512

Telephone: 609-495-2808

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: NA

Non-Proprietary Name (USAN): Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL

Code Name/# (ONDC only): NA

Chem. Type/Submission Priority (ONDC only): NA

- Chem. Type: NA
- Submission Priority: NA

9. LEGAL BASIS FOR SUBMISSION:

The firm listed Doxil® (Doxorubicin HCl liposome injection), 2 mg/mL, 10 mL and 25 mL (NDA# 050718) as the RLD. The firm provided a certification that no patents are listed for the RLD in the electronic Orange Book, and the RLD is entitled for marketing exclusivity (ODE) which will expire on May 17, 2014. The firm is not seeking approval of the indication covered by the above mentioned exclusivity.

10. PHARMACOL. CATEGORY:

Antineoplastic

11. DOSAGE FORM:

Liposome Injection

12. STRENGTH/POTENCY:

2 mg/mL. Supplied in 20 mg/10 mL or 50 mg/25 mL of single dosage vial for IV injection.

13. ROUTE OF ADMINISTRATION:

i.v. infusion

14. Rx/OTC DISPENSED: X Rx OTC

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

_____ SPOTS product – Form Completed

X Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

X NANO product – Form Completed (See Appendix A.4)

_____ Not a NANO product

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

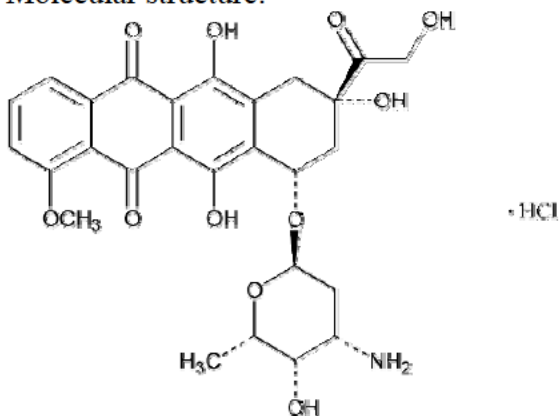
Chemical name: (8*S*,10*S*)-10-[3-Amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl]-oxy-8-glycoloyl]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride

Chemical formula: C₂₇H₂₉NO₁₁HCl

Formula weight: 580

CAS number: 25316-40-9

Molecular structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	1/18/2012 By Nguyen, Ryan	
	(b) (4)		4				
	III		4				
	III		4				
	IV		1			Under review	
	IV		1			Under review	



CHEMISTRY REVIEW



Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	50718 by Centocor Ortho Biotech Products	Doxorubicin HCl Liposome Injection

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Inadequate	2/8/2012	Jesse Wells
EES	Pending	4/23/12	
Methods Validation	NA		
Labeling	NA		
Bioequivalence	Inadequate	2/16/2012 4/3/2012	Shriniwas Nerurkar Suman Dandamudi
EA	Categorical exclusion		
Radiopharmaceutical	NA		



19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes No If no, explain reason(s) below:

On 12/20/2011, expedited review granted due to drug shortage.

Chemistry Review for ANDA 20-3263

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a quality perspective, the application is not approvable due to minor quality deficiencies. This is the 1st generic application of Doxorubicin Hydrochloride Liposome Injection.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance: Doxorubicin Hydrochloride is official in the current USP. The API is supplied by (b) (4). The firm referenced DMF (b) (4), which has been reviewed and found adequate. The control of drug substance is as per USP monograph and drug substance manufacturer's in-house specification. The certificate of analysis from the manufacturer is included for the drug substance material used in the exhibit batches # JK93496 (10 mL) and JK93743 (25 mL). The retesting period is assigned as (b) (4).

Drug product: Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, is a translucent red colored liposomal dispersion. The Unit composition contains Doxorubicin HCl, HSPC, MPEG-DSPE, Cholesterol, Histidine, Sucrose (b) (4), Ammonium sulfate, HCl, NaOH, (b) (4).

(b) (4) The drug product is manufactured (b) (4)

(b) (4) The intended commercial batch size and exhibit batch size are (u) (4). The drug loading is through ammonium sulfate gradient. Upon review, there are not sufficient in-process controls in the manufacturing process. The drug specification tests include Description, Identification, pH, (b) (4)

(b) (4) and Assay. We recommend

Executive Summary Section

that additional tests be included in the release and stability specifications. The firm has submitted stability data from 6 month accelerated condition, 12 month intermediate condition, and 12 month long term condition from both upright and inverted orientations. Based on the submission, the stability data is insufficient to support the (b) (4) month expiration date proposed by the firm.

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

Doxorubicin hydrochloride liposome injection is indicated for the treatment of Ovarian cancer: 50 mg/m² IV every 4 weeks for 4 courses minimum, and AIDS-related Kaposi's Sarcoma: 20 mg/m² IV every 3 weeks.

Review Note: the firm does not propose Multiple Myeloma indication because the exclusivity of RLD has not expired yet.

Maximum daily dose (MDD) for this product is 50 mg/m² (total 90 mg). According to ICH Q3A, for a drug substance with 90 mg MDD, Identification threshold and Qualification threshold are 0.10% and 0.15%, respectively. According to ICH Q3B, for a drug product with 90 mg MDD, Identification threshold and Qualification threshold are 0.20 % and (b) (4) %, respectively. However, since this is a (b) (4) product, the limits may vary from the ICH guidances.

Doxorubicin hydrochloride liposome injection doses up to 90 mg must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in doxorubicin hydrochloride liposome injection. Diluted doxorubicin hydrochloride liposome injection should be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours.

Review Note: In-use dilution stability data should be reviewed to ensure the physicochemical properties are acceptable for infusion. There is no in-line filter used in the infusion. The study should be conducted at the lowest and highest possible concentrations during treatment.

C. Basis for Approvability or Not-Approval Recommendation

The firm needs to revise the drug product specification and implement better in-process controls. The submitted stability data is not supportive towards the proposed (b) (4)-month expiration date. Minor issues are outlined in the draft deficiency letter at the end of this review document.

(b) (4)

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

A. Labeling & Package Insert

Draft carton, container labels, annotated draft labeling text, draft labeling text, and comparison of labeling with the RLD are provided in 1.14.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The firm claimed claims a categorical exclusion from the requirement of an Environmental Assessment (EA) statement.

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203263

APPLICANT: Sun Pharma Global FZE

DRUG PRODUCT: Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

The following are deficiencies related to **Drug Substance**:

1.  (b) (4)

The following are deficiencies related to **Manufacture**:

2.  (b) (4)
3. 

31.

32.

33.

(b) (4)

B. Comments:

In addition to the deficiencies above, please acknowledge the following in your response:

1.

2.

3.

4.

(b) (4)

Sincerely,

{See appended electronic signature page}



CHEMISTRY REVIEW



Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:

HFD-640 /Xiaobin Zhao/ 1/23/2012, 3/12/2012, 4/12/2012; 4/17/2012; 4/20/12

HFD-640 /Radhika Rajagopalan/2/24/2012; 4/9/12; 4/13/12; 4/16/2012;
4/18/2012; 4/22/12

HFD-617/Frank Nice/4/23/12

TYPE OF LETTER: NOT APPROVABLE - MINOR/FACSIMILE

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

/s/

XIAOBIN ZHAO
04/23/2012

FRANK J NICE
04/23/2012

RADHIKA RAJAGOPALAN
04/23/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203263

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203263		
Drug Product Name	Doxorubicin hydrochloride Liposome Injection		
Strength(s)	2 mg/mL, 10 mL and 25 mL		
Applicant Name	Sun Pharma Global FZE		
Address	Office # 43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U.A.E		
Applicant's Point of Contact	Robert Kurkiewicz		
	Sun Pharmaceutical industries Ltd. (C/O Caraco) 1150 Elijah Mccoy Drive, Detroit, MI 48202		
Contact's Telephone Number	313-556-4105		
Contact's Fax Number	248-926-0231		
Original Submission Date(s)	June 16, 2011 March 07, 2012 (Telephone Amendment) April 9, 2012 May 10, 2012 (Telephone Amendment) June 29, 2012 (Telephone Amendment) July 4, 2012 (Telephone Amendment) August 4, 2012 (Amendment) October 5, 2012 (Amendment)		
Submission Date(s) of Amendment(s) Under Review	December 20, 2012		
Reviewer	Suman Dandamudi Ph.D		
Study Number (s)	PKD_09_030	DOX/003/08	FDD-02/10-11/001
Study Type (s)	Fed	Pilot Fed	In-Vitro
Strength (s)	2 mg/mL	2 mg/mL	2 mg/mL
Clinical Site-1	MNJ Institute of Oncology & Regional Cancer Centre		
Clinical Site-1 Address	Red Hills, Hyderabad- 500 004, India		
Clinical Site-2	Kailash Cancer Hospital & Research Centre		
Clinical Site-2 Address	Goraj, Vadodara- 391760, India		
Clinical Site-3	Dr. G. Vishwanathan Speciality Hospitals		
Clinical Site-3 Address	#27, Babu road, Trichy, Tamilnadu- 620 008, India		
Clinical Site-4	Dr. Kamakshi Memorial Hospital		
Clinical Site-4 Address	No.1, Radial Road, Palikaranai, Chennai- 600 100, India		
Clinical Site-5	NRR Hospital		
Clinical Site-5 Address	Chikkasandra, Bangalore- 560090 (India)		
Analytical Site (fed study)	Sun Pharmaceutical Industries Ltd.,		
Analytical Site Address (fed)	Sun Pharmaceutical Industries Ltd.,		

study)	Tandalja, Vadodara -390020, India		
In Vitro Liposome Size Distribution Testing Site	Sun Pharmaceutical Industries Ltd.,		
In Vitro Testing Site Address	Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India		
REVIEW RESULT	ADEQUATE		
OSI REPORT RESULT	ADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 8, 9, 10, 11	IN VITRO DRUG RELEASE*	2 MG/ML	ADEQUATE
1, 8	FED STUDY	2 MG/ML	ADEQUATE
1, 8	IN VITRO STUDY	2 MG/ML	ADEQUATE

*NOTE: There is no dissolution testing for this drug product, but there is in vitro drug release testing.

REVIEW OF AN AMENDMENT (OSI/ORA INSPECTION REPORT)

1 EXECUTIVE SUMMARY

Sun Pharma has submitted ANDA 203263 for its test product, Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL. The submission references NDA 050718, Doxil[®] (Doxorubicin Hydrochloride) Liposomal Injection, 2 mg/mL from Ortho Biotech.

The firm, in the current amendment dated December 20, 2012, submitted its response to the deficiency comments made by the Division of Bioequivalence I (DBI) in the letter dated November 14, 2012 [DARRTS: PARK, LINDA M 11/14/2012 MAIL 11/14/2012 COR-ANDAACTION-09(Complete Response) Original-1 (Unknown) Archive].

At the request of Office of Generic Drugs (OGD)/DBI, the OSI/ORA conducted an audit of the clinical portion of in-vivo fed bioequivalence study at the clinical site NRR Hospital Bangalore, India. This was one of the five clinical sites used for the BE study of the current ANDA. It should be noted that prior to this inspection, the OSI/ORA inspected two other clinical sites, MNJ Institute of Oncology & Regional Cancer Center, Hyderabad, India and Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai, India for another application and classified these two sites No Action Indicated (NAI).

Following the inspection of the third site (August 27- September 4, 2012), a Form 483 was issued to NRR Hospital Bangalore, India [DARRTS: CHOI, YOUNG M 11/29/2012 N/A 11/29/2012 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Unknown) Archive]. The inspection of the clinical site was

conducted by Mr. Scott B. Laufenberg (OIP – India FDA Office) at NRR Hospital, Bangalore, India (NRR)

Due to the expedite status of the ANDA, the DBI reviewed Form 483 (which was provided to the division on 11/09/2012) before the OSI complete its review of Form 483 and the site's response to the form. Based on the above Form 483, the DBI found the objectionable findings by the OSI at the clinical site which could potentially compromise the integrity of the study results. Therefore, the firm was asked to address the above specific inspection findings by the OSI/ORA, providing any necessary supporting documents in its response [DARRTS: DANDAMUDI, SUMAN 11/13/2012 N/A 11/13/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].

In the current amendment, the firm submitted adequate responses for the objectionable OSI/ORA findings. Therefore, the fed bioequivalence study submitted for Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL is acceptable.

Additionally, the reviewer of the current ANDA evaluated Form 483, the OSI review of Form 483 and the site's response to Form 483, for the purpose of providing relevant inspection findings to reviewers of related ANDAs, for which the studies were conducted at the same site. Although the OSI inspection findings were found not to affect the integrity and outcome of the BE studies of the current ANDA, some OSI findings may be considered systemic and potentially impact the studies of other related ANDAs.

OSI Inspectional Findings' Impact on Other Related ANDAs:

The OSI/ORA report contains some systemic findings and therefore, should be reviewed for the impact on the related ANDAs.

☐ Isolated	☒ Systemic

OSI Inspections:**Clinical site for Fed BE Study:**

The fed BE study was conducted at multiple sites.

No	Name of Clinical Site	Group number/Site ID	Number of Patients	OSI Inspection Status
1	MNJ Institute of Oncology & Regional Cancer Center, Hyderabad	1/A	31	NAI
2	Kailash Cancer Hospital and research Center, Goraj, Vadidara	2/B	5	-
3	Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu	3/D	11	-
4	Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai	4/E	4	NAI
5	NRR Hospital, Bangalore	5/G	9	VAI

MNJ Institute of Oncology & Regional Cancer Center, Hyderabad and Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai

The above clinical sites were inspected for ANDA 201742 (Routine) on 02/22/2012 and the outcome was NAI [DARRTS: MADA, SRIPAL R 02/22/2012 N/A 02/22/2012 CONSULT REV-BIOEQ-01(General Consult Review) Original-1 (Not Applicable) Archive].

NRR Hospital, Bangalore

The above clinical site was inspected for current ANDA 203263 (Routine) on 11/20/2012 and the outcome was VAI [DARRTS: CHOI, YOUNG M 11/29/2012 N/A 11/29/2012 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Unknown) Archive].

Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu

Due to the expedited status of the application, as well as the fact that the three inspection sites accounted for 44 out of 66 patients enrolled in the BE study, or 73% of the total number of study patients, the OGD/DBI has determined that the pending inspection was not necessary [DARRTS: DANDAMUDI, SUMAN 11/13/2012 N/A 11/13/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].

Analytical site for Fed BE Study:

A for-cause Office of Scientific Investigations (OSI) inspection was requested for the analytical site of ANDA 090886 on May 20, 2010 and is still pending the outcome of the request [DARRTS: POPAT, ALPITA 05/21/2010 N/A 05/21/2010 FRM-CONSULT-09 (DSI Bioequivalence Audit Request) Original-1 Archive].

However upon further consideration, the DBI identified an available For-Cause OSI inspection at the same site, which was conducted previously for ANDA 090362, with the outcome of the inspection of VAI. The study sample analyses of the fasting and fed BE

studies of ANDA 090362 were conducted between Oct-Dec 2007, whereas the sample analyses for the fed BE study in the current application was performed between June 2010 and March 2011.

Due to the expedite status of the current ANDA 203263 based on the drug shortage, the OSI inspection findings for ANDA 090362 were considered even though there is greater than three year difference between the studies of ANDA 090362 and current ANDA 203263. The analytical site was inspected for ANDA 090362 (for cause) on 6/14/2010 and the outcome of the OSI inspection was VAI [**DARRTS for ANDA 090362: BISWAS, GOPA 06/17/2010 N/A 06/17/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection report Review) Original-1 Archive**]. After the evaluation of the OSI inspection report for ANDA 090362, the DBI determined that the OSI's findings at this site **do not have any significant impact** on fed BE study of the current ANDA 203263 [**DARRTS: DANDAMUDI, SUMAN 11/13/2012 N/A 11/13/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive**].

In Vitro Testing Site (Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India)

The above site was inspected for current ANDA 203263 (routine inspection) on 11/20/2012 and the outcome was VAI [**DARRTS: CHEN, XIKUI 08/17/2012 N/A 08/17/2012 CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) Original-1 (Unknown) Archive**]. After the evaluation of the OSI/ORA inspection report, the DBI determined that the OSI's finding **may have an impact** on the in vitro BE study. The firm was asked to address the DBI concerns related to the OSI/ORA's finding. The firm's responses were found acceptable [**DARRTS: DANDAMUDI, SUMAN 11/13/2012 N/A 11/13/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive**].

The application is now **adequate (acceptable) with respect to bioequivalence testing**.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information, PK/PD Information, and Relevant DB History

See the review of the original submission, DARRTS: NERURKAR, SHRINIWAS G 02/16/2012 N/A 02/16/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive.

3.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

3.3 Review of Current Amendment

DBI's Previous Deficiency Comments:

Between 8/27/2012 and 9/4/2012, the Office of Scientific Investigations (OSI) inspected the clinical site, NRR Hospital, Bangalore, India, which was used as one of the clinical sites for your fed bioequivalence (BE) study of the current application. A form 483 was issued to the site following the inspection.

Please address the following inspection findings cited in the Form 483 and their impact on the integrity of the BE study results:

OSI/ORA Finding #1: *Failure to maintain possession and/or control of investigational product test and reference retention samples. Specifically test and reference retention samples maintained per regulatory requirements were shipped to a third party archival site on 18 Aug 2011; per the sponsor's request. The study sponsor made the arrangements with the third party archival facility, entered into a contract with the archival facility and requested the PI send the retention samples to that facility for storage. Due to the fact the sponsor was the only entity that signed this contract, the sponsor may have had access to the samples. There was no assurance provided that only the PI could access and retrieve the retention samples.*

OSI Evaluation of ORA Finding #1: OSI has provided the following detailed explanation for the above finding along with their evaluation for the firm's response to the Form FDA-483:

In their response to Form FDA-483, NRR stated that the product was transferred from the clinical site to a third party (b) (4) directly and returned to the clinical site for the FDA inspection. Following NRR's request, the third party contact (b) (4) provided a letter confirming that the sponsor *has not accessed* the reserve samples at (b) (4)

The sponsor shipped test and reference products to this clinical site on three occasions. NRR retained a total of eight test units and three reference units. However, NRR did not retain the reserves from each shipment, as required by the Final Rule, item 3d. The dates of shipment from drug accountability and dispensing records show that the three units of reference and test products must have been retained from the first shipment on 10/28/2010. However, we cannot ascertain where the additional five units of test reserve were originated. NRR selection of reserve samples for retention did not meet the requirements of the Final Rule. However, this reviewer notes that each of the three shipments of test and reference products came from the same respective lots.

Firm's Response to OSI/ORA Finding#1: As per the compliance report of the Principal Investigator, the sponsor *did not access* the investigational product test/reference retention

samples during the course of archival, hence there is no impact on the integrity of the bioequivalence study results.

Reviewer’s Comments on Firm’s Response #1:

- As per CFR § 320.63, “*The applicant of an ANDA or a supplemental application submitted under section 505 of the Federal Food, Drug and Cosmetic Act or if bioequivalence testing was performed under contract, the contract research organization shall retain reserve samples of any test article and reference standard used in conducting an in vivo or in vitro bioequivalence study required for approval of application*”. During the inspection, the inspector found that **the firm failed to maintain control of investigational test and reference retention samples.**
- In the response the firm stated that the product was transferred from the clinical site to a third party ((b) (4)) directly and returned to the clinical site for the FDA inspection.
- The ORA inspector suspects that the sponsor may have had access to these retention samples that were stored in the third party archival facility, since the sponsor was the only entity that signed this contract. In addition there was no assurance provided that only the PI could access and retrieve the retention samples.
- The OSI reviewer stated that, in response submitted to the CDER (OSI) for the 483 findings the firm provided a letter from the third party confirming that the sponsor has not accessed the reserve samples at (b) (4) .
- NRR retained a total of eight test units and three reference units. The OSI reviewer stated that even though the NRR selection of reserve samples for retention did not meet the requirements, but each of the three shipments of test and reference products came from the same respective lots (See attachment section).
- The reviewer agrees with the OSI/ORAs finding and conclusion. The reviewer agrees with the firm’s response that since the sponsor did not access the investigational product test/reference retention samples during the course of archival, there is no impact on the integrity of the bioequivalence study results. **The firm’s response is acceptable.**

Parent ANDA Reviewer Comment #1 for Related ANDAs:

Because of the systemic problems in clinical conduct, the above OSI/ORAs finding may have potential impact on related ANDAs conducted at the same clinical site during the similar study period.

☐ Isolated	☒ Systemic

¹ DARRTS for ANDA 203263: CHOI, YOUNG M 11/29/2012 N/A 11/29/2012 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Unknown) Archive

OSI/ORA Finding #2: *Failure to assure that an Ethics committee complying with applicable regulatory requirements and following their own written procedures was responsible for the initial and continuing review and approval of a clinical study.*

Specifically,

A) Letter dated 03 Nov 2010 from the PI, provides the IEC with protocol amendment/version D05 (dated 30 Oct 2010) and informed consent document Version D05, dated 14 Oct 2010 in English and Kannada languages. There was no correspondence from the IEC that the documents had been reviewed and approved; however the study was conducted per amendment D05 and consent Version D05 was used to consent/re-consent subjects.

B) Letter dated 15 Dec 2010 from the PI, provides the IEC with informed consent document Version D06, dated 10 Dec 2010 in English and Kannada languages. There was no correspondence from the IEC that the documents had been reviewed and approved; however consent version D05 was used to consent/re-consent subjects.

OSI Evaluation of ORA Finding #2: OSI has provided the following detailed explanation for the above finding along with their evaluation for the firm's response to the Form FDA-483:

In response to this observation in Form FDA-483, NRR asked the ethics committee for review and approval of the protocol amendment/informed consent version D05 and D06. The chairperson of the IEC evaluated the documents and sent correspondence indicating that the changes (increasing subject recruitment from 24 to 36, and subject injury compensation) are minor with respect to the safety of patients, because the procedures and safety criteria approved in the earlier protocol were not affected.

This reviewer is of the opinion that post-hoc review and approval by the IEC are not ideal; however, the correspondence clarifies the IEC chairperson's position that the protocol changes had no significant impact on subject safety.

Firm's Response to OSI/ORA Finding #2: As per the compliance report of the Principal Investigator, the Ethics Committee had clarified that the changes in ICF were minor and were for betterment of the subjects study participation liabilities and provided the communication for approval concurrently based on FDA 483 citation. Since the approval of Ethics Committee is in place there is no impact on the integrity of the Bioequivalence study results.

Reviewer's Comments on Firm's Response #2:

- The firm conducted the clinical study following the protocol (version D05) and ICF (version D06). During the inspection, ORA inspector found that the firm conducted the study without prior approval of the versions D05 and D06 by the Ethics Committee.

- As per the clinical report (study No PKD_09_030), the firm has taken the approvals for the conductance of the study from the respective ethics committees of all the five centers. The following statements were provided regarding the NRR Hospital: *“The clinical Protocol Number DOX_2I_1476_09, Version D04; (Dated 22nd September 2010) and Informed Consent Form, Version D04 (Dated 22nd September 2010) were approved by Institutional Ethics committee NRR Hospital, Bangalore on 25th October 2010. Same protocol and ICF was amended to version D05 regarding change in sample size and used for the study. Summary of changes in this approved ICF was taken regarding change in subject’s compensation. Amendment in this approved protocol and ICF was taken and same was communicated to IEC. Protocol with version D05 (Dated 30th October 2010) and ICF with version D06 (Dated 10th December 2010) was used for the study”.*
- In Module 5.3.1.2.4, the firm provided the protocol version D05, which includes the summary page for changes from protocol version 04 to 05. The only change made was increasing the number of patients from 24 to 36. The protocol version D05 submitted has ethics committee approved stamp at the end of the page. See below for the snapshot of protocol version D05 (Figure 1).
- Similarly, in Module 5.3.1.2.6, the firm provided the Informed Consent Form version 6, which includes the summary page for changes from ICF version 05 to 06. The only change was made in the compensation of patients for injury due to the participation in the study. See below for the snapshot of ICF version D06 (Figure 2)
- In response to the 483 findings, the firm stated that based on the FDA observation, ethics committee was further approached regarding the review and approval of protocol (version D05) and ICF (version D06). The firm also stated that the IEC chairman has clarified that these are minor changes due to which safety criteria approval in earlier protocol are unaffected and the changes made in ICF version D06 are for betterment of subjects.
- The OSI reviewer is of opinion that post-hoc review and approval by the IEC are not ideal; however, the correspondence clarifies the IEC chairperson’s position that the protocol changes had no significant impact on subject safety.
- The reviewer agrees with the OSI finding and conclusion. The reviewer finds that the above OSI finding does not have any impact the outcome of the bioequivalence study results. **The firm’s response is acceptable.**



Parent ANDA Reviewer Comment #2 for Related ANDAs:

Reviewers of related ANDA's should verify if the version of protocol and ICF used for the clinical study were approved by the ethics committee before the conductance of the

bioequivalence study. Because of the systemic problems in clinical conduct, the above OSI finding may have potential impact on related ANDAs conducted at the same clinical site during the similar study period.

☐ Isolated	☒ Systemic

OSI/ORA Finding #3: *Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study related activities. Specifically, the original, signed study specific Informed Consent Form for Subjects #44 and #59 was a poor quality scanned copy of original document. This scanned copy of the form is very difficult to read, possibly illegible.*

OSI Evaluation of ORA Finding #3: OSI has provided the following detailed explanation for the above finding along with their evaluation for the firm's response to the Form FDA-483:

In their response to Form FDA-483, NRR acknowledged that the copy of the informed consent form (ICF), written in the vernacular language, for subjects #44 and #59 was difficult to read, but that it was legible by a person familiar with the vernacular language.

Subjects #44 and #59 were discontinued from the study because of severe adverse events in period 1. This reviewer is of the opinion that the adverse events in these patients were due to the investigational drug products, and unrelated to the legibility of the ICF.

Firm's Response to OSI/ORA Finding #3: As per the compliance report of the investigator, during study, the ICF copy (Vernacular Language) used in the study were printed copies of Scanned copy of the original ICF and ICF copies for subject number 044 and 059 were poor in quality, but readable to the persons conversant in vernacular language, the content of the ICF has been understood by the subject, thus there is no impact on the integrity of the bioequivalence results. However Principal Investigator has adapted corrective measures for the controlled access and usage of control copy of ICF for further studies.

Reviewer's Comments on Firm's Response #3: During the inspection, ORA inspector found that the ICF's for subjects 44 and 59 written in native language were difficult to read. In response to the 483 findings, the firm stated that the ICF copies were printed copies of Scanned copy of the original ICF. In addition, the firm acknowledged that these copies were poor in quality. However, the firm stated that these copies are readable to the people who are fluent in the native language and thus the content was understood by the patients.

In any case, patients# 44 and 59 were dropped from the clinical study due to adverse events. Therefore, the above OSI finding does not affect the outcome of the bioequivalence study. **The firm's response is acceptable.**

Parent ANDA Reviewer Comment #3 for Related ANDAs:

The above OSI/ORA finding is specific to the current/parent ANDA and should have no significant impact on related ANDAs.

☒ Isolated	☐ Systemic

OSI/ORA Finding #4: *There was no statement in the informed consent for screening document that described the extent, if any, to which confidentiality of records identifying the subjects would be maintained, and that noted the possibility that regulatory agencies might inspect the records.*

OSI Evaluation of ORA Finding #4: OSI has provided the following detailed explanation for the above finding along with their evaluation for the firm's response to the Form FDA-483:

In response, the firm proposes to modify future ICFs to include confidentiality of records. In the opinion of this reviewer, the corrective action is adequate.

Firm's Response to OSI/ORA Finding#4: As per the compliance report of the Principal Investigator, the subject has consented in the study ICF apart from screening ICF, in which the statement of confidentiality is captured. Hence there is no impact on the integrity of the bioequivalence study results.

As a corrective action the screening and the study ICF shall be merged by the Principal Investigator for future studies.

Reviewer's Comments on Firm's Response #4: During the inspection, ORA inspector found that the screening documents do not contain the statement on "confidentiality maintenance of the subjects". In the response to the 483 findings, the firm stated that when the clinical study was conducted, the process of obtaining screening consent was followed in which statement of maintaining the confidentiality of the subjects is not captured. However, the subjects also had consented in study ICF, in which the statement of maintaining the confidentiality of the subjects is captured.

The firm stated that as a corrective action, in the forthcoming studies the process of obtaining the screening consent separately will be removed and the study ICF of obtaining informed consent will be followed capturing the confidentiality statements.

The reviewer agrees with the OSI finding and conclusion. The reviewer finds that the above OSI finding does not have any impact the outcome of the bioequivalence study results. **The firm's response is acceptable.**

Parent ANDA Reviewer Comment #4 for Related ANDAs:

The above OSI/ORA finding is considered systemic for clinical studies that were conducted prior to the revision of the screening consent form that includes the statement on “confidentiality record maintenance of the subjects”.

☐ Isolated	☒ Systemic

OSI/ORA Finding #5: *Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the clinical investigation.*

Specifically,

A) Subject #42 was scheduled for dosing on 03 Nov 2010 but was not dosed, due to tachycardia which was documented in the CRF. However, there was no AE Reporting Form completed for this event as required by the protocol which required daily documentation of AEs. Due to the fact the PI/site did not complete an Adverse Event Reporting form, the event was not identified as an AE and not carried forward to the sponsor.

OSI Evaluation of ORA Finding #5A: OSI has provided the following detailed explanation for the above finding along with their evaluation for the firm's response to the Form FDA-483:

In response to Form FDA-483, NRR said they reported tachycardia to the sponsor as a pre-dose adverse event in Subject #42, after FDA's inspection.

The ORA investigator confirmed that all other AEs documented in NRR records were described accurately in the study report.

Firm's Response to OSI/ORA Finding #5: This observation is pertaining to complete documentation for an adverse event, and laboratory reports evaluation based on telephonic discussion, training has been provided to study personnel for appropriate documentation for future studies, however these were incomplete transcription details which did not impact on the integrity of the Bioequivalence study results.

Reviewer's Comments on Firm's Response #5A: During the inspection, ORA inspector found that the firm did not fill the adverse event form for patient 42. Prior to dosing in Period I, patient 42 experienced the adverse event tachycardia. Therefore, the firm did not dose the patient on that day and documented the event in the CRF. However, the firm failed to fill the adverse event report form. In the response, the firm stated that the “the observation is acknowledged and understood as a pre-dose adverse event and thus not

reported as adverse event as per protocol requirements”. Since the adverse event observed was prior to dosing and all the other AEs were accurately recorded, the above OSI finding does not affect the integrity of the study results.

The reviewer agrees with the OSI finding and conclusion. The reviewer finds that the above OSI finding does not have any impact the outcome of the bioequivalence study results. **The firm’s response is acceptable.**

Parent ANDA Reviewer Comment #5A for Related ANDAs:

The above OSI/ORA finding is considered systemic for clinical studies that were conducted prior to the implementation of procedure to report the pre dose adverse events in the adverse event form.

☐ Isolated	☒ Systemic

OSI/ORA Finding 5B: *Laboratory Reports for at least 4 subjects (including #41, #42, #43, #44) contained signatures/dates for the review of the report which was prior to the date the lab report was generated. For example, Subject #42 Period II, check-In Lab Report was generated on 02/12/2010; however the PI signed/dated the review on 01/12/10. There was no explanation in the study records concerning the date discrepancies.*

OSI Evaluation of ORA Finding #5B: OSI has provided the following detailed explanation for the above finding along with their evaluation for the firm’s response to the Form FDA-483:

In response to Form FDA-483, NRR explained that the investigator evaluated clinical lab results through phone prior to the generation of lab report. However, due to the oversight, the NRR acknowledged that they could not record this event. In addition, NRR explained that they recorded the phone conversation for the other five subjects. As corrective action, the NRR shall sign the current date of receipt of lab report and cross reference the phone discussion form or add an explanatory remark. This reviewer is of the opinion that this observation will have no impact on study outcome.

Firm’s Response to OSI/ORA Finding #5: This observation is pertaining to complete documentation for an adverse event, and laboratory reports evaluation based on telephonic discussion, training has been provided to study personnel for appropriate documentation for future studies, however these were incomplete transcription details which did not impact on the integrity of the Bioequivalence study results.

Reviewer’s Comments on Firm’s Response #5B: During the inspection, ORA reviewer found that lab reports for some of the subjects contain the principal investigator review date even prior to the lab report generated.

In the response, the firm stated that to evaluate the subject eligibility after dosing, lab results had been checked with the principal investigator through the telephonic conversations. When report was received, the lab report has been signed and recorded the date when it was telephonically evaluated which was prior to the report generation date. The firm also stated that the date of telephonic discussion of subject evaluation should be documented, however due to the oversight it was missed for some subjects. Since only few subjects lab reports are missing the documentation of telephonic conversations, the above OSI finding does not affect the integrity of the study results.

In addition, the firm stated that the training manual of site will include the following:

- If lab reports are evaluated through telephonic discussion with laboratory, a telephonic discussion form/ other applicable format should be filed describing the matter discussed and discussion taken.
- On receipt of lab report, it shall be signed with current date and cross reference of telephonic discussion form or remark should be added.

The OSI reviewer is of the opinion that the above observation will have no impact on study outcome. The reviewer agrees with the OSI finding and conclusion. The reviewer also finds that the above OSI finding does not have any impact the outcome of the bioequivalence study results. **The firm's response is acceptable.**

Parent ANDA Reviewer Comment #5B for Related ANDAs:

The above OSI/ORA finding is considered systemic for clinical studies that were conducted prior to the implementation of procedure to record lab evaluation through telephonic evaluation.

☐ Isolated	☒ Systemic

OSI/ORA Finding 5C: *A total of three aliquots were generated from each PK sampling time point. Two aliquots were stored on site, the third was apparently immediately provided to members of the sponsor's Bioanalytical department who were on-site for special handling of the aliquots. There was no documentation of the tracking or transfer of this third aliquot.*

OSI Evaluation of ORA Finding #5C: OSI has provided the following detailed explanation for the above finding along with their evaluation for the firm's response to the Form FDA-483:

In response to Form FDA-483, NRR explained that during the study, the third aliquot was physically handed to an analyst from the sponsor's bioanalytical department who was on-site for special handling of the aliquots, and the analysts recorded the time and date of sample receipt in their own records, although the firm did not document tracking or transfer

of the third aliquot at the clinical site in the study records. As a preventive action, the firm amended 'training manual 01' to require recording of such events. This reviewer is of the opinion that this observation has no impact on study outcome, as the events could be verified from other documents, including the analytical data.

Firm's Response to OSI/ORA Finding #5: This observation is pertaining to complete documentation for an adverse event, and laboratory reports evaluation based on telephonic discussion, training has been provided to study personnel for appropriate documentation for future studies, however these were incomplete transcription details which did not impact on the integrity of the Bioequivalence study results.

Reviewer's Comments on Firm's Response #5: The doxorubicin analysis requires special handling of plasma samples in the clinical site itself prior to transfer to the analytical facility. The collected plasma is divided in to three aliquots. Two aliquots were stored in the freezer until shipped to the analytical facility, where as the third aliquot was processed on site by the analyst from the bioanalytical department. During the inspection, ORA inspector found that there was no documentation of the tracking or transfer of this third aliquot.

In the response to the 483 findings, the firm stated that the third aliquot was physically received by the analyst form the clinical site representative and recorded the time and date of sample receipt on their record. The firm acknowledged that the transfer of third aliquot to the analytical facility was missed to record in clinical site. However this is due to the above procedure for special handling of the plasma sample.

The OSI reviewer is of the opinion that this observation has no impact on study outcome, as the events could be verified from other documents, including the analytical data. The reviewer agrees with the OSI finding and conclusion. The analytical report submitted during the original submission contains the sample receipt summary, which includes the number of samples and date received (Figure 3).

Figure 3: Snapshot of sample received dates by the analytical lab

Cartridges receipt dates are as follows:

Subject no:	Batch No.	Time point	Original (1/3) / Duplicate (2/3) (3/3)		
			No of Samples		
			Date Received	P I	P II
52	1 to 9	P-1 (0.0 to 337.0)	13-02-11	19	-
30,52	1 to 9	P-2 (0.0 to 337.0)	13-02-11	-	38
53,54	1 to 9	P-2 (0.0 to 337.0)	09-02-11	-	38
57,58,61	1 to 9	P-2 (0.0 to 337.0)	05-02-11	-	57
53	1 to 9	P-1 (0.0 to 337.0)	18-01-11	19	-
54	1 to 8	P-1 (0.0 to 241.0)	18-01-11	18	-
45,60	1 to 9	P-2 (0.0 to 337.0)	18-01-11	-	38
58,61	1 to 9	P-1 (0.0 to 337.0)	06-01-11	38	-
30	1 to 9	P-1 (0.0 to 337.0)	06-01-11	19	-
51	1 to 9	P-2 (0.0 to 337.0)	06-01-11	-	19
27 to 29	1 to 9	P-2 (0.0 to 337.0)	30-12-10	-	57
45,60	1 to 9	P-1 (0.0 to 337.0)	25-12-10	38	-
41 to 43	1 to 9	P-2 (0.0 to 337.0)	25-12-10	-	57
47,48	1 to 9	P-2 (0.0 to 337.0)	21-12-10	-	38
40,50,57	1 to 9	P-1 (0.0 to 337.0)	17-12-10	57	-
38 to 40	1 to 9	P-2 (0.0 to 337.0)	17-12-10	-	57
26	1 to 9	P-2 (0.0 to 337.0)	09-12-10	-	19
29	1 to 9	P-1 (0.0 to 337.0)	09-12-10	19	-
47,48,51	1 to 9	P-1 (0.0 to 337.0)	05-12-10	57	-
34,35	1 to 9	P-2 (0.0 to 337.0)	05-12-10	-	38

The reviewer also finds that the above OSI finding does not have any impact the outcome of the bioequivalence study results. **The firm’s response is acceptable.**

Parent ANDA Reviewer Comment #5C for Related ANDAs:

The above OSI/OR A finding is systemic but specific to liposomal products. Therefore only related ANDAs of liposomal injection drug products should be evaluated for the impact of the above finding from the inspection of the clinical site.

☐ Isolated ☒ Systemic

OSI/OR A Overall Comments and Conclusions:

DBGC recommends that the clinical data from study PKD_09_030 are acceptable for review.

The initial classification of the field investigator was OAI. However, OSI reviewer, upon review, *downgraded to VAI* because each of the three shipments of test and reference products came from the same respective lots, and the impact of the observations on the study outcome is not significant, and the data were found acceptable by the OSI for review.

DB Reviewer Overall Comments and Conclusions for the Current ANDA:

Based on the evaluation of the ORA/OSI inspection evaluation above, the data from the fed study No. PKD_09_030 for current application are considered **adequate**.

DB Reviewer Overall Comments and Conclusions for Related ANDAs:

The OSI/ORA report contains some systemic findings and therefore, should be reviewed for the impact on the related ANDAs.

☐ Isolated ☒ Systemic

3.4 Deficiency Comments

None

3.5 Recommendations

1. The Division of Bioequivalence accepts the fed BE study (C10112) conducted by the Sun Pharma Global FZE. on its Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL, lot # JK93496A, comparing it to Ortho Biotech’s Doxil® Liposomal Injection, 2 mg/mL, lot # 0907642.
2. The Division of Bioequivalence accepts the in vitro equivalence study (Liposome Size Distribution) conducted by the Sun Pharma Global FZE. on its Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL, comparing it to Ortho Biotech’s Doxil® Liposomal Injection, 2 mg/mL.
3. The firm’s in vitro drug release testing is acceptable. The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4)) using 100 mL cylinder glass bottles (b) (4)) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr: NMT (b) (4) 0%
1.5 hr: (b) (4) 0%
3 hr: 0%
5 hr: 0%
7 hr: NLT (b) (4) 0%

3.6 Comments for Other OGD Disciplines

Discipline	Comment
None	

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 203263

APPLICANT: Sun Pharma Global FZE

DRUG PRODUCT: Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL (10 mL and 25 mL)

The Division of Bioequivalence has completed the review of your submission acknowledged on the cover page and has no further question at this time.

We acknowledge that you will conduct in vitro drug release testing for the test product using the following FDA-recommended method and specification: 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr:	NMT	(b) (4) %
1.5 hr:	(b) (4)	0%
3 hr:	(b) (4)	0%
5 hr:	(b) (4)	0%
7 hr:	NLT	(b) (4) %

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4 OUTCOME PAGE

ANDA: 203263

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
18760	12/20/2012	Other (REGULAR)	OSI Inspection Report Review (Clinical Site 3)	1	1
				Total:	1

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

/s/

SUMAN DANDAMUDI
01/08/2013

SHRINIWAS G NERURKAR
01/09/2013

HOAINHON N CARAMENICO
01/09/2013

HOAINHON N CARAMENICO on behalf of DALE P CONNER
01/09/2013

DIVISION OF BIOEQUIVALENCE REVIEW- ADDENDUM

ANDA No.	203263		
Drug Product Name	Doxorubicin hydrochloride Liposome Injection		
Strength(s)	2 mg/mL, 10 mL and 25 mL		
Applicant Name	Sun Pharma Global FZE		
Address	Office # 43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U.A.E		
Applicant's Point of Contact	Robert Kurkiewicz Sun Pharmaceutical industries Ltd. (C/O Caraco) 1150 Elijah Mccoy Drive, Detroit, MI 48202		
Contact's Telephone Number	313-556-4105		
Contact's Fax Number	248-926-0231		
Original Submission Date(s)	June 16, 2011 March 07, 2012 (Telephone Amendment) April 9, 2012 May 10, 2012 (Telephone Amendment) June 29, 2012 (Telephone Amendment) July 4, 2012 (Telephone Amendment) August 4, 2012		
Submission Date(s) of Amendment(s) Under Review	October 5, 2012		
Reviewer	Suman Dandamudi Ph.D		
Study Number (s)	PKD_09_030	DOX/003/08	FDD-02/10-11/001
Study Type (s)	Fed	Pilot Fed	In-Vitro
Strength (s)	2 mg/mL	2 mg/mL	2 mg/mL
Clinical Site-1	MNJ Institute of Oncology & Regional Cancer Centre		
Clinical Site-1 Address	Red Hills, Hyderabad- 500 004, India		
Clinical Site-2	Kailash Cancer Hospital & Research Centre		
Clinical Site-2 Address	Goraj, Vadodara- 391760, India		
Clinical Site-3	Dr. G. Vishwanathan Speciality Hospitals		
Clinical Site-3 Address	#27, Babu road, Trichy, Tamilnadu- 620 008, India		
Clinical Site-4	Dr. Kamakshi Memorial Hospital		
Clinical Site-4 Address	No.1, Radial Road, Palikaranai, Chennai- 600 100, India		
Clinical Site-5	NRR Hospital		
Clinical Site-5 Address	Chikkasandra, Bangalore- 560090 (India)		
Analytical Site (fed study)	Sun Pharmaceutical Industries Ltd.,		
Analytical Site Address (fed)	Sun Pharmaceutical Industries Ltd.,		

study)	Tandalja, Vadodara -390020, India		
In Vitro Liposome Size Distribution Testing Site	Sun Pharmaceutical Industries Ltd.,		
In Vitro Testing Site Address	Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India		
REVIEW RESULT	INADEQUATE		
OSI REPORT RESULT	INADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 8, 9, 10, 11, 16	IN VITRO DRUG RELEASE*	2 MG/ML	ADEQUATE
1, 8	FED STUDY	2 MG/ML	ADEQUATE
1, 8, 16	IN VITRO STUDY	2 MG/ML	ADEQUATE

*NOTE: There is no dissolution testing for this drug product, but there is in vitro drug release testing.

ADDENDUM TO AN AMENDMENT REVIEW

1. EXECUTIVE SUMMARY

This addendum is to revise the DB's previous review for the amendment dated October 5, 2012 to add the review of the latest OSI inspection results for both, a clinical and an analytical site. In the previous review of the ANDA (See Section 1.7 Attachment), the ANDA was found **inadequate** pending the outcome of the OSI inspections for the analytical site and some of the clinical sites of the fed BE study. (NOTE: This previous BE review was not finalized in DARRTS, since the OSI inspection consults were pending.) This addendum is for addressing the pending OSI inspections and completing the evaluation of all relevant OSI inspections linked to the BE study of the current ANDA.

OSI/ORA Inspection of the Clinical Site NRR Hospital Bangalore, India: At the request of Office of Generic Drugs (OGD)/DBI, the OSI conducted an audit of the clinical portion of in-vivo fed bioequivalence study at the clinical site NRR Hospital Bangalore, India. This was one of the five clinical sites used for the BE study of the current ANDA. It should be noted that prior to this inspection, the OSI/ORA inspected two other clinical sites, MNJ Institute of Oncology & Regional Cancer Center, Hyderabad, India and Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai, India for another application and classified these two sites No Action Indicated (NAI). In addition to the three sites already inspected, there is currently another clinical site pending the OSI/ORA inspection. Due to the expedited status of the application, as well as the fact that the three inspection sites accounted for 44 out of 66 patients enrolled in the BE study, or 73% of the total number of study patients, the OGD/DBI has determined that the pending inspection was not necessary at this time.

Following the inspection of the third site inspection (occurring between 8/27/2012 and 9/4/2012), a Form 483 was issued to NRR Hospital Bangalore, India (See Attachment for OSI Report). Due to the expedite status of the ANDA, the DBI reviewed Form 483 (which was provided to the division on 11/09/2012) before the OSI complete its review of Form 483 and the site's response to the form (See the emails concerning the status of the OSI's review of the EIR for the same inspection). Based on the above Form 483, the DBI found the objectionable findings by the OSI at the clinical site which could potentially compromise the integrity of the study results. Therefore, the firm will be asked to address the above specific inspection findings by the OSI/ORA, providing any necessary supporting documents in its response.

OSI Inspection of the Analytical Site: This addendum also contains the evaluation of Office of Scientific Investigations (OSI) inspection report for the analytical site, Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara, India. This For Cause inspection report was prepared for the BE studies of **ANDA 090362**. The analytical portion of the BE studies for ANDA 090362 were conducted between Oct 2007 and December 2007, as compared to the dates of the sample analysis for the current ANDA, between June 2010 and March 2011. There is currently a pending For Cause OSI inspection scheduled for the same site (to be initiated in December 2012) for ANDA 090886. The analytical portion of the BE studies for ANDA 090886 was conducted between June 2008 and August 2008. However, due to the expedite status of the current application, the OGD/DBI has determined that the inspection report for ANDA 090362 should provide adequate assessment of the site and any potential impact the site conduct and procedures might have had on the BE study of the current application. Therefore, the pending OSI inspection of the analytical site is not considered critical for ANDA 203263, and will not be reviewed for its impact on the current ANDA, when the inspection results become available.

After the evaluation of the OSI inspection report for ANDA 090362, the DBI determined that the OSI's findings at this site **do not have any significant impact** on fed BE study of the current ANDA 203263.

Summary of the BE Review Status:

The review of the in vivo BE study, in vitro study and in vitro drug release testing has been completed and the DBI has no further question for the firm concerning these tests. However, per the review of the latest OSI/ORA inspection of the one of the clinical site, mentioned above, the application is considered **incomplete/inadequate** pending the firm's satisfactory response to the inspection-related deficiencies, which are given at the end of the review addendum (page 44 of the current document).

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3. REVIEW OF FORM 483 ISSUED TO THE CLINICAL SITE NRR HOSPITAL, BANGALORE, INDIA

The fed BE study was conducted at multiple sites.

No	Name of Clinical Site	Group number/Site ID	Number of Patients	OSI Inspection Status
1	MNJ Institute of Oncology & Regional Cancer Center, Hyderabad	1/A	31	NAI
2	Kailash Cancer Hospital and research Center, Goraj, Vadidara	2/B	5	
3	Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu	3/D	11	Pending new site inspection
4	Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai	4/E	4	NAI
5	NRR Hospital, Bangalore	5/G	9	Pending new site inspection

Pending OSI Inspections of Clinical Sites: In the review of the original amendment, the following was stated for the pending OSI inspection of the clinical sites (See Attachment):

NRR Hospital, Bangalore: A new site OSI inspection was requested for this clinical site on February 16, 2012 and is still pending the outcome of the request [DARRTS: RAMSON, TERESA V 02/16/2012 N/A 02/16/2012 FRM-CONSULT-09 (DSI Bioequivalence Audit Request) Original-1 (Unknown) Archive]

Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu: A new site OSI inspection was requested for this clinical site on July 20, 2012 and is still pending the outcome of the request [DARRTS: RAMSON, TERESA V 07/24/2012 N/A 07/24/2012 FRM-CONSULT-09(DSI Bioequivalence Audit Request) Original-1 (Unknown) Archive]

Inspection Findings at NRR Hospital, Bangalore, India: At the request of Office of Generic Drugs (OGD)/DBI, the OSI conducted an audit of the clinical site between 8/27/201 and 9/4/2012), a Form 483 was issued to NRR Hospital Bangalore, India (See Attachment for OSI Report). At the current time, the OSI has not completed its review of the inspection EIR and the site has not provided its response to the Form 483. Due to the expedite status of the current ANDA, the DBI evaluates the Form 483 and communicates any findings considered significant to the ANDA applicant. Below is the inspection findings and the reviewer's comments:

OSI/ORA Finding# 1: Failure to maintain possession and/or control of investigational product test and reference retention samples.

DBI Reviewer's Comments: As the identity of the test and reference products is critical to the BE testing and determination, the applicant will be asked to address this finding.

OSI/ORA Finding# 2: Failure to assure that an Ethics Committee complying with applicable regulatory requirements and following their own written procedures was responsible for the initial and continuing review and approval of a clinical study.

DBI Reviewer's Comments: The impact of this questionable practice on the integrity of the BE study is unknown. The applicant will be asked to address this finding and its impact on the study.

OSI Finding# 3: Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study related activities.

DBI Reviewer's Comments: The applicant will be asked to address this violation and its impact on the BE study.

OSI Finding # 4: There was no statement in the informed consent for screening document that described the extent, if any, to which confidentiality of records identifying the subjects would be maintained; and that noted the possibility that regulatory agencies might inspect the records.

DBI Reviewer's Comments: The impact of this violation on the BE study is not known. The applicant will be asked to address this finding.

OSI Finding# 5: Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the clinical investigation.

DBI Reviewer's Comments: This finding may have an impact on the safety evaluation of the test as well as reference products. The applicant will be asked to address this violation and its impact on the BE study.

Firm's Responses to the above Findings by the OSI: Pending

Reviewer's Comments: After the firm's responses to the above OSI findings for the clinical site are received, the reviewer will further evaluate and determine the adequacy of the responses.

Pending Inspection at Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu, India:

Based on the email from the OSI representative, Dr. Sripal Mada, this site is scheduled for inspection on December 15, 2012 (See attachment for the email). Based on the expedite status of this application (based on the drug shortage urgency), the OSI inspection for this clinical site is presently considered by the OGD/DBI as not critical as a part of the application evaluation: The number of patients enrolled in this fourth clinical site is eleven (11) or 18.3% of the total number of study subjects. The three clinical sites with completed inspections accounted for 44 out of 66 patients enrolled in the BE study, or 73% of the total number of study subjects. Therefore, the OGD/DBI has determined that these inspected sites adequately represented the study for the compliance evaluation purpose.

4. REVIEW OF THE OSI REPORT OF THE ANALYTICAL SITE

In the review of the original amendment, the following was stated for the OSI inspection of the analytical site (See Attachment):

“A for-cause Office of Scientific Investigations (OSI) inspection was requested for the analytical site of ANDA 090886 on May 20, 2010 and is still pending the outcome of the request [DARRTS: POPAT, ALPITA 05/21/2010 N/A 05/21/2010 FRM-CONSULT-09 (DSI Bioequivalence Audit Request) Original-1 Archive]”.

However upon further consideration, the DBI identified an available For-Cause OSI inspection at the same site, which was conducted previously for **ANDA 090362**, with the outcome of the inspection of VAI. The study sample analyses of the fasting and fed BE studies of ANDA 090362 were conducted between Oct-Dec 2007, whereas the sample analyses for the fed BE study in the current application was performed between June 2010 and March 2011.

Due to the expedite status of the current ANDA 203263 based on the drug shortage, the OSI inspection findings for ANDA 090362 will be considered even though there is greater than three year difference between the studies of ANDA 090362 and current ANDA 203263. At this time, it is not clear to the OGD/DBI when the pending For Cause

inspection for the analytical site for ANDA 090886 will be initiated, although the request for the inspection was submitted in more than 2 years earlier.

OSI Report pertaining to ANDA 090362:

The OSI conducted an audit of the analytical portion (April 14-16 and 19- 23, 2010) of the BE studies for ANDA 090362 and following the inspection a Form 483 was issued to the Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara, India. The analytical site of ANDA 090362 is the same as the analytical site of the fed BE study in the current application. The outcome of the OSI inspection of the analytical site for ANDA 090362 (for cause) was VAI [**DARRTS for ANDA 090362: BISWAS, GOPA 06/17/2010 N/A 06/17/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection report Review) Original-1 Archive**]. The OSI findings, the site's responses and the DBI reviewer's comments are as follows (as given in the OSI report):

OSI Finding #1: *Failure to conduct Incurred Sample Reproducibility assessments. The firm did not evaluate method reproducibility for plasma samples collected from study subjects.*

OSI Evaluation: ISR assessment was not performed as the above studies were conducted in July 2007. The firm did not have any SOP for ISR evaluation at the time of study conduct. Thereafter, the firm developed their ISR SOP: PKD/s/035 Rev 0. This SOP effective 8/25/08 was found to be adequate during the audit. In their response, the firm acknowledged the observation and provided summarized data for QCs and calibration standards from all the analytical runs conducted during the study to demonstrate the accuracy and precision of the analytical method. The results are found within the acceptance limits. However, it should be noted that spiked QCs and calibration standards are not incurred study samples. Nevertheless, the firm has assured the agency in their written response that ISR assessment has been implemented and ISR data was included in all the studies conducted after the implementation of the ISR SOP , effective 8/25/08.

Reviewer's Comments: In the current application, a total of 123 samples (out of 1470) were analyzed as incurred repeats for free doxorubicin, liposomal doxorubicin and liposomal doxorubicin. Incurred Samples Reanalysis (ISR) was demonstrated with 90.2%, 89.4% and 91.1% of these samples for free doxorubicin, liposomal doxorubicin and liposomal doxorubicin respectively being within $\pm 20\%$ variability of their respective original reported values. In addition, currently, the DBI does not have any specific criteria to assess incurred sample reproducibility (ISR) in bioequivalence studies for ANDA submissions. **So the OSI finding-1 does not have any impact on the outcome of the current fed BE study.**

OSI Finding# 2: *Failure to provide adequate controls for electronic source records:*

A) Specific requirements and expiration times for credentials used to access electronic source records and to apply electronic signatures were not defined;

B) Physical access to electronic source records were not limited to authorized personnel.

OSI Evaluation: The firm's SOP for access control to the LC-MS/MS instruments did not detail (1) the complexity required for passwords, nor (2) the length of time passwords could be used. Passwords were used for system access and application of electronic signatures. The firm should consider implementing adequate logical access security to the electronic source records to improve data integrity.

Access to the entire analytical laboratory is key-card controlled. However, access to the computer room and the computers that store the source electronic data is not monitored or controlled. During the inspection, the firm said they plan to add key-card access to the appropriate rooms.

In the response to the logical and physical access concerns noted above, the firm indicated that they have updated their SOP to better define logical security measures (password complexity, expiration, recovery) and have implemented additional physical security in the areas where electronic data are stored (keycard controlled and monitored, minimum of 2 person occupancy in data room).

The proposed corrective measures indicated in the firm's response are adequate.

Reviewer's Comments: The OSI noted that the site has updated its SOP to better define logical security measures following the inspection. The fed BE study was conducted more than 3 years after the inspection when the corrective measures were already in place. Therefore, **the OSI finding-2 should not have any impact on the outcome of the current fed BE study.**

OSI Finding# 3A: *Precision and accuracy (P&A) validation data generated in run PA01 for levocitirizine method was excluded from P&A global summary results without valid justification.*

OSI Evaluation: During the inspection, the firm was requested to recalculate the precision and accuracy after including the data from the rejected run P&A01. The recalculated results showed that the assay was not as precise and accurate as originally reported but remained within the acceptable limits. The firm should correct their practice cited above but this observation should not have any significant impact on the study results.

In their written response, firm states that they will include all validation runs when evaluating method performance, omitting only those that have assignable cause for exclusion.

Reviewer's Comments: Due to the complex and delicate nature of the current drug product and study samples, the prestudy validation data should be evaluated in conjunction with the quality control (QC) and calibration data obtained during the sample analysis in order to assess the reproducibility, accuracy and ruggedness of the method. The QCs were processed with the study samples at the clinical site and they were analyzed against freshly

prepared calibration standards. Since the QC and calibration data from the sample analysis were found acceptable, the prestudy validation data, even if inadequately reported, should not have a direct impact on the integrity of the study results. In addition, as the site had been informed of its unacceptable practice of reporting validation data by the OSI, it is likely that this practice has since been corrected with other cited findings following the inspection three years earlier. **So the OSI finding-3A does not have any impact on the outcome of the current fed BE study.**

OSI Finding# 3B: *Dilution linearity was not performed using the study sample matrix (K₃EDTA human plasma). It was performed using only the dilution matrix (CPDA plasma).*

OSI Evaluation: As the subject samples contained K₃EDTA as the anticoagulant, the firm should have performed dilution linearity in plasma matrix containing K₃EDTA. In their response, the firm acknowledged the observation and revised their SOP to include conduct of dilution linearity experiment in all the blank matrices used during a study. However, there is only one study sample (subject 17, period II, 4h of fed study PKD/07/072) with concentration above the ULOQ (496.55ng/mL) and this sample was reanalyzed after dilution. Moreover, the dilution QCs were included in the run during the reanalysis. As all the dilution QCs met run acceptance criteria, the observation is not likely to have any significant impact on the results.

Reviewer's Comments: In the current application, the firm used K₃EDTA as anticoagulant in their fed BE study. The calibration standards and quality control samples were prepared with human plasma containing K₃EDTA. The dilution integrity was demonstrated using plasma containing K₃EDTA as the matrix. Regardless, no study samples were diluted during the sample analyses, **so the OSI finding-3B does not have any impact on the outcome of the current fed BE study.**

OSI Finding# 3C: For levocetirizine, post-extract stability was performed using standards and QCs stored in auto-amplifier (10°C) before auto-sampler stability was demonstrated.

OSI Evaluation: The firm did not use a fresh calibration curve to establish the post extract sample stability at room temperature. The standard and QC samples were extracted together with the post extraction stability samples. The standard and QC samples were stored in the autosampler at 10°C and the extracted study samples were kept at room temperature for 48h before injecting the samples. The firm did not have stability data for sample storage at 10°C before the conduct of this experiment.

In response the firm agreed to this observation and revised their SOP to include fresh calibration curve standards and QC samples to determine post extract sample stability. Nevertheless, source records indicated that the study samples were stored in the autosampler for approximately 3h during the longest runs. As the firm demonstrated autosampler stability for 64h at 10°C therefore, the observation is not likely to affect the study data.

Reviewer's Comments: In the current application also, the firm stored the calibration standards and two sets of QC samples on autosampler. The stability samples which were stored at room temperature were compared to the above CCs and QCs to determine the Post Extraction Bench Top Stability. However, the firm demonstrated the auto sampler stability at 10°C for 53 hrs, 81 hrs and 55 hrs for free doxorubicin, liposomal doxorubicin and liposomal doxorubicin respectively. **Therefore, the OSI finding-3C does not have any impact on the outcome of the current fed BE study.**

5. DEFICIENCY COMMENTS

A Form FDA- 483 was issued following the inspection of the clinical site, NRR Hospital, Bangalore, India, between August 27 and September 4, 2012, by the Office of Scientific Investigations (OSI) for fed bioequivalence (BE) study.

Based on the findings listed in the Form 483, the DBI requests that the applicant address each finding and its impact on the integrity of the BE study.

- Failure to maintain possession and/or control of investigational product test and reference retention samples.
- Failure to assure that an Ethics Committee complying with applicable regulatory requirements and following their own written procedures was responsible for the initial and continuing review and approval of a clinical study.
- Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study related activities.
- There was no statement in the informed consent for screening document that described the extent, if any, to which confidentiality of records identifying the subjects would be maintained; and that noted the possibility that regulatory agencies might inspect the records.
- Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the clinical investigation.

The firm should address the above specific finding by the OSI, providing any necessary supporting documents in its response.

6. RECOMMENDATIONS

1. The Division of Bioequivalence finds the fed BE study (C10112) inadequate pending the firm's acceptable response to the inspection-related deficiencies mentioned above. The study was conducted by the Sun Pharma Global FZE. on its Doxorubicin

Hydrochloride Injection, Liposomal , 2 mg/mL, lot # JK93496A, comparing it to Ortho Biotech's Doxil® Liposomal Injection, 2 mg/mL, lot # 0907642.

2. The Division of Bioequivalence accepts the in vitro equivalence study (Liposome Size Distribution) conducted by the Sun Pharma Global FZE. on its Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL, comparing it to Ortho Biotech's Doxil® Liposomal Injection, 2 mg/mL.
3. The firm's in vitro drug release testing is acceptable. The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr:	NMT	(b) (4) %
1.5 hr:	(b) (4)	0 %
3 hr:	(b) (4)	0 %
5 hr:	(b) (4)	0 %
7 hr:	NLT	(b) (4) %

7. ATTACHMENTS

7.1. Form 483 Issued for the Clinical Site, NRR Hospital, Bangalore, India

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER Dr. Sam Haidar, Center For Drug Evaluation and Research 10903 New Hampshire Avenue, Bldg 51, Room 5330 Silver Spring MD 20993 Phone: 1-(301)-496-3393 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 27 Aug - 04 Sept 2012	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Dr. Yathish Kumar H.M., M.B.B.S., M.S., DNB, Mch DNB, Principal Investigator		FEI NUMBER 3009654552	
FIRM NAME Dr. Yathish Kumar at N.R.R. Hospital	STREET ADDRESS No. 3 & 3A, Hesarghatta Main Road, Chikkasandra		
CITY, STATE AND ZIP CODE Bangalore 560 090 Karnataka, India	TYPE OF ESTABLISHMENT INSPECTED Clinical Investigator		
THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE. DURING AN INSPECTION OF YOUR FIRM (I) ☒ OBSERVED: Pertaining to the conduct of clinical study: PKD-09-030 "A randomized, multi-center, open-label, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study of Doxorubicin Hydrochloride Liposome Injection, 2mg/mL (50 mg/m2 dose)...." 1) Failure to maintain possession and/or control of investigational product test and reference retention samples. Specifically, Test and reference retention samples maintained per regulatory requirements were shipped to a third party archival site on 18 Aug 2011; per the sponsor's request. The study sponsor made the arrangements with the third party archival facility, entered into a contract with the archival facility and requested the PI send the retention samples to that facility for storage. Due to the fact the sponsor was the only entity that signed this contract, the sponsor may have had access to the samples. There was no assurance provided that only the PI could access and retrieve the retention samples. 2) Failure to assure that an Ethics Committee complying with applicable regulatory requirements and following their own written procedures was responsible for the initial and continuing review and approval of a clinical study. Specifically, A) Letter dated 03 Nov 2010 from the PI, provides the IEC with protocol amendment/version D05 (dated 30 Oct 2010) and informed consent document Version D05, dated 14 Oct 2010 in English and Kannada languages. There was no correspondence from the IEC that the documents had been reviewed and approved; however the study was conducted per amendment D05 and consent Version D05 was used to consent/re-consent subjects. B) Letter dated 15 Dec 2010 from the PI, provides the IEC with informed consent document Version D06, dated 10 Dec 2010 in English and Kannada languages. There was no correspondence from the IEC that the documents			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Scott B. Laufenberg, Assistant Country Director, FDA Office - India	DATE ISSUED 09/04/2012

FORM FDA 483 (9/98) PREVIOUS EDITION OBSOLETE

INSPECTIONAL OBSERVATIONS

Page 1 of 2

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Dr. Sam Haidar, Center For Drug Evaluation and Research 10903 New Hampshire Avenue, Bldg 51, Room 5330 Silver Spring MD 20993 Phone: 1-(301)-496-3393 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 27 Aug - 04 Sept 2012
	FEI NUMBER 3009654552

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Dr. Yathish Kumar H.M., M.B.B.S., M.S., DNB, Mch DNB, Principal Investigator

FIRM NAME Dr. Yathish Kumar at N.R.R. Hospital	STREET ADDRESS No. 3 & 3A, Hesarghatta Main Road, Chikkasandra
CITY, STATE AND ZIP CODE Bangalore 560 090 Karnataka, India	TYPE OF ESTABLISHMENT INSPECTED Clinical Investigator

had been reviewed and approved; however consent Version D05 was used to consent/re-consent subjects.

3) Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study related activities.
 Specifically,

The original, signed study specific Informed Consent Form for Subjects #44 and #59 was a poor quality scanned copy of original document. This scanned copy of the form is very difficult to read, possibly illegible.

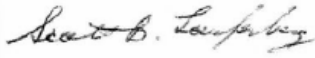
4) There was no statement in the informed consent for screening document that described the extent, if any, to which confidentiality of records identifying the subjects would be maintained; and that noted the possibility that regulatory agencies might inspect the records.

5) Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the clinical investigation.
 Specifically,

A) Subject #42 was scheduled for dosing on 03 Nov 2010 but was not dosed due to tachycardia which was documented in the CRF. However, there was no AE Reporting Form completed for this event as required by the protocol which required daily documentation of AEs. Due to the fact the PI/site did not complete an Adverse Event Reporting form, the event was not identified as an AE and not carried forward to the sponsor.

B) Laboratory Reports for at least 4 subjects (including #41, #42, #43, #44) contained signatures/dates for the review of the report which was prior to the date the lab report was generated. For example, Subject #42 Period II, Check-In Lab Report was generated on 02/12/2010; however the PI signed/dated for the review on 01/12/10. There was no explanation in the study records concerning the date discrepancies.

C) A total of three aliquots were generated from each PK sampling time point. Two aliquots were stored on site,

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Scott B. Laufenberg, Assistant Country Director, FDA Office - India	DATE ISSUED 09/04/2012

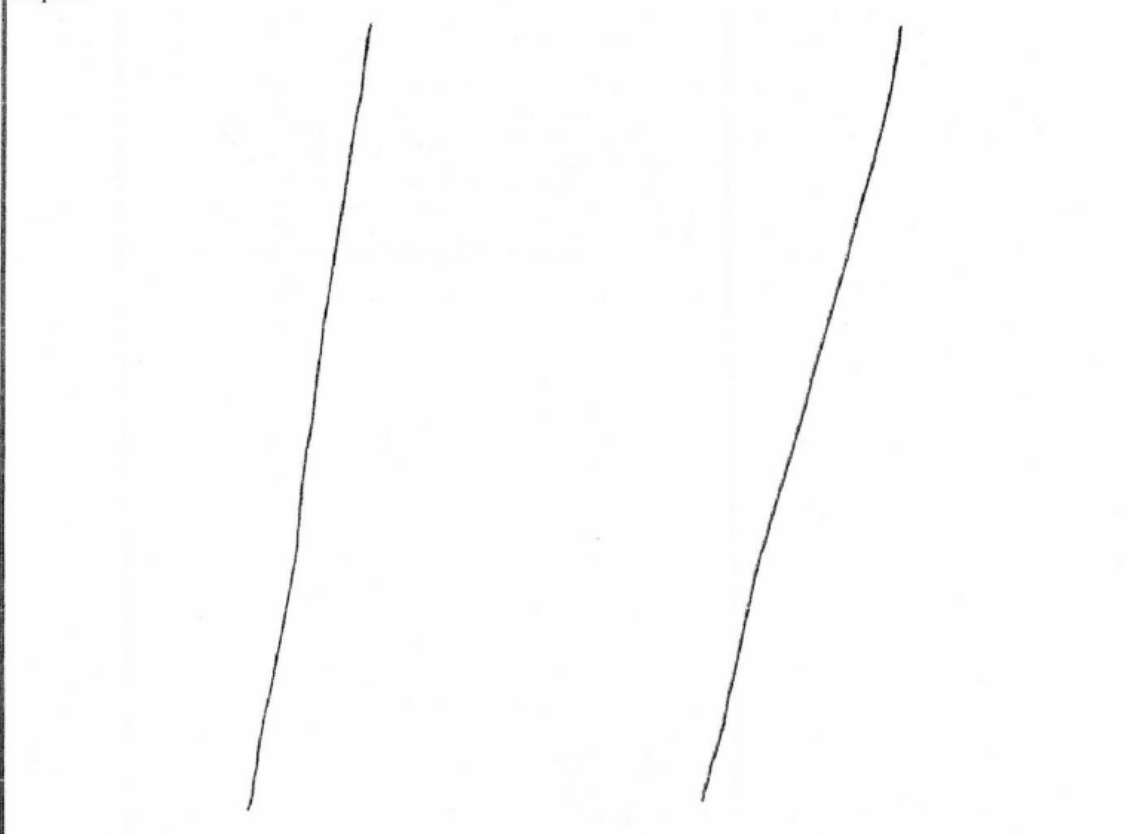
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Dr. Sam Haidar, Center For Drug Evaluation and Research 10903 New Hampshire Avenue, Bldg 51, Room 5330 Silver Spring MD 20993 Phone: 1-(301)-496-3393 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 27 Aug - 04 Sept 2012 FEI NUMBER 3009654552

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Dr. Yathish Kumar H.M., M.B.B.S., M.S., DNB, Mch DNB, Principal Investigator

FIRM NAME Dr. Yathish Kumar at N.R.R. Hospital	STREET ADDRESS No. 3 & 3A, Hesarghatta Main Road, Chikkasandra
CITY, STATE AND ZIP CODE Bangalore 560 090 Karnataka, India	TYPE OF ESTABLISHMENT INSPECTED Clinical Investigator

the third was apparently immediately provided to members of the sponsor's Bioanalytical department who were on-site for special handling of the aliquots. There was no documentation of the tracking or transfer of this third aliquot.



SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Scott B. Laufenberg, Assistant Country Director, FDA Office - India	DATE ISSUED 09/04/2012

7.2. E-Mail Correspondence between DBI and OSI

From: Mada, Sripal R

Sent: Friday, November 09, 2012 12:20 PM
To: Nguyen, Hoainhon T; Yoon, Martin
Cc: Skelly, Michael F; Haidar, Sam H; Taylor, William (CDER); Mada, Sripal R
Subject: RE: VERY URGENT!!! RE: SUN'S ANDA 203263 FOR DOXORUBICIN HCL LIPOSOME INJECTION, USP - URGENT STATUS REQUEST

Hi Hoai and Martin,

Per your email request below, the clinical site inspection at NRR Hospital, Bangalore, India was completed on Sep 4, 2012. The Form FDA-483 issued to NRR following inspection is attached below for your review.

<< File: NRRHosp-Bangalore-082712.pdf >>

We will draft the review of EIR for the inspection at NRR, Bangalore after we get the original EIR (we are expecting EIR early next week) from ORA.

In addition, inspection of second clinical site at Dr. G. Viswanathan Specialty Hospital, Tamil Nadu, India is scheduled for Dec 15, 2012. Per your email below "If necessary, this last inspection may be cancelled, but only if the inspection has NOT been started as of today", please confirm if you still need inspection at Dr. G. Viswanathan Specialty Hospital, Tamil Nadu.

Please let me know if you need any additional information.

Thanks,
Sripal

Sripal Reddy Mada, PhD

BE Team Leader (Acting)
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations, OC, USFDA
White Oak 51, Room 1119
10903 New Hampshire Avenue, Silver Spring, MD 20993
Tel: 301-796-4112/Fax: 301-847-8443
sripal.mada@fda.hhs.gov

From: Nguyen, Hoainhon T
Sent: Thursday, November 08, 2012 11:54 AM
To: Skelly, Michael F; Mada, Sripal R
Cc: Nguyen, Hoainhon T
Subject: FW: VERY URGENT!!! RE: SUN'S ANDA 203263 FOR DOXORUBICIN HCL LIPOSOME INJECTION, USP - URGENT STATUS REQUEST

FYI

From: Nguyen, Hoainhon T
Sent: Thursday, November 08, 2012 11:52 AM
To: CDER OSI BEQ; Haidar, Sam H
Cc: Nguyen, Hoainhon T; Yoon, Martin
Subject: VERY URGENT!!! RE: SUN'S ANDA 203263 FOR DOXORUBICIN HCL LIPOSOME INJECTION, USP - URGENT STATUS REQUEST

Hi Sam et al,

I would like to add to Martin's email below that due to the CDER's high profile, high priority status of this drug product which has been on the drug shortage list, the OGD had a meeting this morning and the Office director, Dr. Geba, recommended that the Complete Response (CR) letter for ANDA 203263 be issued immediately. However, per GDUFA regulations, the CR letter can not go out if there are pending OSI inspections and other consults. For this reason, we would like to expedite our evaluation of the pending inspection results for the Bangalore clinical site as soon as possible, as we understand that the inspection has been completed but the EIR review is in progress. We urgently request that the OSI and ORA provide us with any inspection documentation that can help us move this ANDA forward, even if the OSI inspection report has not yet been finalized. In addition, if possible, please let us know if there is a Form 483 issued as a result of this inspection. For the remaining clinical site in Tamil Nadu, for which the OSI has submitted an inspection request to the Division of Foreign Field Investigations on August 21, 2012, could you please update us of the status and confirm whether this inspection has been initiated? If necessary, this last inspection may be cancelled, but only if the inspection has NOT been started as of today.

Thanks,
Hoai

From: Yoon, Martin
Sent: Thursday, November 08, 2012 11:37 AM
To: CDER OSI BEQ
Cc: Nguyen, Hoainhon T
Subject: RE: SUN'S ANDA 203263 FOR DOXORUBICIN HCL LIPOSOME INJECTION, USP - URGENT STATUS REQUEST

Hello OSI Team,

Can you please provide us the status of the EIR Review for the clinical portion on ANDA 203263? The last update from OSI was on 10/16/12 "The inspection of the clinical portion of ANDA 203-263 requested on 2/16/2012 was conducted 8/27-9/4/12 and the EIR Review is in progress". Currently, we have not received the EIR Review. Please send in any information that would be helpful to expedite this application as soon as possible. Note that ANDA 203263 is on the FDA drug shortage list and was granted "expedited review" status nearly a year ago. If possible, please determine if form 483 has been issued and if there is any serious issues that we need to know.

Thank you,

Martin Yoon, Pharm.D.
LT, U.S. Public Health Service
Bio Project Manager, Branch VIII
Division of Bioequivalence I
CDER/FDA/OGD
7520 Standish Place,
Rockville, MD 20855
work: 240.276.8771
fax: 240.276.8766

From: Yoon, Martin
Sent: Wednesday, October 17, 2012 10:50 AM
To: CDER OSI BEQ
Cc: Park, Linda
Subject: RE: SUN'S ANDA 203263 FOR DOXORUBICIN HCL LIPOSOME INJECTION, USP - URGENT STATUS REQUEST

Thank you for the update.

Martin Yoon, Pharm.D.
LT, U.S. Public Health Service
Bio Project Manager, Branch VIII
Division of Bioequivalence I
Office of Generic Drugs
Food & Drug Administration

From: CDER OSI BEQ
Sent: Tuesday, October 16, 2012 10:28 PM
To: Yoon, Martin; CDER OSI BEQ
Cc: Park, Linda
Subject: RE: SUN'S ANDA 203263 FOR DOXORUBICIN HCL LIPOSOME INJECTION, USP - URGENT STATUS REQUEST

The inspection of the in vitro portion of ANDA 203-263 was conducted in June and the EIR Review was posted to DARRTS 8/17/12. The inspection of the clinical portion of ANDA 203-263 requested on 2/16/2012 was conducted 8/27-9/4/12 and the EIR Review is in progress. The inspection of the clinical portion of ANDA 203-263 requested on 7/24/12 has not yet been completed.

The inspection of the bioanalytical portion of a study under ANDA 90-886 has been tentatively scheduled. We are waiting for ORA to assign an investigator this week, to travel with the OSI scientist for the inspection. It appears that this inspection may be done in December and reported soon afterward.

From: Yoon, Martin
Sent: Tuesday, October 16, 2012 4:52 PM
To: CDER OSI BEQ
Cc: Park, Linda
Subject: FW: SUN'S ANDA 203263 FOR DOXORUBICIN HCL LIPOSOME INJECTION, USP - URGENT STATUS REQUEST

Good Afternoon,

Can you please provide us the inspection status of ANDA 090886, which was requested on 5/21/2010 and ANDA 203263, which was requested on 2/16/2012. Please note that ANDA 203263 is on the FDA drug shortage list and it is pending the outcomes of those two inspections.

Thanks,

Martin Yoon, Pharm.D.
LT, U.S. Public Health Service
Bio Project Manager, Branch VIII
Division of Bioequivalence I
Office of Generic Drugs
Food & Drug Administration

From: West, Robert L
Sent: Tuesday, October 16, 2012 1:52 PM
To: Park, Linda; Yoon, Martin
Cc: Nice, Frank; Rajagopalan, Radhika; Payne, Angela; Nerurkar, Shriniwas G; Geba, Gregory; Greenberg, Harvey A; Lee, Sau; Yu, Lawrence; Middleton, Sandra T; CDER EESQUESTIONS; Shen, Kun; Schwartz, Paul
Subject: SUN'S ANDA 203263 FOR DOXORUBICIN HCL LIPOSOME INJECTION, USP - URGENT STATUS REQUEST

Review Team:

We've been requested to provide the current review status of this ANDA. Please note that "expedited review" status was granted nearly a year ago to this critical oncology drug product because it is the subject of a nationwide drug shortage.

Please provide your best estimate of when the current review will be completed. I understand that you have probably been asked this question before, but the situation has become increasingly urgent. It appears that both labeling and microbiology have been completed. We need to know the current bio and CMC status - including the review of 2 drug master files associated with this product. What is our timeline for completing these reviews?

I also note that there are two inspections in India that are pending (one inspection under review, the other appears to be unscheduled, but can't tell for certain).

I know that we are faced with many priorities, but nationwide drug shortages clearly go to the top. I also understand that this ANDA represents new technology, but I'm certain the have the knowledge and skills to address it.

Thank you,

Bob

7.3. Original Review of Amendment

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203263		
Drug Product Name	Doxorubicin hydrochloride Liposome Injection		
Strength(s)	2 mg/mL, 10 mL and 25 mL		
Applicant Name	Sun Pharma Global FZE		
Address	Office # 43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U.A.E		
Applicant's Point of Contact	Robert Kurkiewicz Sun Pharmaceutical industries Ltd. (C/O Caraco) 1150 Elijah Mccoy Drive, Detroit, MI 48202		
Contact's Telephone Number	313-556-4105		
Contact's Fax Number	248-926-0231		
Original Submission Date(s)	June 16, 2011 March 07, 2012 (Telephone Amendment) April 9, 2012 May 10, 2012 (Telephone Amendment) June 29, 2012 (Telephone Amendment) July 4, 2012 (Telephone Amendment) August 4, 2012		
Submission Date(s) of Amendment(s) Under Review	October 5, 2012		
Reviewer	Suman Dandamudi Ph.D		
Study Number (s)	PKD_09_030	DOX/003/08	FDD-02/10-11/001
Study Type (s)	Fed	Pilot Fed	In-Vitro
Strength (s)	2 mg/mL	2 mg/mL	2 mg/mL
Clinical Site-1	MNJ Institute of Oncology & Regional Cancer Centre		
Clinical Site-1 Address	Red Hills, Hyderabad- 500 004, India		
Clinical Site-2	Kailash Cancer Hospital & Research Centre		
Clinical Site-2 Address	Goraj, Vadodara- 391760, India		
Clinical Site-3	Dr. G. Vishwanathan Speciality Hospitals		
Clinical Site-3 Address	#27, Babu road, Trichy, Tamilnadu- 620 008, India		
Clinical Site-4	Dr. Kamakshi Memorial Hospital		
Clinical Site-4 Address	No.1, Radial Road, Palikaranai, Chennai- 600 100, India		
Clinical Site-5	NRR Hospital		

Clinical Site-5 Address	Chikkasandra, Bangalore- 560090 (India)		
Analytical Site (fed study)	Sun Pharmaceutical Industries Ltd.,		
Analytical Site Address (fed study)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India		
In Vitro Liposome Size Distribution Testing Site	Sun Pharmaceutical Industries Ltd.,		
In Vitro Testing Site Address	Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India		
REVIEW RESULT	INADEQUATE (Pending only OSI Inspection)		
OSI REPORT RESULT	INADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 8, 9, 10, 11, 16	IN VITRO DRUG RELEASE*	2 MG/ML	ADEQUATE
1, 8	FED STUDY	2 MG/ML	ADEQUATE
1, 8, 16	IN VITRO STUDY	2 MG/ML	ADEQUATE

*NOTE: There is no dissolution testing for this drug product, but there is in vitro drug release testing.

7.3.1 Executive Summary

This portion of the review contains the evaluation of firm's responses submitted in the amendment date October 5, 2012. For the review of OSI report, please see the addendum to the amendment review.

Sun Pharma has submitted ANDA 203263 for its test product, Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL. The submission references NDA 050718, Doxil[®] (Doxorubicin Hydrochloride) Liposomal Injection, 2 mg/mL from Ortho Biotech.

The firm in the current amendment, dated October 5, 2012, submitted its response to the deficiency comments made by the Division of Bioequivalence I (DBI) in the letter dated September 24, 2012.

The firm initially conducted comparative drug release testing using its own proposed method [Bottle Rotating Apparatus in 90 mL of USP phosphate buffer pH 6.4 (b)(4) at a speed of 12 rpm at 52°C]. In addition, in the amendment dated April 09, 2012, the firm also provided in vitro drug release data using FDA-recommended method [2.97ml of 100% FBS (Fetal Bovine Serum (pH 7.10)) containing 214 mg/ml Ammonium Chloride in water (pH 5.3), with pH adjusted to 6.5 +/- 0.1].

In the review of the amendment dated, April 09, 2012, the in vitro drug release method as recommended for the NDA was considered not suitable for the test product. The DBI accepted the firm's proposed in vitro drug release method. However, the firm's proposed specifications for the test product were found not acceptable. Based on the data submitted, the DBI recommended the following specifications:

0.5 hr: NMT (b) (4) %
1.5 hr: (b) (4) %
3 hr: %
5 hr: %
7 hr: NLT (b) (4) %

[DARRTS: DANDAMUDI, SUMAN 07/20/2012 N/A 07/20/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].

In the current amendment, dated October 5, 2012, the firm accepted the DB recommended specifications. The firm's in vitro drug release testing for Doxorubicin hydrochloride Liposome Injection is acceptable.

At the request of the DBI, the OSI/ORA conducted an inspection of in vitro drug testing site on June 11-13, 2012 for Sun pharmaceutical India Ltd., Halol, Gujarat, India. The OSI outcome was voluntary action indicated (VAI). The OSI concluded that the analytical data for the particle size distributions for Doxorubicin Hydrochloride Liposome Injection are acceptable if the refractive indexes of liposome particles and the suspending media, and viscosity of the suspending media for liposome particles are confirmed **[DARRTS: CHEN, XIKUI 08/17/2012 N/A 08/17/2012 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Unknown) Archive].**

The DBI reviewed the inspection report and determined that the OSI's finding **may have an impact** on the in vitro BE study. The firm was asked to address the DBI concerns related to the OSI/ORA's finding **[DARRTS: DANDAMUDI, SUMAN 09/18/2012 N/A 09/18/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].** In the current amendment, the firm submitted the SAS files for the new size distribution data which were obtained by off-line processing of the histograms using the new refractive index and viscosity values of the dispersion medium. The firm's response is acceptable. Therefore, the in vitro equivalence study (Liposome Size Distribution) submitted for Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL is acceptable.

OSI Inspection:**Clinical site for Fed BE Study:**

The fed BE study was conducted at multiple sites.

No	Name of Clinical Site	Group number/Site ID	Number of Patients	OSI Inspection Status
1	MNJ Institute of Oncology & Regional Cancer Center, Hyderabad	1/A	31	NAI
2	Kailash Cancer Hospital and research Center, Goraj, Vadidara	2/B	5	
3	Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu	3/D	11	Pending new site inspection
4	Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai	4/E	4	NAI
5	NRR Hospital, Bangalore	5/G	9	Pending new site inspection

MNJ Institute of Oncology & Regional Cancer Center, Hyderabad and Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai

The above clinical sites were inspected for ANDA 201742 (Routine) on 02/22/2012 and the outcome was NAI [DARRTS: MADA, SRIPAL R 02/22/2012 N/A 02/22/2012 CONSULT REV-BIOEQ-01(General Consult Review) Original-1 (Not Applicable) Archive].

Pending OSI Inspections of Clinical Sites:

NRR Hospital, Bangalore

A new site OSI inspection was requested for this clinical site on February 16, 2012 and is still pending the outcome of the request [DARRTS: RAMSON, TERESA V 02/16/2012 N/A 02/16/2012 FRM-CONSULT-09 (DSI Bioequivalence Audit Request) Original-1 (Unknown) Archive]

Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu

A new site OSI inspection was requested for this clinical site on July 20, 2012 and is still pending the outcome of the request [DARRTS: RAMSON, TERESA V 07/24/2012 N/A 07/24/2012 FRM-CONSULT-09(DSI Bioequivalence Audit Request) Original-1 (Unknown) Archive]

Pending OSI Inspection of the Analytical Site for the BE Study:

A for-cause Office of Scientific Investigations (OSI) inspection was requested for the analytical site of ANDA 090886 on May 20, 2010 and is still pending the outcome of the request [DARRTS: POPAT, ALPITA 05/21/2010 N/A 05/21/2010 FRM-CONSULT-09 (DSI Bioequivalence Audit Request) Original-1 Archive].

In Vitro Testing Site:

Office of Scientific Investigations (OSI)/Office of Regulatory Affairs Inspection for the Current *Parent* ANDA:

A routine OSI/ORA inspection for this site was requested on February 16, 2012 for the current ANDA. The inspection was completed on June 13, 2012 and the outcome was VAI [DARRTS: CHEN, XIKUI 08/17/2012 N/A 08/17/2012 CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) Original-1 (Unknown) Archive]. The form 483 was issued for this site. After the evaluation of the OSI/ORA inspection report, the DBI determined that the OSI's finding **may have an impact** on the in vitro BE study. The firm was asked to address the DBI concerns related to the OSI/ORA's finding [DARRTS: DANDAMUDI, SUMAN 09/18/2012 N/A 09/18/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive]. In the current amendment, the firm provided an adequate response to the objectionable OSI finding.

The ANDA is **inadequate** pending the outcome of the OSI inspections for the analytical site and some of the clinical sites of the BE study.

NOTE: Since currently the OSI inspection consults are pending for the analytical site and some of the clinical sites, the BE review will not be finalized in DARRTS, per the new review procedure adopted on October 1, 2012. Once the OSI inspection results are available, a review addendum will be added to the current review version to address the OSI inspection findings, if any, or to indicate the acceptable inspection status, if applicable.

7.3.2 Background

1. Sun has submitted ANDA 203263 for its product, Doxorubicin Hydrochloride Liposome injection, 2 mg/mL. The submission references NDA 050718, Doxil® (Doxorubicin Hydrochloride) Liposomal Injection, 2 mg/mL from Ortho Biotech.
2. The firm, in its original application, submitted fed (normal low fat breakfast) bioequivalence study comparing its, Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL to the Ortho Biotech's Doxil® Injection, Liposomal, 2 mg/mL. The BE study was found incomplete [DARRTS: NERURKAR, SHRINIWAS G 02/16/2012 N/A 02/16/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive] due to deficiencies related to the analytical part of the BE study. The firm did not provide explanation for multiple summary tables of CC and QC data of free and encapsulated doxorubicin. The method validation lacked cross validation study for liposomal doxorubicin in presence of free doxorubicin.

3. In the original application, the firm also submitted the results of in vitro Liposome Size Distribution Study comparing three lots of the test product with 3 lots of reference product. However the study was found incomplete as the firm did not submit the electronic SAS transport files for in vitro liposome size distribution data.
4. The DBI did not conduct a “dissolution only” review on this ANDA. The in vitro drug release testing was evaluated in the “full ANDA” review. The firm conducted in vitro drug release testing using its own proposed method:

Medium: 90 mL of USP Phosphate buffer, pH 6.4 (b) (4)
Apparatus: Bottle Rotating Apparatus
Speed: 12 rpm
Temperature: 52°C

5. Since Bottle rotating apparatus is not a compendial apparatus, the firm’s proposed method was considered incomplete. The firm was asked to submit detailed information concerning the development, optimization and validation of their proposed in vitro drug release testing method for a full evaluation.
6. In addition, the firm was also requested to conduct additional testing using the following FDA recommended method (b) (4)

Six samples of 1 mL of the vial content should be transferred to six separate glass tubes containing the medium of 98% fetal bovine serum with 80 mM NH₄Cl at pH 6.0, to obtain the final sample volume of 100 mL. These glass tubes should be incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome should be determined at the following six time points: 0 hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs.

7. On February 21, 2012 the firm contacted the Project Manager Teresa Ramson of the division and inquired additional guidance from the division regarding the FDA-recommended in vitro drug release testing method given to the firm in the deficiency letter. Due to the expedited status of the ANDA based on the current drug shortage, the DBI responded to the firm’s inquiry by email on Feb 24, 2012 providing clarification on the method recommendation and asked the firm to conduct *preliminary* in vitro release testing using only the test product since the firm indicated that there was only a limited supply of the RLD available for testing (i.e., about 10 vial units).
8. The *preliminary* data were submitted by email on March 7, 2012 and were reviewed by the DBI. Subsequently, based on the *preliminary* data submitted, on March 8, 2012 the DBI provided additional details and suggested modifications of the recommended method. The DBI asked the firm to conduct additional *preliminary*

testing based on the provided method details and suggested modifications of the method.

9. On March 12, 2012, the firm submitted the second set of *preliminary* data following the DBI's advice. The DBI reviewed the second set of *preliminary* data, and recommended the firm conduct its official in vitro testing on both test and reference product using the following method:

“Sun's Medium 3 [2.97ml of 100% Fetal Bovine Serum (pH 7.10) containing 214 mg/ml Ammonium Chloride in water (pH 5.3), with pH adjusted to 6.5 +/- 0.1].

10. In the amendment dated April 9, 2012, the firm provided the justification for the multiple CC and QC for free and encapsulated doxorubicin. The firm also provided cross validation study for liposomal doxorubicin in presence of free doxorubicin. In addition, the firm also submitted the SAS transport files for in vitro liposome size distribution data. The firm's responses to the deficiency comments related to in vitro liposome size distribution study and analytical part of fed bioequivalence study were found acceptable. Therefore, the in vivo bioequivalence and in vitro liposome size distribution studies are acceptable.
11. In this amendment (dated April 9, 2012), the firm also submitted the comparative in vitro drug release testing data using the FDA-recommended method. Since doxorubicin is not stable in the release medium used in the FDA-recommended method and change in FBS lots resulted in variation in the in vitro drug release profile, the DBI accepted the firm's proposed in vitro drug release method. However, the firm was asked to acknowledge the FDA-recommended in vitro drug release specifications [DARRTS: DANDAMUDI, SUMAN 07/20/2012 N/A 07/20/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].
12. In the amendment dated August 4, 2012, the firm did accept the FDA-specifications for in vitro drug release testing for only two time points (0.5 hrs and 7 hrs). However for the time points of 1.5, 3 and 5 hrs, the firm proposed different specifications than those recommended by the DB. The firm referred to imported lots in vitro drug release data to justify its proposed specifications. The firm was informed that it is not acceptable to justify the proposed drug release specifications for test product based on the drug release data of the imported lots. The firm was asked submit in vitro drug release data of 3 fresh lots of test product to justify its proposed specifications or alternatively acknowledge its acceptance of the DB recommended specifications, which the test product meets at the L1 level [DARRTS: DANDAMUDI, SUMAN 09/18/2012 N/A 09/18/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].
13. At the request of the DBI, the OSI/ORAs conducted an inspection of in vitro drug testing site on June 11-13, 2012 for Sun pharmaceutical India Ltd., Halol, Gujarat, India. The OSI outcome was voluntary action indicated (VAI) [DARRTS: CHEN,

XIKUI 08/17/2012 N/A 08/17/2012 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Unknown) Archive]. The DBI reviewed the inspection report and determined that the OSI's finding may have an impact on the in vitro BE study. The firm was asked to address the DBI concerns related to the OSI/ORA's finding [DARRTS: DANDAMUDI, SUMAN 09/18/2012 N/A 09/18/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].

14. In the current amendment dated October 5, 2012, the firm accepted the DBI recommended in vitro drug release specifications for the test product, Doxorubicin Hydrochloride Liposome injection. In addition, the firm also submitted its response to the OSI/ORA finding of the in vitro BE study.

7.3.3 Submission Summary

7.3.3.1 Drug Product Information, PK/PD Information, and Relevant DB History

See the review of the original submission, DARRTS: NERURKAR, SHRINIWAS G 02/16/2012 N/A 02/16/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive.

7.3.3.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

7.3.3.3 Review of Current Amendment

Deficiency Comment #1: *Although the imported batches were accepted by the Agency for importation purpose, you have been informed in the past that the acceptance criteria for importation should not be considered the same as the criteria for the ANDA approval. Please note that the quality testing program for the imported lots is more limited than that used to support the approval of an application. Therefore, it is not acceptable to justify the proposed in vitro drug release specifications for the test product based on the in vitro drug release data of the imported lots.*

Based on the additional in vitro drug release data submitted for the 25 mL vial of the test product, Lot No. JK93743A, in the amendment dated Aug 04, 2012, the release

specifications previously recommended by the Agency (based on the release data of the test bio-lot, Lot No. - JK93496) were confirmed, and therefore, no change in the recommended specifications is justified.

However, per our consultation with the Division of Chemistry II (DCII), Office of Generic Drugs, you may consider submitting *in vitro* release data from at least 3 fresh imported lots (in place of any 3 other fresh test lots) to justify your proposed specifications at the time points of 1.5 hours, 3 hours and 5 hours, provided that the complete Manufacturing, Chemistry and Controls (CMC) data and records for these 3 imported lots (or any 3 other fresh test lots) are submitted, reviewed and accepted by the Division of Chemistry, Office of Generic Drugs. The CMC records for these test lots should demonstrate that they are manufactured and tested under the same approved manufacturing site, conditions, specifications, controls, and are pharmaceutically equivalent to the test lot used in the bioequivalence study. Please contact the DCII for the information concerning additional testing necessary for these selected imported lots.

Alternatively, please acknowledge your acceptance of the following FDA-recommended method and specifications stated in the previous letter dated July 25, 2012.

The *in vitro* drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr: NMT (b) (4) %
1.5 hr: (b) (4) %
3 hr: %
5 hr: %
7 hr: NLT (b) (4) %

Firm's Response to Deficiency 1: As recommended by the Agency, Sun hereby acknowledges acceptance of following *in-vitro* drug release testing method and specification:

***In-vitro* Release Method:**

Apparatus : Bottle rotating apparatus
Speed : 12 rpm

Medium : Phosphate buffer, pH 6.4
Temperature : 52°C ± 0.5°C
Volume : 90 ml

In-vitro Release Specification:

0.5 hr : NMT (b) (4) %
1.5 hr : (b) (4) %
3 hr : %
5 hr : %
7 hr : NLT (b) (4) %

The testing shall be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, shall be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011). Analytical test procedure shall be in accordance with test procedure # 0011548 for 10 mL and 0011547 for 25 mL (Revision No.4, effective date 3 April 12).

Please also note that a separate chemistry amendment shall be submitted to Division of Chemistry with reference to above change in the *in vitro* release specification.

Reviewer's Comments on Firm's Response # 2: In the current amendment, the firm acknowledged the FDA-recommended in- vitro drug release specifications for Doxorubicin Hydrochloride Liposome Injection. **The firm's response to 1st deficiency is acceptable.**

Deficiency Comment #2: *The Office of Regulatory Affairs (ORA) conducted an audit of the in vitro bioequivalence study for the current ANDA. A Form 483 was issued following the inspection of the study site, Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India between June 11-13, 2012. The DBI has reviewed the inspection report by the ORA pertinent to the in vitro bioequivalence study and found the following objectionable findings by the ORA could potentially compromise the integrity of the in vitro study results.*

"The calibration of (b) (4) Laser Diffraction instrument was inadequate"

For particle size measurements, samples from each vial of test or reference product were poured into a cuvette and the particle size was determined using the defined parameters. Due to the (b) (4) the inspector suspects that the refractive index should have been (b) (4), and the viscosity should have been (b) (4) (b) (4) for the suspending medium. The parameter of (b) (4) for refractive index of liposome particles was not verified.

The D10, D50, D90, and span values in particle size distributions reported in the in vitro study were calculated from scattered light signals by the (b) (4) DLS software. (b) (4)

(b) (4)

The particle size data for D10, D50, D90, and span in the in vitro bioequivalence (BE) study should be evaluated only after the refractive index, viscosity of the suspending medium and the refractive index of liposome particles can be confirmed.

Please address the above findings, and provide any appropriate supporting documentation in your response.

Firm's Response to Deficiency #2: Please note that the literature from the manufacturer of

(b) (4) instrument states that

(b) (4)

With reference to Doxorubicin

(b) (4)

(b) (4)

electronic SAS transport file for the new size distribution data (D10, D50, D90 and SPAN) is provided herewith in section 5.3.1.3.

To validate the off-line processing of the data with respect to new RI and viscosity of dispersion medium, the online measurement of sample has been performed with old and new RI and viscosity of dispersant medium and is presented in the following table.

The below data of three batches shows that the particle size obtained by processing the old acquired data with new RI and viscosity of the dispersant medium is comparable to that of online acquisition with the new RI and viscosity of the dispersant medium (% RSD is in agreement with that obtained in the validation study). Hence based on below data it can be concluded that particle size distribution results obtained by off-line processing of already acquired data are comparable with that determined by on-line processing.

Please note that the population bioequivalence values obtained from the new particle size distribution data provided herewith in *section 5.3.1.3* for D50 and SPAN is ^{(b) (4)} ^{(b) (4)} for D50 and ^{(b) (4)} for SPAN) and on its basis it can be concluded that test product is bio-equivalent to reference product.

Table 1: Comparison of the particle size data obtained by online and offline measurement using both old and new RI and viscosity values

Batch No	Parameter	D10(nm)	D50(nm)	D90(nm)	SPAN (b) (4)
JKL3922 A	Online measurement with OLD parameter (A)				
	Online measurement with NEW parameter (B)				
	Off-line processing with new parameter for acquired histogram with old parameter (C)				
	% RSD b/w New-online (B) and Off-line with new parameter (C)				
JKL4065 A	Online measurement with OLD parameter (A)				
	Online measurement with NEW parameter (B)				
	Off-line processing with new parameter for acquired histogram with old parameter (C)				
	% RSD b/w New-online(B) and Off-line with new parameter (C)				
JKL4067 A	Online measurement with OLD parameter (A)				
	Online measurement with NEW parameter (B)				
	Off-line processing with new parameter for acquired histogram with old parameter (C)				
	% RSD b/w New-online(B) and Off-line with new parameter (C)				

Old Parameters: RI: (b) (4) Viscosity: (b) (4)
 New Parameters: RI: (b) (4) Viscosity: (b) (4)

Reviewer’s Comments on Firm’s Response # 2:

- During the inspection, OSI/ORR found that the frequency of calibration of (b) (4) Laser Diffraction instrument was inadequate.
- The particle size was determined using the defined instrumental parameters by (b) (4) particle size analyzer. The firm used the (b) (4) manufacturer’s recommended parameters of (b) (4) for particle refractive index, (b) (4) for dispersant refractive index (b) (4) and (b) (4) for dispersant viscosity at (b) (4) in the measurement of particle size.

- The OSI/ORA inspector suspected that the (b) (4) (b) (4) might have contributed to the refractive index and the viscosity of the suspending medium. Therefore, the refractive index should have been (b) (4) (b) (4) and the viscosity should have been (b) (4) (b) (4) for the suspending medium.
- The OSI/ORA concluded that the analytical data for the particle size distributions for Doxorubicin Hydrochloride Liposome Injection are acceptable only if the refractive indexes of liposome particles and the suspending media, and viscosity of the suspending media for liposome particles are confirmed. If the instrument settings did not use correct refractive index and viscosity values for the suspending media and correct refractive index of the liposome particles, the particle size distribution data are not usable.
- In the deficiency letter, dated September 24, 2012, the firm was asked to confirm the instrument parameter values set for particle refractive index, dispersant refractive index and dispersant viscosity in the determination of particle size using (b) (4) Particle Size Analyzer [DARRTS: RAMSON, TERESA V 09/24/2012 FAX 09/24/2012 COR-ANDAIDE-01(Bio Incomplete Deficiencies) Original-1 (Unknown) Archive.
- In the current amendment, the firm justified the viscosity value of (b) (4), by stating that the liposomes are dispersed in the aqueous media, therefore water properties are used in the measurement based on the instrument's manual.
- In case of refractive index value, the firm stated that particle refractive index is not applicable for histograms obtained by scattering light intensity. This is based on instrument's manual which states that "It is unnecessary for the distribution based on scattering light intensity to use this particle refraction index".
- However, the firm determined RI and viscosity of the dispersant medium i.e. (b) (4) (b) (4). The obtained values are (b) (4) for refractive index and viscosity respectively.
- The firm stated that software of the (b) (4) DLS instrument has the off-line facility to calculate the size distribution of acquired sample by entering the new values for RI and Viscosity of the dispersant medium. The histograms of all 60 samples were processed by using the new RI and viscosity values to get the particle size distribution.
- In order to validate the off-line processing of the data, the firm also performed the online measurement of study samples with new RI and viscosity values. The off-line and the new-online values of D50, D90 and Span (obtained with RI and viscosity values of (b) (4) respectively) were compared. The particle size data of the three test batches obtained by processing the old acquired data with new

RI and viscosity values is comparable to that of online acquisition with the new RI and viscosity values of the dispersant medium (Table 1).

- Therefore, it is acceptable to perform off-line re-processing of the histograms by using the new RI and viscosity values to get the particle size distribution. The firm submitted the SAS transport file for the new size distribution data. The reviewer analyzed this new study sample data. The test product PASSED the PBE statistical criteria for both D50 and span.

D₅₀ Summary									
	Mean Distance		Variability (%CV)					Mean Ratio (T/R)	
			Within Lot (n=10)			Between Lot (n=3)	Total (n=30)	Arithm (n=30)	Geo (n=30)
	Arithm	Geo	Lot 1	Lot 2	Lot 3				
Test	(b) (4)								
Ref	(b) (4)								

SPAN Summary									
	Mean Distance		Variability (%CV)					Mean Ratio (T/R)	
			Within Lot (n=10)			Between Lot (n=3)	Total (n=30)	Arithm (n=30)	Geo (n=30)
	Arithm	Geo	Lot 1	Lot 2	Lot 3				
Test	(b) (4)								
Ref	(b) (4)								



- The reviewer compared the geometric mean values of D50 and Span for the test and reference products determined with the new and old RI and viscosity values of the dispersion medium (See table below). The D50 obtained with the new values of the RI and viscosity parameters for both test and reference products are low compared to the original data submitted. However, the T/R ratio of D50 is same for the data obtained with old and new RI and viscosity values.

Product	D50 (Geometric Mean), N=30		Span (Geometric Mean), N=30	
	Obtained by old RI and viscosity values	Obtained by new RI and viscosity values	Obtained by old RI and viscosity values	Obtained by new RI and viscosity values
Test				
Reference				

(b) (4)

The firm’s response to 2nd deficiency is acceptable.

Deficiency Comment #3: *In our previous letter dated July 25, 2012, we informed you that “if and when the RLD product becomes available, additional comparative characterization testing may be requested by the Agency, as appropriate, to obtain more complete information on the in vitro release of the test product, as compared with the reference product.” In the current amendment, you responded by noting that you have submitted in vitro release testing for both 10-mL and 25 mL vials of the test and RLD product, using your proposed method. Since your proposed in vitro release testing method has been accepted by the DBI for your test product, the in vitro release testing data as submitted by you thus far are considered adequate for your application at this time, given the current shortage of the RLD product. However, in order to confirm the comparability of in vitro release characteristics between the test and the RLD products, under other relevant in vitro release testing conditions, for instance, the Agency may request additional in vitro comparative characterization testing in the future, if and when the RLD product becomes available.*

Firm’s Response to Deficiency #3: Please note that Sun acknowledges agency’s comment and on request shall submit additional comparative characterization testing data for test and reference product as appropriate if and when the reference product becomes available.

Reviewer’s Comments on Firm’s Response #3: The firm’s response to 3rd deficiency is acceptable.

Deficiency Comment #4: Please provide appropriate documentation and evidence that the reference lot, Doxil Liposomal Injection, Lot No. JK93496 used in your BE study, was US-approved and marketed product. The documentation may include but may not be limited to purchase invoice, package labeling etc.

Firm's Response to Deficiency #4: Please note that purchase invoice for Doxil® (doxorubicin HCl liposome injection) Lot # 0907642 used for the BE study has been provided herewith in section 5.3.1.2. Please note that Caraco Pharmaceutical Laboratories, US subsidiary of Sun Pharmaceutical Industries Limited had shipped these samples to Sun, India. Airway bill for this shipment is also provided herewith in section 5.3.1.2. Please also note that vial label for reference product lot # 0907642 is also provided in section 1.14.3.3 of the original ANDA.

Reviewer's Comments on Firm's Response #4: As requested by the DBI, the firm submitted the purchase invoice for Doxil® and also the airway bill of the shipment to Sun Pharmaceuticals. **The firm's response to 4th deficiency is acceptable.**

7.3.3.4 Deficiency Comments

The OSI inspections for two clinical sites and the analytical site are pending.

7.3.3.5 Recommendations

1. The Division of Bioequivalence tentatively accepts the fed BE study (C10112) conducted by the Sun Pharma Global FZE. on its Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL, lot # JK93496A, comparing it to Ortho Biotech's Doxil® Liposomal Injection, 2 mg/mL, lot # 0907642.
2. The Division of Bioequivalence accepts the in vitro equivalence study (Liposome Size Distribution) conducted by the Sun Pharma Global FZE. on its Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL, comparing it to Ortho Biotech's Doxil® Liposomal Injection, 2 mg/mL.
3. The firm's in vitro drug release testing is acceptable. The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr: NMT (b) (4) %
1.5 hr: (b) (4) %
3 hr: %
5 hr: %
7 hr: NLT (b) (4) %

4. The Division of Bioequivalence *tentatively* deems the test product Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL manufactured by Sun Pharma Global FZE, to be bioequivalent to the reference product, Doxil® Liposomal Injection, 2 mg/mL manufactured by Ortho Biotech.

NOTE: THIS LETTER IS GENERATED BASED ON THE REVIEW ADDENDUM TO THE ORIGINAL AMENDMENT REVIEW AND INCLUDES DEFICIENCIES RELATED TO OSI INSPECTION OF A CLINICAL SITE

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 203263

APPLICANT: Sun Pharma Global FZE

DRUG PRODUCT: Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL (10 mL and 25 mL)

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledge on the cover sheet. The following deficiencies have been identified:

Between 8/27/2012 and 9/4/2012, the Office of Scientific Investigations (OSI) inspected the clinical site, NRR Hospital, Bangalore, India, which was used as one of the clinical sites for your fed bioequivalence (BE) study of the current application. A Form 483 was issued to the site following the inspection.

Please address the following inspection findings cited in the Form 483 and their impact on the integrity of the BE study results:

- Failure to maintain possession and/or control of investigational product test and reference retention samples.
- Failure to assure that an Ethics Committee complying with applicable regulatory requirements and following their own written procedures was responsible for the initial and continuing review and approval of a clinical study.
- Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study related activities.
- There was no statement in the informed consent for screening document that described the extent, if any, to which confidentiality of records identifying the subjects would be maintained; and that noted the possibility that regulatory agencies might inspect the records.
- Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the clinical investigation.

Please provide any necessary supporting documents in your response.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

8. OUTCOME PAGE

ANDA: 203263

Productivity for Original Review Amendment:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
18194	10/5/2012	Other (REGULAR)	Study Amendment	1	1
				Total:	1

Productivity for Addendum of Original Review Amendment:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
18372	6/16/2011	Other (REGULAR)	OSI Inspection Report Review (Analytical)	1	1
				Total:	1

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

/s/

SUMAN DANDAMUDI
11/13/2012

SHRINIWAS G NERURKAR
11/13/2012

HOAINHON N CARAMENICO
11/13/2012

DALE P CONNER
11/13/2012

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203263		
Drug Product Name	Doxorubicin hydrochloride Liposome Injection		
Strength(s)	2 mg/mL, 10 mL and 25 mL		
Applicant Name	Sun Pharma Global FZE		
Address	Office # 43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U.A.E		
Applicant's Point of Contact	Robert Kurkiewicz Sun Pharmaceutical industries Ltd. (C/O Caraco) 1150 Elijah Mccoy Drive, Detroit, MI 48202		
Contact's Telephone Number	313-556-4105		
Contact's Fax Number	248-926-0231		
Original Submission Date(s)	June 16, 2011 March 07, 2012 (Telephone Amendment) April 9, 2012 May 10, 2012 (Telephone Amendment) June 29, 2012 (Telephone Amendment) July 4, 2012 (Telephone Amendment)		
Submission Date(s) of Amendment(s) Under Review	August 4, 2012		
Reviewer	Suman Dandamudi Ph.D		
Study Number (s)	PKD_09_030	DOX/003/08	FDD-02/10-11/001
Study Type (s)	Fed	Pilot Fed	In-Vitro
Strength (s)	2 mg/mL	2 mg/mL	2 mg/mL
Clinical Site-1	MNJ Institute of Oncology & Regional Cancer Centre		
Clinical Site-1 Address	Red Hills, Hyderabad- 500 004, India		
Clinical Site-2	Kailash Cancer Hospital & Research Centre		
Clinical Site-2 Address	Goraj, Vadodara- 391760, India		
Clinical Site-3	Dr. G. Vishwanathan Speciality Hospitals		
Clinical Site-3 Address	#27, Babu road, Trichy, Tamilnadu- 620 008, India		
Clinical Site-4	Dr. Kamakshi Memorial Hospital		
Clinical Site-4 Address	No.1, Radial Road, Palikaranai, Chennai- 600 100, India		
Clinical Site-5	NRR Hospital		
Clinical Site-5 Address	Chikkasandra, Bangalore- 560090 (India)		
Analytical Site (fed study)	Sun Pharmaceutical Industries Ltd.,		
Analytical Site Address (fed)	Sun Pharmaceutical Industries Ltd.,		

study)	Tandalja, Vadodara -390020, India		
In Vitro Liposome Size Distribution Testing Site	Sun Pharmaceutical Industries Ltd.,		
In Vitro Testing Site Address	Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India		
REVIEW RESULT	INADEQUATE		
OSI REPORT RESULT	INADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 8, 9, 10, 11	IN VITRO DRUG RELEASE*	2 MG/ML	INADEQUATE
1, 8	FED STUDY	2 MG/ML	ADEQUATE
1, 8	IN VITRO STUDY	2 MG/ML	INADEQUATE

*NOTE: There is no dissolution testing for this drug product, but there is in vitro drug release testing.

REVIEW OF AN AMENDMENT AND AN OSI/ORA INSPECTION REPORT

1 EXECUTIVE SUMMARY

Sun Pharma has submitted ANDA 203263 for its test product, Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL. The submission references NDA 050718, Doxil[®] (Doxorubicin Hydrochloride) Liposomal Injection, 2 mg/mL from Ortho Biotech.

The firm in the current amendment, dated August 4, 2012, submitted its response to the deficiency comments made by the Division of Bioequivalence I (DBI) in the letter dated July 25, 2012.

The firm initially conducted comparative drug release testing using its own proposed method [Bottle Rotating Apparatus in 90 mL of USP phosphate buffer pH 6.4 (b) (4) (b) (4) at a speed of 12 rpm at 52°C]. In addition, in the amendment dated April 09, 2012, the firm also provided in vitro drug release data using FDA-recommended method [2.97ml of 100% FBS (Fetal Bovine Serum (pH 7.10)) containing 214 mg/ml Ammonium Chloride in water (pH 5.3), with pH adjusted to 6.5 +/- 0.1].

In the review of the amendment dated, April 09, 2012, the FDA recommended in vitro drug release method was considered not suitable for the test product. DB accepted the firm's proposed in vitro drug release method. However, the firm's proposed specifications for the

test product were found not acceptable. Based on the data submitted, the DB recommended the following specifications:

0.5 hr: NMT (b) (4) %
1.5 hr: (b) (4) %
3 hr: %
5 hr: %
7 hr: NLT (b) (4) %

[DARRTS: DANDAMUDI, SUMAN 07/20/2012 N/A 07/20/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].

In the current amendment, dated August 4, 2012, the firm accepted the DB recommended specifications for only 0.5 hr (NMT (b) (4) %) and 7 hr (NLT (b) (4) %) time points. However for the time points of 1.5, 3 and 5 hrs, the firm proposed different specifications than those recommended by the DB. The firm referred to imported lots in vitro drug release data to justify its proposed specifications. Although the imported batches were accepted by the agency for importation, the firm has been informed in the past that the acceptance criteria for importation should not be considered the same as the criteria for the ANDA approval. Therefore, it is not acceptable to justify the proposed drug release specifications for test product based on the drug release data of the imported lots.

In the current amendment, the firm also submitted the comparative drug release testing on the 50 mg/25 mL strength of the test and reference products. Based on the in vitro drug release data submitted for this new lot, the DB's previously recommended specifications are still appropriate for the firm's test product (passes at the L1 level). Since there is not sufficient information to support the firm's newly proposed specifications, the DB recommended in vitro drug release specifications for the test product will remain the same as previously communicated to the firm.

The firm should submit in vitro drug release data of 3 fresh lots of test product to justify its proposed specifications or alternatively should acknowledge its acceptance of the DB recommended specifications, which the test product meets at the L1 level. The firm may also choose to submit in vitro release data from 3 imported lots to justify its proposed specifications at the time points of 1.5 hours, 3 hours and 5 hours. However the CMC for these 3 imported lots should be reviewed and accepted by the Division of Chemistry, Office of Generic Drugs.

**OSI Inspection:
Clinical site for Fed BE Study:**

The fed BE study was conducted at multiple sites.

No	Name of Clinical Site	Group number/Site ID	Number of Patients	OSI Inspection Status
1	MNJ Institute of Oncology & Regional Cancer Center, Hyderabad	1/A	31	NAI
2	Kailash Cancer Hospital and research Center, Goraj, Vadidara	2/B	5	
3	Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu	3/D	11	Pending new site inspection
4	Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai	4/E	4	NAI
5	NRR Hospital, Bangalore	5/G	9	Pending new site inspection

MNJ Institute of Oncology & Regional Cancer Center, Hyderabad and Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai

The above clinical sites were inspected for ANDA 201742 (Routine) on 02/22/2012 and the outcome was NAI [DARRTS: MADA, SRIPAL R 02/22/2012 N/A 02/22/2012 CONSULT REV-BIOEQ-01(General Consult Review) Original-1 (Not Applicable) Archive].

NRR Hospital, Bangalore

A new site OSI inspection was requested for this clinical site on February 16, 2012 and is still pending the outcome of the request [DARRTS: RAMSON, TERESA V 02/16/2012 N/A 02/16/2012 FRM-CONSULT-09 (DSI Bioequivalence Audit Request) Original-1 (Unknown) Archive]

Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu

A new site OSI inspection was requested for this clinical site on July 20, 2012 and is still pending the outcome of the request [DARRTS: RAMSON, TERESA V 07/24/2012 N/A 07/24/2012 FRM-CONSULT-09(DSI Bioequivalence Audit Request) Original-1 (Unknown) Archive]

Analytical site for Fed BE Study:

A for-cause Office of Scientific Investigations (OSI) inspection was requested for the analytical site of ANDA 090886 on May 20, 2010 and is still pending the outcome of the request [DARRTS: POPAT, ALPITA 05/21/2010 N/A 05/21/2010 FRM-CONSULT-09 (DSI Bioequivalence Audit Request) Original-1 Archive].

In Vitro Testing Site:

Office of Scientific Investigations (OSI)/Office of Regulatory Affairs Inspection for the Current Parent ANDA:

A routine OSI/ORI inspection for this site was requested on February 16, 2012 for the current ANDA. The inspection was completed on June 13, 2012 and the outcome was VAI

[DARRTS: CHEN, XIKUI 08/17/2012 N/A 08/17/2012 CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) Original-1 (Unknown) Archive]. The form 483 was issued for this site. After the evaluation of the OSI/ORA inspection report, the DBI determined that the OSI's finding **may have an impact** on the in vitro BE study. The firm is asked to address the DBI concerns related to the OSI/ORA's finding.

OSI Inspectional Findings' Impact on Other ANDAs:

The OSI/ORA report contains finding that is systemic but specific to testing of the liposomal products. Therefore only related ANDAs of liposomal injection drug products should be evaluated for the impact of the findings from the inspection of the in vitro testing site.

☐ Isolated ☒ Systemic

The application is **incomplete**.

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3 BACKGROUND

1. Sun has submitted ANDA 203263 for its product, Doxorubicin Hydrochloride Liposome injection, 2 mg/mL. The submission references NDA 050718, Doxil® (Doxorubicin Hydrochloride) Liposomal Injection, 2 mg/mL from Ortho Biotech.
2. The firm, in its original application, submitted fed (normal low fat breakfast) bioequivalence study comparing its, Doxorubicin Hydrochloride Injection,

Liposomal, 2 mg/mL to the Ortho Biotech's Doxil® Injection, Liposomal, 2 mg/mL. The BE study was found incomplete [DARRTS: NERURKAR, SHRINIWAS G 02/16/2012 N/A 02/16/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive] due to deficiencies related to the analytical part of the BE study. The firm did not provide explanation for multiple summary tables of CC and QC data of free and encapsulated doxorubicin. The method validation lacked cross validation study for liposomal doxorubicin in presence of free doxorubicin.

3. In the original application, the firm also submitted the results of in vitro Liposome Size Distribution Study comparing three lots of the test product with 3 lots of reference product. However the study was found incomplete as the firm did not submit the electronic SAS transport files for in vitro liposome size distribution data.
4. The DBI did not conduct a "dissolution only" review on this ANDA. The in vitro drug release testing was evaluated in the "full ANDA" review. The firm conducted in vitro drug release testing using its own proposed method:

Medium: 90 mL of USP Phosphate buffer, pH 6.4 (b) (4)
Apparatus: Bottle Rotating Apparatus
Speed: 12 rpm
Temperature: 52°C

5. Since Bottle rotating apparatus is not a compendial apparatus, the firm's proposed method was considered incomplete. The firm was asked to submit detailed information concerning the development, optimization and validation of their proposed in vitro drug release testing method for a full evaluation.
6. In addition, the firm was also requested to conduct additional testing using the following FDA recommended method (b) (4)

Six samples of 1 mL of the vial content should be transferred to six separate glass tubes containing the medium of 98% fetal bovine serum with 80 mM NH₄Cl at pH 6.0, to obtain the final sample volume of 100 mL. These glass tubes should be incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome should be determined at the following six time points: 0 hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs.

7. On February 21, 2012 the firm contacted the Project Manager Teresa Ramson of the division and inquired additional guidance from the division regarding the FDA-recommended in vitro drug release testing method given to the firm in the deficiency letter. Due to the expedited status of the ANDA based on the current drug shortage, the DBI responded to the firm's inquiry by email on Feb 24, 2012

providing clarification on the method recommendation and asked the firm to conduct *preliminary* in vitro release testing using only the test product since the firm indicated that there was only a limited supply of the RLD available for testing (i.e., about 10 vial units).

8. The *preliminary* data were submitted by email on March 7, 2012 and were reviewed by the DBI. Subsequently, based on the *preliminary* data submitted, on March 8, 2012 the DBI provided additional details and suggested modifications of the recommended method. The DBI asked the firm to conduct additional *preliminary* testing based on the provided method details and suggested modifications of the method.
9. On March 12, 2012, the firm submitted the second set of *preliminary* data following the DBI's advice. The DBI reviewed the second set of *preliminary* data, and recommended the firm conduct its official in vitro testing on both test and reference product using the following method:

“Sun's Medium 3 [2.97ml of 100% Fetal Bovine Serum (pH 7.10) containing 214 mg/ml Ammonium Chloride in water (pH 5.3), with pH adjusted to 6.5 +/- 0.1].

10. In the amendment dated April 9, 2012, the firm provided the justification for the multiple CC and QC for free and encapsulated doxorubicin. The firm also provided cross validation study for liposomal doxorubicin in presence of free doxorubicin. In addition, the firm also submitted the SAS transport files for in vitro liposome size distribution data. The firm's responses to the deficiency comments related to in vitro liposome size distribution study and analytical part of fed bioequivalence study were found acceptable. Therefore, the in vivo bioequivalence and in vitro liposome size distribution studies are acceptable.
11. In this amendment (dated April 9, 2012), the firm also submitted the comparative in vitro drug release testing data using the FDA-recommended method. Since doxorubicin is not stable in the release medium used in the FDA-recommended method and change in FBS lots resulted in variation in the in vitro drug release profile, the DBI accepted the firm's proposed in vitro drug release method. However, the firm was asked to acknowledge the FDA-recommended in vitro drug release specifications [DARRTS: DANDAMUDI, SUMAN 07/20/2012 N/A 07/20/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].
12. In the current amendment (dated August 4, 2012), the firm did accept the FDA-specifications for in vitro drug release testing for only two time points (0.5 hrs and 7 hrs). However for the time points of 1.5, 3 and 5 hrs, the firm proposed different specifications than those recommended by the DB. In addition, the firm also submitted the comparative in vitro drug release testing data for drug product, 2 mg/ml of 25 mL strength.

4 SUBMISSION SUMMARY

4.1 Drug Product Information, PK/PD Information, and Relevant DB History

See the review of the original submission, DARRTS: NERURKAR, SHRINIWAS G
02/16/2012 N/A 02/16/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown)
Archive.

4.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

4.3 Review of Current Amendment

Deficiency Comment #1: *The in vitro drug release testing using your proposed method with Bottle Rotating Apparatus is acceptable. Based on the data submitted for the test lot used in the in vivo bioequivalence study, the DBI has recommended appropriate specifications for the test product. Please acknowledge your acceptance of the following method and specifications:*

The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in your SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr:	NMT	(b) (4) %
1.5 hr:	(b) (4)	%
3 hr:	(b) (4)	%
5 hr:	(b) (4)	%
7 hr:	NLT	(b) (4) %

Firm's Response to Deficiency 1: Sun hereby acknowledges acceptance of following *in-vitro* drug release testing method:

Apparatus:	Bottle rotating apparatus
Speed:	12 rpm
Medium:	Phosphate buffer, pH 6.4
Temperature:	52°C ± 0.5°C
Volume:	90 ml

The testing shall be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, shall be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011). Analytical test procedure shall be in accordance

with test procedure # 0011548 for 10 mL and 0011547 for 25 mL (Revision No.4, effective date 3 April 12).

With respect to specification please note the following points:

- a) Sun hereby accepts following FDA recommended specification for 0.5 hour and 7 hours time point. These specifications are also identical to Sun’s proposed specification

Time point	Specification
0.5 hour	NMT (b) (4) %
7 hour	NLT (b) (4) %

- b) For 1.5, 3 and 5 hour time points comparison of Sun’s specification and FDA recommended specifications is given below :

Time point	Sun’s specification	FDA recommended specification
1.5 hour	(b) (4) %	(b) (4) %
3 hour	%	%
5 hour	%	%

Please also note that in original ANDA, Sun’s above mentioned specification were proposed for mean dissolution.

Subsequently, for drug product certificates of analysis submitted to FDA, drug shortage program (for batches imported under enforcement discretion), FDA informed Sun to provide ranges for dissolution instead of mean value. Based on this requirement, *in-vitro* drug release specifications were revised. In the revised specification, previously specified limits for mean dissolution were adopted for individual units, along with it testing criteria at L1, L2 and L3 stages was also included in accordance with USP <711>.

In-vitro release data from 35 fresh batches (for which certificate of analysis has been submitted to Christina Bina, FDA Drug shortage program) has been evaluated with regards to acceptance of FDA recommended specification.

At 1.5, 3 and 5 hour time point all mean and minimum values are complying with the FDA recommended specification. Graphical presentations of *in-vitro* release data for mean and minimum values have been provided herewith in **figure 1 and 2**.

For maximum values, *in-vitro* release data at 1.5, 3 and 5 hours time point for some of the batches is exceeding FDA recommended specification at L1 stage. Graphical

presentations of *in-vitro* release data for maximum values have been provided herewith in *figure 3*.

Considering above mentioned data, if FDA recommended specification are accepted, routine testing at L2/L3 stages may be required. Therefore Sun respectfully request FDA to accept Sun’s following proposed specification for 1.5, 3 and 5 hour time point.

Time point	Sun’s specification		FDA recommended specification
	Existing	Proposed	
1.5 hour	(b) (4) %	(b) (4) %	(b) (4) %
3 hour	%	%	%
5 hour	%	%	%

Deficiency Comment #2: *You may request revision of the above FDA-recommended release specifications by submitting additional in vitro release data from fresh test lots, for which the validation has been reviewed and accepted by the Division of Chemistry, Office of Generic Drugs (OGD): The Manufacturing, Chemistry and Controls (CMD) records for these test lots should be submitted to the chemistry review division, and demonstrate that they are manufactured under the same approved manufacturing site, conditions, specifications, controls, and are pharmaceutically equivalent to the test lot used in the bioequivalence study. We note that at the present time, the evaluation of the proposed finished product specifications for the test product by the OGD chemistry division is ongoing.*

Firm’s Response to Deficiency #2: Please note based on the explanation provided in above response, Sun respectfully request acceptance of Sun’s proposed *in-vitro* release specification.

Please note that the emergency supplied batches referred above are manufactured under the same approved manufacturing site, conditions, specifications, controls, and are pharmaceutically equivalent to the test lot used in the bioequivalence study.

Reviewer’s Comments on Firm’s Response #1 and 2:

- The firm in the original submission provided the in vitro drug release data using its own proposed method:

Apparatus: Bottle rotating apparatus
 Medium: Phosphate buffer, pH 6.4
 Volume: 90 mL
 RPM: 12
 Temperature: 52 ± 0.5 °C
 Time Point: 0.5, 1.5, 3, 5 and 7 hours

The firm was asked to conduct additional dissolution testing using the FDA-recommended in vitro drug release method [DARRTS: DANDAMUDI, SUMAN 04/03/2012 N/A 04/03/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive and DANDAMUDI, SUMAN 07/20/2012 N/A 07/20/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].

- In the review of the amendment (dated 04/9/2012), the in vitro drug release testing using the firm’s proposed method was found to be more appropriate for the test product. Therefore, the in vitro drug release testing on the Doxorubicin Hydrochloride Liposomal Injection using its own proposed method was found to be acceptable. However, based on the data submitted, the firm’s initially proposed specifications were not acceptable and thus the DB recommended the following specifications which were deemed more appropriate for the test product.

0.5 hr: NMT (b) (4) %
 1.5 hr: (b) (4) %
 3 hr: %
 5 hr: %
 7 hr: NLT (b) (4) %

- In the current amendment, the firm accepted the DB recommended specifications for only the 0.5 hr (NMT (b) (4) %) and 7 hr (NLT (b) (4) %) time points. However, for the time points of 3, 5 and 7 hrs, the firm did not accept the DB recommended specifications and proposed a different specification for each of the respective time points

Time (hrs)	DB Recommended Specifications	Firm Proposed Specifications
0.5	NMT (b) (4) %	NMT (b) (4) %
1.5	(b) (4) %	(b) (4) %
3	%	%
5	%	%
7	NLT (b) (4) %	NLT (b) (4) %

- The firm provided the following justification for not accepting DB recommended specification for 3, 5 and 7 hrs time points ***“In-vitro release data from 35 fresh batches (Imported lots for which certificate of analysis has been submitted to Christina Bina, FDA Drug shortage program) has been evaluated with regards to acceptance of FDA recommended specification. At 1.5, 3 and 5 hour time point all mean and minimum values are complying with the FDA recommended specification. For maximum values, in-vitro release data at 1.5, 3 and 5 hours time point for some of the batches is exceeding FDA recommended specification at L1 stage. If FDA recommended specifications are accepted, routine testing at L2/L3 stages may be required”.***

- Temporary importation of foreign drugs is considered only in cases when there is a shortage of an approved US drug that is critical to patients and the shortage cannot be resolved by manufacturers of approved US drug in the immediate future. FDA evaluates the overseas drug to ensure that it is adequate quality and that the drug does not pose significant risks for US patients. However, FDA's exercise of enforcement discretion does not mean that the overseas drug is now FDA approved in the US.
- Although the imported batches were accepted by the agency for importation, the firm has been informed in the past that the acceptance criteria for importation should not be considered the same as the criteria for the ANDA approval. The quality testing program for the imported lots is more limited than that used to support the approval of the ANDA. The firm did not submit complete Chemistry, Manufacturing and Control information for the importation batches to the Division of Chemistry to assess whether these batches were manufactured, controlled and tested under identical manufacturing conditions as those used for the test bio-lot.
- The Division of Bioequivalence I met with the Division of Chemistry II (DCII) to discuss whether these importation batches can be used to set the specifications for the in vitro drug release testing (Please see section 4.6 Attachments for Meeting Minutes).
- The DCII agreed with the DBI that only the data for the bio-lot should be used to set the specifications for the test product. This is because, the CMC information of the importation batches has not been deemed to be acceptable by the DCII.
- Since there is not sufficient information to support the firm's newly proposed specifications, the DB recommended dissolution specifications for the test product will remain the same as previously communicated to the firm.
- The firm may submit additional in vitro drug release data of *fresh* lots to justify its proposed specifications, or alternatively should acknowledge the DB recommended method and specifications.
- As per the Division of Chemistry II (DCII) reviewer, Dr. Xiaobin Zhao suggestion, considering the drug shortage situation, the importation batches in vitro drug release data can be used for the justification of the firm's proposed drug release specifications provided that the firm submits additional CMC information as recommended by the DCII (Please section 4.6 Attachments for email correspondence with chemistry reviewer).
- The firm should provide complete CMC information for the importation lots to the DCII for the review. And if the DCII finds these imported lots to be equivalent to

the bio-lot that that data would be considered to set the specifications for the in vitro drug release.

- **The firm's responses to the 1st and 2nd deficiencies are not acceptable.**

Deficiency Comment #3: *Due to the reported limited availability of the reference listed drug (RLD) product, Doxil®, the Agency has not requested a complete comparative characterization of the in vitro release profile for the test versus the RLD product at this time. However, if and when the RLD product becomes available, additional comparative characterization testing may be requested by the Agency, as appropriate, to obtain more complete information on the in vitro release of the test product, as compared with the reference product.*

Firm's Response to Deficiency #3: Please note that *in-vitro* release profile of test versus RLD for 10 mL vial, 2 mg/mL strength has already been provided in original ANDA in Module 5, section 5.3.1.3. *In-vitro* release profile of test versus RLD for 25 mL strength has been provided herewith in Module 5, **section 5.3.1.3**. CTD summary table for this *in-vitro* release study has also been provided herewith in Module 2, **section 2.7.1**.

Please also note that *in-vitro* release and characterization studies for three lots of test and reference product have already been performed and submitted to the agency as a part of product development report (page 77 - 93) provided in section 3.2.P.2 of the submitted ANDA

Reviewer's Comments on Firm's Response #3:

- The test product, Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL is manufactured with the fill volume of 10 mL and 25 mL. The firm originally conducted in vivo bioequivalence study and in vitro drug release study on the 2 mg/mL strength, (10 mL vial).
- In the current amendment, the firm submitted the comparative drug release testing on the 2 mg/mL strength (25 mL vial) of the test (Lot No JK93743A) and reference product (1007992).
- The reviewer consulted the DCII reviewer, Dr. Xiaobin Zhao, to verify if this new test lot (Lot No JK93743A) can be considered the same as the bio-lot (Lot No JK93496) in term of the manufacturing quality.
- The chemistry reviewer confirmed that the lot# JK93743A can be considered as the same as the bio-lot (Lot No JK93496). He also stated the following ***“It has the same components, manufacturing process, in process controls and release tests as the JK93496 batch, except the fill volume (25 mL for JK93743 vs. 10 mL for JK93496). The firm has provided executed batch manufacturing record for this lot in the original submission. It was submitted as one of the three exhibit batches (JK93743, JKJ0142, JKJ0322) for the 2 mg/mL, 25 mL strength. It was manufactured in 12/ 2009. The batch size is (b) (4)”***.

- Since the DCII considers the CMC information for the lot# JK93743A to be acceptable, the in vitro drug release data for this lot will be considered to set the specifications for the in vitro drug release testing.
- Based on the in vitro drug release data submitted for this new lot, the DB's previously recommended specifications are still appropriate for the firm's test product (passes at the L1 level). No change in the specifications is deemed necessary based on the release data of this lot.
- The firm will be informed that Deficiency #3 is for the firm's information. The in vitro testing data provided for both 10 mL vials and 25 mL vials of the test and RLD products, using the firm's method are considered adequate at this time. However, per our previous comments, additional release characterization testing may be necessary, using different release methods, for example, if and when the RLD product becomes available again in the market.
- Currently the firm is requested to show proof of the US-approved product used as the reference product in BE studies. Therefore, the firm is asked to provide appropriate documentation and evidence that the reference lot, Doxil Liposomal Injection, Lot No. JK93496 used in your BE study, was US-approved and marketed product. The documentation may include but may not be limited to purchase invoice, package labeling etc.

Table 1: Comparative In Vitro drug release testing for 2 mg/mL, 25 mL

Dissolution Conditions		Apparatus:	Bottle Rotating Apparatus								
		Sinker:	No								
		Speed of Rotation:	12 rpm								
		Medium:	USP phosphate buffer pH 6.4 (b) (4)								
		Volume:	90 mL								
		Temperature:	52°C								
Firm's Proposed Specifications		0.5 hr: NMT (b) (4)%, 1.5 hr: (b) (4)%, 3 hr: (b) (4)%, 5 hr: (b) (4)%, 7 hr: NLT (b) (4)%									
Dissolution Testing Site (Name, Address)		Sun Pharma Advanced Research Company Limited, Nima Compound, Tandalja, Vadodara-390012, Gujarat, India.									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units*	Collection Times (hr)					Study Report Location	
					0.5	1.5	3	5	7		
FN11014 52 & FN11019 06	07/16/2011 and 07/18/2011	Doxorubicin Hydrochloride Liposome Injection Batch # JK93743A Mfg date: Dec 21, 2009	2 mg/mL, 25 mL Injection	12	Mean	5.92	18.79	40.52	66.19	86.02	Module# 5.3.1.3
					Range	(b) (4)					
					%CV	22.97	8.54	7.82	5.1	2.91	
		Doxil® Liposome Injection Batch # 1007992 Exp. date: March 31, 2012	2 mg/mL, 25 mL Injection	12	Mean	7.12	20.54	44.17	70.91	90.8	
					Range	(b) (4)					
					%CV	18.2	12.13	8.42	6.17	3.90	

* Each lot of Test and Reference were tested on two different dates with 6 tubes of test and 6 tubes of reference on each date

Table 2: Comparison of in vitro drug release data between two strength lots (2 mg/mL; 10 mL and 25 mL)

Time Point (hrs)	Bio-lot (Lot No JK93496) 2 mg/mL, 10 mL			Lot No JK93743A 2 mg/mL, 25 mL		DB Recommended Specifications
	Mean	Range	S.D.	Mean	Range	
0.5	6	(b) (4)	1.25	8	(b) (4)	NMT (b) (4) %
1.5	19	(b) (4)	2.91	20	(b) (4)	(b) (4) %
3	41	(b) (4)	4.06	46	(b) (4)	(b) (4) %
5	66	(b) (4)	3.39	70	(b) (4)	(b) (4) %
7	86	(b) (4)	2.97	87	(b) (4)	NLT (b) (4) %

- In the response to the FDA’s comment the firm also stated that the in-vitro release data for 3 lots of test and reference product have already been performed and submitted to the agency as part of product development report provided in section 3.2.P.2.

Table 3: Comparative in vitro release results for three lots submitted in Module 3.2.P.2

Time Point (hrs)	Lot # JK93371		Lot # JK93496		Lot # JK93699		DB Recommended Specifications
	Mean	SD	Mean	SD	Mean	SD	
0.5	9	0.64	8	1.01	5	1.06	NMT (b) (4) %
1.5	24	1.36	18	1.87	21	2.06	(b) (4) %
3	41	2.02	48	3.53	44	1.72	(b) (4) %
5	66	3.69	71	2.89	66	2.09	(b) (4) %
7	84	3.71	87	3.2	85	1.55	NLT (b) (4) %

The firm submitted the mean and standard deviation (SD) of the % drug release at each time point, however did not provide the individual tablet data. Therefore, the range of the % drug release values cannot be calculated. Since the SD for the percent drug release at each time point for the above three lots are comparable to the bio-lot, the ranges of the percent drug release for these 3 lots may be considered similar to the bio-lot. Based on the mean values of the % drug release for the above three lots, the previously DB recommended specifications seems appropriate for the test product.

- Since there is not sufficient information to support the firm’s newly proposed specifications, the DB recommended dissolution specifications for the test product will remain the same as previously communicated to the firm.

4.4 OSI/ORA Inspection Report Review: In Vitro Testing Site

At the request of OGD/DBI, the OSI/ORA conducted an audit of the in vitro bioequivalence study for Sun Pharma's Doxorubicin Hydrochloride Liposomal Injection, 2 mg/mL. Per the inspection report dated August 17, 2012 from the OSI/ORA, Form FDA-483 was issued following the inspection at Sun pharmaceutical India Ltd., Halol, Gujarat, India (June 11-13, 2012). The inspection of the in vitro bioequivalence study was conducted by Office of Regulatory Affairs (ORA) inspectors, Dr. Scott B. Laufenberg and Dr. Mural B. Gavini, both of OIP-India. The firm did not provide its responses to the Form 483 observations. The OSI concluded that the analytical data for the particle size distributions for Doxorubicin Hydrochloride Liposome Injection are acceptable if the refractive indexes of liposome particles and the suspending media, and viscosity of the suspending media for liposome particles are confirmed. If the instrument settings did not use correct refractive index and viscosity values for the suspending media, and correct refractive index of the liposome particles, the particle size distribution data are not usable [DARRTS: CHEN, XIKUI 08/17/2012 N/A 08/17/2012 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Unknown) Archive].

OSI/ORA Finding 1: *The frequency of calibration of (b) (4) Laser Diffraction instrument was inadequate. The instrument was used for (b) (4)*

- *The (b) (4) – Performance Qualification Procedure stated "****The following nominal size standards will be needed for this test: (b) (4) (b) (4) nm****". However, during the Performance Qualification (conducted on 18 Aug. 2004) for instrument (b) (4) testing was only performed for the (b) (4) nm size. This is the instrument used for analysis on the in vitro BEQ study of Doxorubicin HCl Liposome Injection, 2 mg/ml, 10 ml (FDD-02/10-11/001).*
- *Additionally, during the calibration/verification conducted on this instrument on 27 Aug 2010; just prior to the aforementioned study, only the (b) (4) nm size standard was used. The study was designed to analyze at (b) (4) nm particle size.*

OSI has provided the following detailed explanation for the above finding along with their evaluation for the firm's response to the Form FDA-483:

Performance verification or performance check is necessary to demonstrate the accuracy and precision of measurements by the (b) (4) Dynamic Light Scattering (DLS) Particle Size Analyzer (b) (4) because the equipment was not adjusted according to calibrators. Instead, staff relied on the wavelength of incident and scattered light

adjusted by the refractive index of the suspending medium, and the viscosity of the suspending medium for the instrument's calibration.

Individual values for the refractive index and viscosity for the suspending medium of calibrators and test samples are appropriate, especially if they are not identical, because these values are used in the calculations of particle sizes from the scattered light signals. Demonstration of accuracy and precision for measuring a range of known particle sizes of standards would require knowledge of their absolute sizes, typically from microscopic measurements. Because incorrect refractive index and viscosity values may have been used (see below), and they enter the calculation as nonlinear operators, a range of particle size calibrators approximately the same size as study sample particles (b) (4) should have been used to demonstrate accuracy of the size measurement. Calibrators also were not used in calculation of particle sizes for unknown (test) samples.

The performance qualification (PQ) for particle size analyzer- (b) (4) in the Halol manufacturing facility was conducted by the instrument vendor on August 18, 2004, using only a nominal standard (b) (4) particle. Nominal standards (b) (4) nm were not used in the PQ, although nominal standards (b) (4) nm were listed on the (b) (4). The same instrument in the Halol facility was used for particle size measurements in the in vitro BEQ study and in manufacturing controls of the finished product.

The same model of (b) (4) was installed in the nearby Vadodara R&D facility. However, at that facility, the PQ for installation and annual performance checks were conducted using three nominal (b) (4) standards with diameters (b) (4) nm. Method validation of the particle size analysis was conducted using the (b) (4) (u) (4) instrument in Vadodara R&D facility on October 5 and 6, 2010.

According to standard operating procedure (SOP) QCI-132/01, entitled "Operation and Performance Check of Particle Size Analyzer," effective 25 November 2006, performance check frequency is recommended once per year. (b) (4)

An annual performance check for the (b) (4) in the Halol facility was performed using only the (b) (4) nm size standard on August 27, 2010, prior to the in vitro BE study. Results of mean particle size diameters (nm) for standard (b) (4) nm using (b) (4) in the Halol facility are listed as follows:

Run No.	1	2	3	4	5	Mean
						(b) (4)

The results for standard (b) (4) nm met the acceptance criteria of within 20% of the average mean diameter of (b) (4) nm and relative standard deviation (RSD) of the data within 20%, specified in SOP QCI-132/01.

In vitro Study FDD-02/10-11/001 for Doxorubicin Hydrochloride Liposome Injection was conducted on November 19, 2010. Another annual performance check for the (b) (4) in the Halol facility was conducted using three standards: (b) (4) nm on September 20, 2011. Results of mean particle size diameters (nm) for the three standards using the (b) (4) in Halol facility are listed as follows:

Run No.	(b) (4)
1	(b) (4)
2	(b) (4)
3	(b) (4)
4	(b) (4)
5	(b) (4)
Mean	(b) (4)

(b) (6) performed the method validation for particle size analyses using the (b) (4) in Vadodara R&D facility. The validation included particle size analyses within (b) (4) analysts (b) (6), and within and between days (October 5 and 6). (b) (6) was the main analyst in the in vitro study, and (b) (6) performed the role of quality control on the in vitro study, using the same model of (b) (4) in the Halol manufacturing facility. The same reference product Doxil lot# 907642 was used in both the validation and the in vitro study. Results of mean particle size diameters (nm) for Doxil lot# 907642 performed by (b) (6) (Analyst 2) using (b) (4) are listed as follows:

Vial No.	10/5/2010 in Vadodara	10/6/2010 in Vadodara	11/19/2010 in Halol
1	(b) (4)	(b) (4)	(b) (4)
2	(b) (4)	(b) (4)	(b) (4)
3	(b) (4)	(b) (4)	(b) (4)
4	(b) (4)	(b) (4)	(b) (4)
5	(b) (4)	(b) (4)	(b) (4)
6	(b) (4)	(b) (4)	(b) (4)
7	(b) (4)	(b) (4)	(b) (4)
8	(b) (4)	(b) (4)	(b) (4)
9	(b) (4)	(b) (4)	(b) (4)
10	(b) (4)	(b) (4)	(b) (4)
Mean	(b) (4)	(b) (4)	(b) (4)

The reference product Doxil lot# 907642 was used as a secondary standard for performance verification of (b) (4) in the Halol facility. Performance results of the standards and the Doxil lot were within acceptance criteria of 20% difference from nominal

standard values, and the performance verifications on (b) (4) in the Halol facility are within these criteria.

Additional Observations from EIR review:

We note that Sun Pharmaceutical used the (b) (4) manufacturer's recommended values of (b) (4) for particle refractive index, (b) (4) for dispersant refractive index ((b) (4) % sucrose in water), and (b) (4) for dispersant viscosity at (b) (4) in the method validation and in the in vitro study. For particle size measurements, samples from each vial of test or reference product were poured into a cuvette and the particle size was determined using the defined parameters. Due to the (b) (4) we suspect that the refractive index should have been (b) (4), and the viscosity should have been (b) (4) for the suspending medium. The parameter of (b) (4) for refractive index of liposome particles was not verified.

The D10, D50, D90, and span values in particle size distributions reported in the in vitro study were calculated from scattered light signals by the (b) (4) DLS software. (b) (4)

The particle size data for D10, D50, D90, and span in the in vitro BE study need to be evaluated when the refractive index and viscosity of suspending medium and the refractive index of liposome particles can be confirmed.

Preliminary ORA Classification was OAI. After OSI evaluation of the Form FDA 483 observations and the EIR, the final classification for the firm was VAI because performance checks on (b) (4) in the Halol facility were conducted for standard (b) (4) nm on August 27, 2010, prior to the in vitro BE study; for Doxil lot# 907642 (a secondary standard) on November 19, 2010, during the in vitro BE study; and for three standards: (b) (4) nm on September 20, 2011, after the in vitro BE study, and the performance results met the acceptance criteria.

Reviewer's Comments:

- During the inspection, OSI/ORAs found that the frequency of calibration of (b) (4) Laser Diffraction instrument was inadequate.
- According to standard operating procedure (SOP) QCI-132/01, entitled "Operation and Performance Check of Particle Size Analyzer," effective 25 November 2006, performance checks of once in a year is recommended. In addition the performance qualification should be conducted using nominal size standards of (b) (4) nm. However, an annual performance check for the (b) (4) was performed using only the (b) (4) nm size standard, prior to the in vitro BE study. The

- results for standard (b) (4) nm met the acceptance criteria of within 20% of the average mean diameter.
- The firm should have used a range of particle size calibrators approximately the same size as study sample particles (b) (4) to demonstrate accuracy of the size measurement.
 - The particle size was determined using the defined instrumental parameters by (b) (4) particle size analyzer. The firm used the (b) (4) manufacturer's recommended parameters of (b) (4) for particle refractive index, (b) (4) for dispersant refractive index (b) (4) and (b) (4) for dispersant viscosity at (b) (4) in the measurement of particle size.
 - The sample from each vial of test or reference product was poured into cuvette and the particle size was determined using the above defined parameters.
 - The OSI/ORA inspector suspects that the (b) (4) (b) (4) might have contributed to the refractive index and the viscosity of the suspending medium. Therefore, the refractive index should have been (b) (4) (b) (4) and the viscosity should have been (b) (4) (b) (4) for the suspending medium.
 - In the page no: 2 of "Report for Development of Method for Particle Size Determination of Doxorubicin Liposomes" (Report No FDD-02/MDR/005-00, the firm stated that "*Dispersant Refractive Index and Dispersant Viscosity were kept same as that of water as the formulation is aqueous based i.e. (b) (4) % sucrose*". Therefore the instrument parameters were set as (b) (4) for particle refractive index, (b) (4) for dispersant refractive index and (b) (4) for dispersant viscosity.
 - The OSI/ORA concludes that the analytical data for the particle size distributions for Doxorubicin Hydrochloride Liposome Injection are acceptable only if the refractive indexes of liposome particles and the suspending media, and viscosity of the suspending media for liposome particles are confirmed. If the instrument settings did not use correct refractive index and viscosity values for the suspending media and correct refractive index of the liposome particles, the particle size distribution data are not usable.
 - The firm will be asked to confirm the instrument parameter values set for particle refractive index, dispersant refractive index and dispersant viscosity in the determination of particle size using (b) (4) Particle Size Analyzer.

Impact of the OSI/ORA Inspection Finding on Related ANDAs:

The OSI/ORA report contains finding that is systemic but specific to liposomal products. Therefore only related ANDAs of liposomal injection drug products should be evaluated for the impact of the findings from the inspection of the in vitro testing site.

☐ Isolated ☒ Systemic

4.5 Deficiency Comments

1. Although the imported batches were accepted by the Agency for importation purpose, the firm has been informed in the past that the acceptance criteria for importation should not be considered the same as the criteria for the ANDA approval. The quality testing program for the imported lots is more limited that that used to support the approval of an application. Therefore, it is not acceptable to justify the proposed in vitro drug release specifications for the test product based on the in vitro drug release data of the imported lots.

Based on the additional in vitro drug release data submitted for the 25 mL vial of the test product, Lot No. JK93743A, in the amendment dated Aug 04, 2012, the release specifications previously recommended by the Agency (based on the release data of the test bio-lot, Lot No. - JK93496) were confirmed, and therefore, no change in the recommended specifications is justified.

However, based on consultation with the Division of Chemistry II (DCII), Office of Generic Drugs, the firm may consider submitting in vitro release data from at least 3 fresh imported lots (in place of any 3 other fresh test lots) to justify its proposed specifications at the time points of 1.5 hours, 3 hours and 5 hours, provided that the complete Manufacturing, Chemistry and Controls (CMC) data and records for these 3 imported lots (or any 3 other fresh test lots) are submitted, reviewed and accepted by the Division of Chemistry, Office of Generic Drugs. The (CMC) records for these test lots should demonstrate that they are manufactured and tested under the same approved manufacturing site, conditions, specifications, controls, and are pharmaceutically equivalent to the test lot used in the bioequivalence study. The firm should contact the DCII for the information concerning additional testing necessary for these selected imported lots.

Alternatively, the firm should acknowledge the FDA-recommended method and specifications stated in the previous letter dated July 25, 2012.

The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4) using 100 mL cylinder glass bottles ((u) (u)) with cap with (u) (u) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr: NMT (b) (4) %
1.5 hr: (b) (4) %
3 hr: %
5 hr: %
7 hr: NLT (b) (4) %

2. The Office of Regulatory Affairs (ORA) conducted an audit of the in vitro bioequivalence study for the current ANDA. A Form 483 was issued following the inspection of the study site, Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India between June 11-13, 2012. The DBI has reviewed the inspection report by the ORA pertinent to the in vitro bioequivalence study and found the following objectionable findings by the ORA could potentially compromise the integrity of the in vitro study results.

“The calibration of (b) (4) Laser Diffraction instrument was inadequate”

For particle size measurements, samples from each vial of test or reference product were poured into a cuvette and the particle size was determined using the defined parameters. Due to the (b) (4) the inspector suspects that the refractive index should have been (b) (4), and the viscosity should have been (b) (4) for the suspending medium. The parameter of (b) (4) for refractive index of liposome particles was not verified.

The D10, D50, D90, and span values in particle size distributions reported in the in vitro study were calculated from scattered light signals by the (b) (4) DLS software. (b) (4)

The particle size data for D10, D50, D90, and span in the in vitro bioequivalence (BE) study should be evaluated only after the refractive index, viscosity of the suspending medium and the refractive index of liposome particles can be confirmed.

The firm should address the above findings, and provide any appropriate supporting documentation in its response.

3. In the previous letter dated July 25, 2012, the firm was informed that “if and when the RLD product becomes available, additional comparative characterization testing may be requested by the Agency, as appropriate, to obtain more complete information on the in vitro release of the test product, as compared with the reference product.” In the current amendment, the firm responded by noting that they have submitted in vitro release testing for both 10-mL and 25 mL vials of the test and RLD product, using its own proposed method. Since the firm’s proposed in vitro release testing method has been accepted by the DBI for the test product, the in vitro release testing data as submitted thus far are considered adequate for the application at this time, given the current shortage of the RLD product. However, in order to confirm the comparability of in vitro release characteristics between the test and the RLD products, under other relevant in vitro release testing conditions, for instance, the Agency may request additional in vitro comparative characterization testing in the future, if and when the RLD product becomes available.
4. The firm should provide appropriate documentation and evidence that the reference lot, Doxil Liposomal Injection, Lot No. JK93496 used in BE study, was US-approved and marketed product. The documentation may include but may not be limited to purchase invoice, package labeling etc.

4.6 Recommendations

1. The Division of Bioequivalence tentatively accepts the fed BE study (C10112) conducted by the Sun Pharma Global FZE. on its Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL, lot # JK93496A, comparing it to Ortho Biotech’s Doxil® Liposomal Injection, 2 mg/mL, lot # 0907642.
2. The in vitro equivalence study (Liposome Size Distribution) submitted for Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL, by Sun Pharma Global FZE, comparing it to Doxil® Liposomal Injection, 2 mg/mL, manufactured by Ortho Biotech, is incomplete due to deficiency mentioned above.
3. The firm’s *in vitro* drug release testing is incomplete due to deficiencies mentioned above.

4.7 Comments for Other OGD Disciplines

Discipline	Comment
None	

APPEARS THIS WAY ON ORIGINAL

4.8 Attachments

E-mail correspondence between the DBI and DCII reviewers

From: Zhao, Xiaobin
Sent: Wednesday, August 29, 2012 11:50 AM
To: Dandamudi, Suman
Cc: Rajagopalan, Radhika; Lee, Sau
Subject: RE: Regarding Doxorubicin Liposomes

Hi, Suman,

Considering the shortage situation, the importation batches can be used for setting in vitro release specification if Sun can provide relevant information to ensure that the quality of these batches are consistent with the bio-batch. Thanks,

Ben

From: Dandamudi, Suman
Sent: Wednesday, August 29, 2012 10:51 AM
To: Zhao, Xiaobin
Subject: RE: Regarding Doxorubicin Liposomes

Hello Ben,

In our previous meeting, we came to the conclusion that the imported lots cannot be used to set the specifications for the test product. And to justify the firm's proposed specifications, they have to submit the in vitro drug release data for three new test batches that were manufactured controlled and tested under identical manufacturing conditions as that of the bio-lot.

You have suggested that instead of manufacturing three new lots, the firm can also submit the complete CMC information for three imported lots to the Division of Chemistry for the review. And if the Division of chemistry finds these imported lots to be equivalent to the bio-lot, then that data can be used to set the specifications.

Ben can you please confirm on this before I provide this option to the firm.

Thanks,
Suman

From: Zhao, Xiaobin
Sent: Monday, August 20, 2012 6:15 PM
To: Dandamudi, Suman
Cc: Nerurkar, Shriniwas G; Rajagopalan, Radhika; Lee, Sau
Subject: RE: Regarding Doxorubicin Liposomes

Hi, Suman,

As we discussed, JK93743A is equivalent to the biolot (JK93496). It has the same components, manufacturing process, in process controls and release tests as the JK93496 batch, except the fill

volume (25 mL for JK93743 vs. 10 mL for JK93496). The firm has provided Executed Batch Manufacturing record for this lot in the original submission. It was submitted as one of the three exhibit batches (JK93743, JKJ0142, JKJ0322) for the 2 mg/mL, 25 mL strength. It was manufactured in 12/ 2009. The batch size is (b) (4)

Please let us know if you have any questions.

Ben

From: Dandamudi, Suman
Sent: Monday, August 20, 2012 11:17 AM
To: Zhao, Xiaobin
Cc: Nerurkar, Shrinivas G
Subject: Regarding Doxorubicin Liposomes

Hello Ben,

Based on our earlier meeting on Sun's product (Doxorubicin Liposomes), the dissolution data of the imported lots should not be used to set the dissolution specifications for the test product. However as I mentioned in the meeting, in response to the FDA comment, in the amendment dated Aug 6, 2012 the firm submitted the comparative dissolution data on new lot.

	Test	Reference
Biolot	JK93496	0910338
New lot	JK93743A	1007992

So can you please confirm if this new test lot (JK93743A) is equivalent to the biolot (JK93496).

Thanks,
Suman

Internal Meeting Minutes
ANDA 203263 Sun's Doxorubicin Hydrochloride Liposome Injection
August 9, 2012

ANDA No.: 203263
Drug: Doxorubicin Hydrochloride Liposome Injection
Strength: 2 mg/mL (10 mL and 25 mL)
Organization: Sun Pharma Global FZE
Date: Thursday, August 9, 2012
Time: 11:00 AM to 12:00 PM

Attendees :

- Dale Conner, Pharm.D., Director, Division of Bioequivalence (DB) I
- Hoai Nguyen, Ph.D., Deputy Director, DB I
- Shriniwas Nerurkar, Ph.D., Team Leader, Team 6, DB I
- April Brady, Ph.D., Team Leader, Team 8, DB I
- Suman Dandamudi, PhD., Bioequivalence Reviewer, Team 8, DB I
- Teresa Ramson, Pharm.D., Supervisory PM, DB I
- Glen Smith, Ph.D., Chemistry Division Director, Division of Chemistry II
- Radhika Rajagopalan, Ph.D., Chemistry Team Leader, Team 21, Division of Chemistry II
- Xiaobin Zhao, Ph.D., Chemistry Reviewer, Team 21, Division of Chemistry II
- Frank Nice, Pharm.D., Regulatory Project Manager, Team 21, Division of Chemistry II

Background:

The purpose of the meeting was to discuss with the chemistry division the review of ANDA 203263, Sun's Doxorubicin Hydrochloride Liposomal Injection. In particular, the DBI would like to discuss with the Division of Chemistry II (DCII) about the most recent ANDA amendment in which the firm requested revision of the FDA-recommended drug release specifications based on the release data from imported lots. The DBI also would like to find out from the DCII the CMC review status and if there are currently any major concerns for Sun's product based on the CMC review.

For more information on ANDA 203263, please see the official archival system, DARRTS.

Discussion:

DBI sent a deficiency letter to Sun Pharma Global FZE on 7/25/2012. In this deficiency letter, we asked the firm to acknowledge and accept our recommended method and specifications. The firm responded by stating that the imported lots should be used to set specifications for the test product, and based on the FDA-recommended specifications,

many of the imported lots did not meet the specifications at S1 level. The DBI has already explained in the 7/25/2012 deficiency letter that the firm “*may request revision of the above FDA-recommended release specifications by submitting additional in vitro release data from fresh test lots, for which the validation has been reviewed and accepted by the Division of Chemistry, Office of Generic Drugs (OGD): The Manufacturing, Chemistry and Controls (CMC) records for these test lots should be submitted to the chemistry review division, and demonstrate that they are manufactured under the same approved manufacturing site, conditions, specifications, controls, and are pharmaceutically equivalent to the test lot used in the bioequivalence study.*” Although the imported batches were accepted by the Agency for importation, the firm has been informed in the past that the acceptance criteria for importation should not be considered the same as the criteria for the ANDA approval. Since currently, the DCII has not determined acceptable in-process and final product specifications for Sun’s product, the DBI asked the DCII what is its recommendation concerning the firm’s request for revised specifications in the latest amendment.

The firm did not submit complete information to the DCII to assess whether these import batches can be used to set specifications for the test product. The DCII agreed with the DBI that only the data for the biobatch should be used to set the specifications for the test product, as a standard approach.

The DCII also mentioned that Sun Pharma originally submitted three demonstration batches with extensive manufacturing data and information, and one of these demonstration batches was actually the biobatch. Suman added that drug release data for another new batch was submitted recently in the Bio amendment and the batch number is GK93743A. She will need to confirm with Xiaobin after the meeting if the DCII has evaluated this new lot and if it can be considered by the DCII as manufactured under the same conditions as the biobatch. If there are indeed other test lots with adequate manufacturing data showing that they were produced under the same conditions as the biobatch, the DBI will consider revising the specifications based on the additional release data from these batches as accepted by the DCII.

Drafted by T. Ramson 8/15/2012
Revised by H. Nguyen 8/16/2012
Comments

BIOEQUIVALENCE DEFICIENCIES

ANDA: 203263

APPLICANT: Sun Pharma Global FZE

DRUG PRODUCT: Doxorubicin Hydrochloride Injection,
Liposomal, 2 mg/mL (10 mL and 25 mL)

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledge on the cover sheet.

The following deficiencies have been identified:

1. Although the imported batches were accepted by the Agency for importation purpose, you have been informed in the past that the acceptance criteria for importation should not be considered the same as the criteria for the ANDA approval. Please note that the quality testing program for the imported lots is more limited that that used to support the approval of an application. Therefore, it is not acceptable to justify the proposed in vitro drug release specifications for the test product based on the in vitro drug release data of the imported lots.

Based on the additional in vitro drug release data submitted for the 25 mL vial of the test product, Lot No. JK93743A, in the amendment dated Aug 04, 2012, the release specifications previously recommended by the Agency (based on the release data of the test bio-lot, Lot No. - JK93496) were confirmed, and therefore, no change in the recommended specifications is justified.

However, per our consultation with the Division of Chemistry II (DCII), Office of Generic Drugs, you may consider submitting in vitro release data from **at least** 3 fresh imported lots (in place of any 3 other fresh test lots) to justify your proposed specifications at the time points of 1.5 hours, 3 hours and 5 hours, provided that the complete Manufacturing, Chemistry and Controls (CMC) data and records for these 3 imported lots (or any 3 other fresh test lots) are submitted, reviewed and accepted by the Division of Chemistry, Office of Generic Drugs. The CMC records for these test lots should demonstrate that they are manufactured and tested under

the same approved manufacturing site, conditions, specifications, controls, and are pharmaceutically equivalent to the test lot used in the bioequivalence study. Please contact the DCII for the information concerning additional testing necessary for these selected imported lots.

Alternatively, please acknowledge your acceptance of the following FDA-recommended method and specifications stated in the previous letter dated July 25, 2012.

The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b)(4) Bottle Rotating Apparatus (b)(4) using 100 mL cylinder glass bottles (b)(4) with cap with (b)(4) liner (b)(4). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr:	NMT	(b)(4) %
1.5 hr:	(b)(4)	%
3 hr:	(b)(4)	%
5 hr:	(b)(4)	%
7 hr:	NLT	(b)(4) %

2. The Office of Regulatory Affairs (ORA) conducted an audit of the in vitro bioequivalence study for the current ANDA. A Form 483 was issued following the inspection of the study site, Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India between June 11-13, 2012. The DBI has reviewed the inspection report by the ORA pertinent to the in vitro bioequivalence study and found the following

objectionable findings by the ORA could potentially compromise the integrity of the in vitro study results.

"The calibration of (b) (4) Laser Diffraction instrument was inadequate"

For particle size measurements, samples from each vial of test or reference product were poured into a cuvette and the particle size was determined using the defined parameters. Due to the (b) (4), the inspector suspects that the refractive index should have been (b) (4), and the viscosity should have been (b) (4) for the suspending medium. The parameter of (b) (4) for refractive index of liposome particles was not verified.

The D10, D50, D90, and span values in particle size distributions reported in the in vitro study were calculated from scattered light signals by the (b) (4) DLS software. (b) (4)

The particle size data for D10, D50, D90, and span in the in vitro bioequivalence (BE) study should be evaluated only after the refractive index, viscosity of the suspending medium and the refractive index of liposome particles can be confirmed.

Please address the above findings, and provide any appropriate supporting documentation in your response.

3. In our previous letter dated July 25, 2012, we informed you that *"if and when the RLD product becomes available, additional comparative characterization testing may be requested by the Agency, as appropriate, to obtain more complete information on the in vitro release of the test product, as compared with the reference product."* In the current amendment, you responded by noting that you have submitted in vitro release testing for both 10-mL and 25 mL vials of the test and RLD product, using your proposed method. Since your proposed in vitro release testing

method has been accepted by the DBI for your test product, the in vitro release testing data as submitted by you thus far are considered adequate for your application at this time, given the current shortage of the RLD product. However, in order to confirm the comparability of in vitro release characteristics between the test and the RLD products, under other relevant in vitro release testing conditions, for instance, the Agency may request additional in vitro comparative characterization testing in the future, if and when the RLD product becomes available.

4. Please provide appropriate documentation and evidence that the reference lot, Doxil Liposomal Injection, Lot No. JK93496 used in your BE study, was US-approved and marketed product. The documentation may include but may not be limited to purchase invoice, package labeling etc.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

ANDA: 203263

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
17862	8/4/2012	Other (REGULAR)	Study Amendment	1	1
17862	6/16/2011	Other (REGULAR)	OSI Inspection Review Report	1	1
17862	8/4/2012	Other (REGULAR)	Consult Response Review	1	1
				Total:	3

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

/s/

SUMAN DANDAMUDI
09/13/2012

SHRINIWAS G NERURKAR
09/13/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
09/18/2012

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203263		
Drug Product Name	Doxorubicin hydrochloride Liposome Injection		
Strength(s)	2 mg/mL, 10 mL and 25 mL		
Applicant Name	Sun Pharma Global FZE		
Address	Office # 43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U.A.E		
Applicant's Point of Contact	Robert Kurkiewicz Sun Pharmaceutical industries Ltd. (C/O Caraco) 1150 Elijah Mccoy Drive, Detroit, MI 48202		
Contact's Telephone Number	313-556-4105		
Contact's Fax Number	248-926-0231		
Original Submission Date(s)	June 16, 2011 March 07, 2012 (Telephone Amendment)		
Submission Date(s) of Amendment(s) Under Review	April 9, 2012 May 10, 2012 (Telephone Amendment) June 29, 2012 (Telephone Amendment) July 4, 2012 (Telephone Amendment)		
Reviewer	Suman Dandamudi Ph.D		
Study Number (s)	PKD_09_030	DOX/003/08	FDD-02/10-11/001
Study Type (s)	Fed	Pilot Fed	In-Vitro
Strength (s)	2 mg/mL	2 mg/mL	2 mg/mL
Clinical Site-1	MNJ Institute of Oncology & Regional Cancer Centre		
Clinical Site-1 Address	Red Hills, Hyderabad- 500 004, India		
Clinical Site-2	Kailash Cancer Hospital & Research Centre		
Clinical Site-2 Address	Goraj, Vadodara- 391760, India		
Clinical Site-3	Dr. G. Vishwanathan Speciality Hospitals		
Clinical Site-3 Address	#27, Babu road, Trichy, Tamilnadu- 620 008, India		
Clinical Site-4	Dr. Kamakshi Memorial Hospital		
Clinical Site-4 Address	No.1, Radial Road, Palikaranai, Chennai- 600 100, India		
Clinical Site-5	NRR Hospital		
Clinical Site-5 Address	Chikkasandra, Bangalore- 560090 (India)		
Analytical Site (fed study)	Sun Pharmaceutical Industries Ltd.,		
Analytical Site Address (fed study)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India		
In Vitro Liposome Size Distribution Testing Site	Sun Pharmaceutical Industries Ltd.,		

In Vitro Testing Site Address	Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India		
REVIEW RESULT	INADEQUATE		
OSI REPORT RESULT	INADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 8, 9, 10, 11	IN VITRO DRUG RELEASE*	2 MG/ML	INADEQUATE
1, 8	FED STUDY	2 MG/ML	ADEQUATE
1, 8	IN VITRO STUDY	2 MG/ML	ADEQUATE

*NOTE: There is no dissolution testing for this drug product, but there is in vitro drug release testing.

REVIEW OF AN AMENDMENT

1 EXECUTIVE SUMMARY

Sun Pharma has submitted ANDA 203263 for its test product, Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL. The submission references NDA 050718, Doxil[®] (Doxorubicin Hydrochloride) Liposomal Injection, 2 mg/mL from Ortho Biotech. The DBI had previously reviewed the original submission and issued a deficiency letter to the firm.

The firm in the current amendment, dated April 5, 2012, submitted its response to the deficiency comments made by the Division of Bioequivalence I (DBI) in the letter dated February 16, 2012 and the email correspondence dated March 12, 2012. The firm's responses to the deficiency comments related to in vitro liposome size distribution study and analytical part of fed bioequivalence study are acceptable. Thus the fed BE and in vitro liposome size distribution studies are now acceptable.

There is no USP in vitro drug release testing method for this test product. The external dissolution database for Doxorubicin Hydrochloride Liposome Injection recommends the firm's to develop a method to characterize in vitro release.

The firm conducted comparative drug release testing using its own proposed method [Bottle Rotating Apparatus in 90 mL of USP phosphate buffer pH 6.4 (b) (4), (b) (4), at a speed of 12 rpm at 52°C]. In addition, in the current amendment the firm also provided in vitro drug release data using FDA-recommended method [2.97ml of 100% FBS (Fetal Bovine Serum (pH 7.10)) containing 214 mg/ml Ammonium Chloride in water (pH 5.3), with pH adjusted to 6.5 +/- 0.1]. Doxorubicin is not stable in the release medium used in the FDA-recommended method. In addition, change in FBS lots resulted in variation in the in vitro drug release profile. Therefore, the

DBI accepts the firm's proposed in vitro drug release method. However since the Bottle Rotating Apparatus is not official compendial apparatus, the physical characteristics like size, shape and material composition has to be standardized to avoid any variability associated with the glass bottles. The firm should acknowledge the FDA recommended specification. The application is **incomplete** pending the firm's acknowledgement of the FDA-recommended in vitro drug release method and specification.

OSI Inspection:

Clinical site for Fed BE Study:

The fed BE study was conducted at multiple sites.

No	Name of Clinical Site	Group number/Site ID	Number of Patients	OSI Inspection Status
1	MNJ Institute of Oncology & Regional Cancer Center, Hyderabad	1/A	31	NAI
2	Kailash Cancer Hospital and research Center, Goraj, Vadidara	2/B	5	
3	Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu	3/D	11	Inspection to be requested
4	Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai	4/E	4	NAI
5	NRR Hospital, Bangalore	5/G	9	Pending new site inspection

MNJ Institute of Oncology & Regional Cancer Center, Hyderabad and Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai

The above clinical sites were inspected for ANDA 201742 (Routine) on 02/22/2012 and the outcome was NAI [DARRTS: MADA, SRIPAL R 02/22/2012 N/A 02/22/2012 CONSULT REV-BIOEQ-01(General Consult Review) Original-1 (Not Applicable) Archive].

NRR Hospital, Bangalore

A new site OSI inspection was requested for this clinical site on February 16, 2012 and is still pending the outcome of the request [DARRTS: RAMSON, TERESA V 02/16/2012 N/A 02/16/2012 FRM-CONSULT-09(DSI Bioequivalence Audit Request) Original-1 (Unknown) Archive]

Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu

In the review of the original submission¹ it was mistakenly stated that it's pending a new site OSI inspection for this clinical site. However there is no history of OSI inspection for this site.

¹ DARRTS: NERURKAR, SHRINIWAS G 02/16/2012 N/A 02/16/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive

Based on the number of enrolled patients at each site stated above, the DBI requests that OSI inspections be conducted at least three sites with the highest numbers of enrolled patients. As it was mistaken that the Dr. G. Vishwanathan Speciality Hospital was pending the outcome of the OSI inspection, therefore DBI requested OSI inspection for NRR Hospital, Bangalore India. The number of enrolled patients in Vishwanathan Hospital (11) is more than NRR Hospital (9). **Therefore a new-site OSI inspection will also be requested for this clinical site (Dr. G. Vishwanathan Speciality Hospitals).**

Analytical site for Fed BE Study:

In the review of the original submission¹, it was stated that “The analytical site was inspected for ANDA 090886 on 2/25/2011 and the outcome was NAI [The OSI report is not in the DARRTS till today (01/06/2012) but the information is on this site http://fdswv04385/bioprod/Bioequivalence_Project_Managment/Interface/ASPTest/DSI/dsisearch.asp”.

The above statement should be corrected as follows:

A for-cause Office of Scientific Investigations (OSI) inspection was requested for the analytical site of ANDA 090886 on May 20, 2010 and is still pending the outcome of the request [**DARRTS: POPAT, ALPITA 05/21/2010 N/A 05/21/2010 FRM-CONSULT-09(DSI Bioequivalence Audit Request) Original-1 Archive**].

In Vitro Testing Site:

For in vitro liposome size distribution testing, the site is Sun Pharmaceutical India Ltd. Halol-Baroda Highway, Halol-389350 Gujarat, India. This site has not been inspected for such testing. Therefore, a routine OSI inspection was requested for this site on February 16, 2012 and is still pending the outcome of the request [**DARRTS: RAMSON, TERESA V 02/16/2012 N/A 02/16/2012 FRM-CONSULT-09(DSI Bioequivalence Audit Request) Original-1 (Unknown) Archive**]

The application is **incomplete**.

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3 BACKGROUND

1. Sun has submitted ANDA 203263 for its product, Doxorubicin Hydrochloride Liposome injection, 2 mg/mL. The submission references NDA 050718, Doxil® (Doxorubicin Hydrochloride) Liposomal Injection, 2 mg/mL from Ortho Biotech.
2. The firm, in its original application, submitted fed (normal low fat breakfast) bioequivalence study comparing its, Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL to the Ortho Biotech’s Doxil® Injection, Liposomal, 2 mg/mL. The BE study was found incomplete [DARRTS: NERURKAR, SHRINIWAS G 02/16/2012 N/A 02/16/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive] due to deficiencies related to the analytical part of the BE study. The firm did not provide explanation for multiple summary tables of CC and QC data of free and encapsulated doxorubicin. The method validation lacked cross validation study for liposomal doxorubicin in presence of free doxorubicin.
3. In the original application, the firm also submitted the results of in vitro Liposome Size Distribution Study comparing three lots of the test product with 3 lots of reference product. However the study was found incomplete as the firm did not submit the electronic SAS transport files for in vitro liposome size distribution data.
4. The DBI did not conduct a “dissolution only” review on this ANDA. The in vitro drug release testing was evaluated in the “full ANDA” review. The firm conducted in vitro drug release testing using its own proposed method:

Medium: 90 mL of USP Phosphate buffer, pH 6.4 (b) (4)

Apparatus: Bottle Rotating Apparatus

Speed: 12 rpm

Temperature: 52°C

5. Since Bottle rotating apparatus is not a compendial apparatus, the firm’s proposed method was considered incomplete. The firm was asked to submit detailed information concerning the development, optimization and validation of their proposed in vitro drug release testing method for a full evaluation.
6. In addition, the firm was also requested to conduct additional testing using the following FDA recommended method (b) (4)

Six samples of 1 mL of the vial content should be transferred to six separate glass tubes containing the medium of 98% fetal bovine serum with 80 mM NH₄Cl at pH 6.0, to obtain the final sample volume of 100 mL. These glass tubes should be incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome should be determined at the following six time points: 0 hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs.

7. On February 21, 2012 the firm contacted the Project Manager Teresa Ramson of the division and inquired additional guidance from the division regarding the FDA-recommended in vitro drug release testing method given to the firm in the deficiency letter. Due to the expedited status of the ANDA based on the current drug shortage, the DBI responded to the firm's inquiry by email on Feb 24, 2012 providing clarification on the method recommendation and asked the firm to conduct *preliminary* in vitro release testing using only the test product since the firm indicated that there was only a limited supply of the RLD available for testing (i.e., about 10 vial units).
8. The *preliminary* data were submitted by email on March 7, 2012 and were reviewed by the DBI. Subsequently, based on the *preliminary* data submitted, on March 8, 2012 the DBI provided additional details and suggested modifications of the recommended method. The DBI asked the firm to conduct additional *preliminary* testing based on the provided method details and suggested modifications of the method.
9. On March 12, 2012, the firm submitted the second set of *preliminary* data following the DBI's advice. The DBI reviewed the second set of *preliminary* data, and recommended the firm conduct its official in vitro testing on both test and reference product using the following method:

“Sun's Medium 3 [2.97ml of 100% Fetal Bovine Serum (pH 7.10) containing 214 mg/ml Ammonium Chloride in water (pH 5.3), with pH adjusted to 6.5 +/- 0.1].
10. In the current amendment, the firm submitted to the deficiency comments made by the DBI. The firm provided the justification for the multiple CC and QC for free and encapsulated doxorubicin. The firm also provided cross validation study for liposomal doxorubicin in presence of free doxorubicin.
11. In addition, the firm also submitted the SAS transport file for in vitro liposome size distribution data. The firm also submitted the comparative in vitro drug release testing data using the FDA-recommended method.

4 SUBMISSION SUMMARY

4.1 Drug Product Information, PK/PD Information, and Relevant DB History

See the review of the original submission, DARRTS: NERURKAR, SHRINIWAS G 02/16/2012 N/A 02/16/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive.

The reviewer noted that the time to reach peak concentrations of liposomal doxorubicin for the test and reference products is 1.5 hrs and 2 hrs respectively. So the Tmax of liposomal doxorubicin occurred 1 hour after the completion of infusion (infusion time is 1 hr). Similar findings were also found in the literature. An article was published by Evangelos Briasoulis et. al. on interaction of pharmacokinetics of pegylated liposomal doxorubicin. In their study, Cmax was reached 2 hrs after the initiation of infusion. The article states that *“This finding is not easily explained, as with intravenous administration of conventional nonencapsulated drugs, the maximum concentration in serum is normally reached at the end of the infusion time, that is before the administration of the combination agent. This is in accordance with other studies that have also shown that the maximum concentration of liposomal encapsulated drugs in the blood comes late and is usually achieved after completion of the intravenous infusion”*².

² Evangelos Briasoulis, Vasilis Karavasilis et. Al. Interaction of pharmacokinetics of pegylated liposomal doxorubicin (Caelyx) on coadministration with paclitaxel or docetaxel. *Cancer Chemother Pharmacol* (2004) 53: 452-457

4.2 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	2

Date	Amendment/ Consult
April 9, 2012	Firm's response to the deficiency comments made by DBI on 2/16/2012, section 4.3
May 10, 2012	Telephone Amendment providing information on model and manufacturer of the Bottle Rotating Apparatus, Page No-30
May 21, 2012	Request for Science Team Consult, see section 4.5 and also 4.12 attachments
June 29, 2012	Telephone Amendment providing information on (b) (4) (based on Science Team comments), section 4.6
June 29, 2012	Telephone Amendment providing information on comparative in vitro testing (b) (4) (based on Science Team comments), section 4.7

4.3 Review of Current Amendment

Deficiency Comment #1: *You have provided multiple summary tables of calibration curve (CC) and quality control (QC) data for the analytes of free doxorubicin and liposome encapsulated doxorubicin. Please provide justification for submitting multiple summary tables, instead of one overall summary of the interday accuracy and precision of all the CC's and QC data from the study sample analyses.*

Firm's Response to Deficiency 1: Please note the following reasons for presenting multiple Calibration curve (CC) & Quality Control (QC):

Calibration Curve & Quality Control: The analysis of Free Doxorubicin & Liposome encapsulated doxorubicin, had been performed on two different make instruments {i.e. (b) (4) (using (b) (4) software) and (b) (4) (using (b) (4) Software)} and each instrument's application software provides the % Nominal concentration differently. The (b) (4) instruments uses (b) (4) software, which represents % nominal concentration as % difference, while the (b) (4) instrument uses (b) (4) software which represents % nominal concentration as % Accuracy. Therefore the Calibration curve tables and quality control tables are represented differently considering the mode of representation of % Nominal concentrations, as % Difference (% Diff) and % Accuracy.

Rejected Calibration Curve & Quality Control: Rejected analytical runs are represented under different table identity as these are not being used in global calculation and these are provided in report for information only.

Incurred sample analysis (CC & QC): Incurred sample analysis is not being considered as a part of study sample analysis as these are evaluated for method reproducibility. So, the calibration curve (CC), Quality control samples and incurred sample analysis have been presented separately.

Free doxorubicin: The Quality Control samples for estimation of free doxorubicin were processed along with study samples at the clinical site in batches to assess sample processing accuracy. So quality control samples were prepared in bulk and transferred to the clinical site for onsite processing. Different stock solution were prepared for the bulk spiking of the calibration Curve and Quality Control as the studies were performed for longer duration and at various clinical sites which leads to have different theoretical concentration of Quality Control samples. So with respect to theoretical concentration, separate QC table were provided for free doxorubicin analyte.

Reviewer's Comments on Firm's Response #1:

Free Doxorubicin: In accordance with the clinical study protocol (Protocol No: Dox_21_1476_09, section 10. Analytical procedures), the firm processed the QC samples along with the study samples at the clinical site.

The protocol states that *“For free doxorubicin, since the lysing of the liposomes is observed under freezing conditions, sample processing of free doxorubicin shall be done within 12 hours of plasma separation at each sampling time point. Also for the estimation of encapsulated doxorubicin the eluent at each stage from sample loading eluent to all washing eluent in the involved processing steps for estimation of free doxorubicin will be collected. A group of samples/ single sample in each period of subject shall be processed with predefined number of quality control samples. Hence there shall be multiple analytical batches in each period of a subject and analytical batch acceptance criteria shall be applied for each analytical batch. Samples shall be processed in triplicate as per analytical test procedure by using solid phase extraction cartridges till washing step. After washing step, these solid phase cartridges (having 'Free' doxorubicin retained in the cartridge bed) are stored at 2 - 8°C till analysis. Care shall be taken to avoid freezing. At the time of analysis, analyte shall be eluted from the cartridge as per procedure mentioned in the Analytical Test Procedure. All analytical batches (comprising all samples of a subject in both periods) of a subject shall be analyzed against freshly prepared calibration curve as far as possible”*.

Based on the protocol, group of samples in each period were processed along with the predefined number of quality control samples. Each period is divided into 9 batches:

Batch No	Sampling Times
B1	0.0, 0.25, 0.5, 0.75, 1, 1.083 hrs
B2	1.25, 1.5, 2, 4 hrs
B3	6, 9 hrs
B4	25 hrs
B5	49 hrs
B6	97 hrs
B7	169 hrs
B8	241 hrs
B9	337 hrs

Therefore each batch contains five levels of QC samples in duplicate.

The quality control samples were prepared in bulk and transferred to the clinical site to be processed on site along with the study samples. The firm used working solutions (prepared from the stock and intermediate) for the preparation of QC samples. 5% of working QC solution was spiked in pooled blank K3 EDTA plasma for bulk spiking. Bulk spiking of QC samples were done on different dates which lead to different theoretical concentrations of QC samples.

ID	Preparation Dates: May 20, June 22, Aug 19, Oct 7, Nov 13 2010	Preparation Date: Oct 3 2010
	Final Conc. (ng/mL)	Final Conc. (ng/mL)
QC Low-A	15.14	15.14
QC Low-B	45.12	45.12
QC Med-A	297.81	297.81
QC Med-B	595.61	595.61
QC High	1191.23	1191.23

The QC samples spiked on Oct 3, 2010 were processed and analyzed along with patients 8, 10, 12 and 13 study samples. Since this set of QC theoretical concentrations were different than that were prepared on the other dates, the firm submitted a separate QC data for free doxorubicin for the above 4 patient's plasma samples.

In addition, the firm analyzed the plasma samples for the analyte doxorubicin using two different instruments. Therefore the firm provided a separate summary table of CC and QC data for each instrument

Instrument	Brand /Model	Supplier I Manufacturer
(b) (4)		

Instrument	Brand /Model	Supplier I Manufacturer
(b) (4)		

	(b) (4)	
PKD/227	PKD/725	(b) (4) (PKD/314)
Patient Nos: 2, 3, 8, 10, 12, 13, 16, 17, 18, 20, 22, 23, 26, 27, 28, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 42, 43, 47, 48, 51, 57, 60	29, 30, 52, 53, 54, 58, 61	40, 45

Free Doxorubicin										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	5.06	9.93	19.85	49.63	124.09	248.17	496.34	744.52	992.69	1464.22
Inter day Precision (%CV)	3.3	6.0	4.8	5.7	4.2	3.4	3.5	3.0	3.0	4.9
Inter day Accuracy (%Actual)	103.2	97.4	95.0	96.9	97.0	98.1	101.9	103.9	103.0	104.0
Linearity	0.9956 to 0.9992 (r Value)									
Linearity Range (ng/mL)	5.06 to 1464.22									
Sensitivity/LOQ (ng/mL)	5.06									

Parameter	Quality Control Samples (PKD/227 and PKD/725)				
Concentration (ng/mL)	15.14	45.42	297.81	595.61	1191.23
Inter day Precision (%CV)	8.0	7.3	7.2	6.9	6.5
Inter day Accuracy (%Actual)	-0.1	0.8	1.7	0.8	0.6

Parameter	Quality Control Samples (PKD/314)				
Concentration (ng/mL)	15.14	45.42	297.81	595.61	1191.23
Inter day Precision (%CV)	7.4	8.0	5.6	6.3	9.4
Inter day Accuracy (%Actual)	93.6	94.6	97.5	108.3	109.0
Parameter	Quality Control Samples (Patient No: 8, 10, 12, 13)				
Concentration (ng/mL)	15.03	45.10	300.67	601.33	1202.67
Inter day Precision (%CV)	6.4	5.4	5.9	5.7	7.8
Inter day Accuracy (%Actual)	1.3	0.2	2.7	3.7	2.3

With the samples analyzed by either of the two instruments, the accuracy and precision of free doxorubicin at each QC level is within 15% of the nominal in human plasma containing K3 EDTA.

Liposomal Doxorubicin: In the original submission, the firm submitted multiple summary tables of calibration curve and QC data for the liposomal doxorubicin. So the firm was asked to provide the justification for submitting multiple summary tables instead of one overall summary of the interday accuracy and precision of all the CC's and QC data during the study sample analyses. In the current amendment the firm justified by stating that the analysis of liposome encapsulated doxorubicin, had been performed on two different make instruments {i.e. (b) (4) (using (b) (4) software) and (b) (4) (using (b) (4) Software)} and each instrument's application software provides the % Nominal concentration differently. The reviewer verified the analytical data and as stated, the firm analyzed the plasma samples for the analyte liposomal doxorubicin using two different instruments. Therefore the firm provided a separate summary table of CC and QC data for each instrument.

Instrument conditions:

Instrument	Brand /Model	Supplier I Manufacturer
(b) (4)		

Instrument	Brand /Model	Supplier I Manufacturer
(b) (4)		

(b) (4)	(b) (4)
Patient Nos: 2, 3, 8, 10, 12, 13, 16, 17, 18, 20, 22, 23, 31, 32, 33, 36, 37	Patient Nos: 26, 27, 28, 29, 30, 34, 35, 38, 39, 40, 41, 42, 43, 45, 47, 48, 51, 52, 53, 54, 57, 58, 60, 61,

Liposomal Doxorubicin (Analyzed by ^{(b) (4)} Instrument)								
Parameter	Standard Curve Samples							
Concentration (µg/mL)	1.00	1.99	4.16	13.76	33.50	45.81	56.85	70.25
Inter day Precision (%CV)	3.0	5.6	5.4	4.8	5.9	3.8	4.5	5.3
Inter day Accuracy (%Actual)	1.1	-2.0	-0.6	1.1	0.5	-0.9	-1.7	2.5
Linearity	0.9943 to 0.9998 (r Value)							
Linearity Range (µg/mL)	1.00 to 70.25 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Parameter	Quality Control Samples				
Concentration (µg/mL)	2.99	8.96	14.67	34.40	58.21
Inter day Precision (%CV)	7.0	5.7	6.0	6.1	6.2
Inter day Accuracy (%Actual)	0.6	2.7	1.5	-0.3	2.6

Liposomal Doxorubicin (Analyzed by ^{(b) (4)} Instrument)								
Parameter	Standard Curve Samples							
Concentration (µg/mL)	1.00	1.99	4.16	13.76	33.50	45.81	56.85	70.25
Inter day Precision (%CV)	2.3	5.3	4.7	4.8	4.8	4.0	5.6	4.2
Inter day Accuracy (%Actual)	99.3	101.7	99.3	101.0	99.6	100.6	100.2	98.4
Linearity	0.9943 to 0.9998 (r Value)							
Linearity Range (µg/mL)	1.00 to 70.25 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Parameter	Quality Control Samples				
Concentration (ng/mL)	2.99	8.96	14.67	34.40	58.21
Inter day Precision (%CV)	7.9	7.1	4.6	9.3	12.2
Inter day Accuracy (%Actual)	100.6	103.4	102.2	102.3	103.0

With the samples analyzed by either of the two instruments, the accuracy and precision of free doxorubicin at each QC level is within 15% of the nominal in human plasma containing K3 EDTA.

The firm's response to the 1st deficiency is acceptable.

Deficiency Comment #2: Please submit in vitro liposome size distribution testing data in electronic SAS Transport files using the following table format for verification analysis by the DBI.

PRODUCT	LOT	VIAL	D10	D50	D90	SPAN
TEST	1234	1				
		2				
		3				
		4				
		5				
		6				
		7				
		8				
		9				
		10				

Firm's Response to Deficiency #2: Please note that electronic SAS Transport files for in vitro liposome size distribution testing data has been provided herewith in section 5.3.1.2.

Reviewer's Comments on Firm's Response #2: Liposome size distribution by dynamic light scattering was performed on 3 lots of 10 vials each for the test and reference products. In the original submission, the firm did not submit the SAS Transport files. Therefore the reviewer did not analyze the study samples. In the current amendment, the firm submitted the SAS files as requested by the DBI. The test product PASSED the PBE statistical criteria for both D50 and span.

D ₅₀ Summary									
	Mean Distance		Variability (%CV)					Mean Ratio (T/R)	
			Within Lot (n=10)			Between Lot (n=3)	Total (n=30)	Arithm (n=30)	Geo (n=30)
	Arithm	Geo	Lot 1	Lot 2	Lot 3				
Test	(b) (4)								
Ref	(b) (4)								

SPAN Summary									
	Mean Distance		Variability (%CV)					Mean Ratio (T/R)	
			Within Lot (n=10)			Between Lot (n=3)	Total (n=30)	Arithm (n=30)	Geo (n=30)
	Arithm	Geo	Lot 1	Lot 2	Lot 3				
Test	(b) (4)								
Ref	(b) (4)								

The firm's response to the 2nd deficiency is acceptable.

Deficiency Comment #3: *It did not appear that you conducted cross-validation study for confirmation of the extraction method to estimate only liposomal doxorubicin in the presence of free doxorubicin. Please provide the cross-validation data.*

Firm's Response to Deficiency #3: During the method validation of the free doxorubicin, we have designed and performed an experiment to evaluate the impact of the extraction method on the estimation of free doxorubicin in presence of liposomal doxorubicin in which free is estimated accurately. (Refer ANDA section 5.3.1.4, partial method validation: PMV/F-DXR/141, Section –X, Page No. 85 & Table No. 4, page No. 95).

The full method validation of Liposome Encapsulated Doxorubicin was performed using Liposomal formulation injection as working/ reference standard for the preparation of calibration curve and quality control sample to mimicking the same condition that encountered during the study.

Method applied for cartridge wash to get eluent for estimation of liposomal doxorubicin and free doxorubicin is same. Above two different evaluation confirms accurate estimation

of free and liposomal measurement from study sample (Refer ANDA section 5.3.1.4, method validation: MV_L-DXR_137A, Section-II, Page No. 457 & Section VII, page No. 462).

Following are some evaluations to support above conclusion.

- a. Sample is loaded on cartridge, unretained eluent is used for analysis of liposomal doxorubicin and retained is analyzed as free doxorubicin.
- b. As free is retained accurately, unretained eluent has liposomal doxorubicin only. It means only liposomal is collected as eluent and used for analysis.
- c. LLOQ and ULOQ of free doxorubicin is 5.00 ng/ml to 1500 ng/ml. Mean Cmax is ~280 ng/ml. Cmax is 30% of LLOQ of Liposomal doxorubicin.
- d. LLOQ and ULOQ of Liposomal doxorubicin is 1.00µg/ml (1000 ng/ml) to 70 µg/ml (70000 ng/mL). Mean Cmax observed is ~34 µg/ml = 34000 ng/ml.
- e. If any free doxorubicin, contributes in measurement of liposomal doxorubicin, it is any way insignificant as Cmax of free doxorubicin is 1/3 of LLOQ of Liposomal doxorubicin.
- f. If any Liposomal doxorubicin contributes (retained on cartridge or break and release as a free) in measurement of free doxorubicin, it would be very high as ULOQ (1500 ng/ml) of free Doxorubicin is near to LLOQ of liposomal Doxorubicin (1000 ng/ml).

However, estimation of liposomal doxorubicin and free doxorubicin was not evaluated from same sample during validation. We have additionally performed a cross validation experiment for confirmation of the extraction method to estimate only liposomal doxorubicin in the presence of free doxorubicin and vice versa. Partial method validation report for this study has been provided herewith in section 5.3.1.4.

Reviewer's Comments on Firm's Response #3: In the original submission, the firm conducted partial validation (Report No PMV/F-DXR/141) for the confirmation of extraction method to estimate only free doxorubicin in presence of liposome doxorubicin. Liposomal doxorubicin solution containing free doxorubicin was used for preparation of working solution of free doxorubicin and spiked in Human EDTA K3 plasma at LQC and HQC levels. All samples were analyzed with calibration standard and 2 set of batch QC's. The mean % difference for LQC is 7.6% and for HQC is 2.9%. Therefore, the data indicated that the extraction procedure is appropriate for free doxorubicin in presence of liposomal doxorubicin.

In this amendment, the firm conducted cross validation study for confirmation of the extraction method to estimate only liposomal doxorubicin in the presence of free doxorubicin. Partial method validation was performed as required for accurate estimation of both liposomal and free Doxorubicin from common sample. The common plasma sample was prepared using liposomal injection (containing some percent of free doxorubicin along with the Liposomal doxorubicin) and the analysis was performed using respective analytical test procedures.

Six replicates of low common and high common QC samples were spiked in human K3 EDTA plasma. These samples were processed and analyzed in a single run along with calibration standards, two sets of QCs. Cross estimation of liposomal and free doxorubicin was done in the samples prepared using the Liposomal Doxorubicin Injection.

Cross Estimation of Liposomal & Free Doxorubicin Content

Liposomal Doxorubicin

	Low Common QC (µg/mL)		High Common QC (µg/mL)	
	5.61		37.31	
Range	(b) (4)			
	Measured Conc.	% Difference	Measured Conc.	% Difference
	(b) (4)			
	(b) (4)			
	(b) (4)			
	(b) (4)			
	(b) (4)			
N	6		6	
Mean	5.467		34.195	
SD(+)	0.2639		2.0813	
(%) CV	4.8		6.1	
% Difference	-2.6		-8.3	

Free Doxorubicin

	Low Common QC (ng/mL)		High Common QC (ng/mL)	
	45.23		300.91	
Range	(b) (4)			
	Measured Conc.	% Difference	Measured Conc.	% Difference
	(b) (4)			
	(b) (4)			
	(b) (4)			
	(b) (4)			
	(b) (4)			
N	6		6	
Mean	43.947		295.697	
SD(+)	1.4015		10.8453	
(%) CV	3.2		3.7	
% Difference	-2.8		-1.7	

Based on the above results, % content of free doxorubicin and % liposomal doxorubicin in common samples (mimicking the samples as in vivo study samples) are accurate with respect to the available nominal concentration. Therefore, the extraction method used for

study sample analysis confirms the estimation of only liposomal doxorubicin in presence of free doxorubicin.

The firm's response to the 3rd deficiency is acceptable.

Deficiency Comment #4: *You have submitted in vitro drug release testing data using your proposed testing method with bottle rotating apparatus. However, currently the DBI does not encourage the use of non-compendial apparatus in in vitro drug release testing. Since the bottle rotating apparatus is not considered a compendial apparatus, your proposed method is considered incomplete at this time. Please submit all detailed information concerning the development, optimization and validation of your proposed test method for a full evaluation.*

Firm's Response to Deficiency #4: Please note that detailed information for the development and optimization of Sun's proposed testing method with bottle rotating apparatus has been provided herewith in section 5.3.1.3.

Please note that validation of this in-vitro drug release testing method has already been provided in ANDA section 3.2.P.5.3, copy of this report has also been provided herewith in section 5.3.1.3 for your ready reference.

Reviewer's Comments on Firm's Response #4: In the current amendment, the firm submitted development of in vitro drug release testing method report.

- Based on the literature search, the firm first conducted the in vitro drug release testing using (b) (4) [redacted], which may not be sufficient to evaluate the release profile.
- Further the testing was carried out without (b) (4) [redacted] with the other parameters being same as the above method. The results indicated faster release from the initial time points.
- Based on the in vitro drug release method reported in the summary of the approval of Doxil®, the firm further conducted the in vitro testing using (b) (4) [redacted]. However with this method, the release of doxorubicin was very fast i.e. (b) (4) % in 0.5 hr.

- Therefore the firm decided to do testing in Bottle Rotating apparatus instead of USP II apparatus and using the same medium and temperature as the above method but reducing the speed to (b) (4) rpm. The firm stated that they choose Bottle Rotating Apparatus as it is compact system and prevents the loss of medium and provides uniform dynamic conditions. Even under these conditions, the fast release doxorubicin from liposomes was observed i.e. (b) (4) % in 0.5 hrs.
- (b) (4)
- Attempts were made to establish a slower release of drug from the liposomes by modifying the above method. The change of experimental temperature from 52°C ±0.5°C to (b) (4) °C ±0.5° showed slower drug release rate over a period of (b) (4) hrs.
- Further study was carried out using the same experimental conditions with a change of medium, i.e., phosphate buffer pH 6.4 was tried instead of (b) (4) (b) (4) where a satisfactory rate and extent of release (more than 80%) of Label claim was achieved over a period of (b) (4) hrs. The firm preferred USP phosphate buffer pH 6.4 as it is a compendium medium and also similar to the physiological condition.

Dissolution Conditions:

Apparatus: Bottle rotating apparatus
Medium: Phosphate buffer, pH 6.4
Volume: 90 mL
RPM: (b) (4)
Temperature: ± 0.5 °C
Time Point: 0.5, (b) (4) hours.

The % drug release is calculated by subtracting the residual assay (encapsulated drug) at every time point from the assay value of same liposomal batch.

% Release of Doxorubicin from liposomes by different methods

A	B	C	D
(b) (4)			

Based on the above experiments the firm concluded that the optimal conditions for in vitro drug release testing will be bottle rotating apparatus using phosphate buffer, pH 6.4 as medium, rotating at a speed of (b) (4) rpm at (b) (4) °C ± 0.5°C.

Sample Preparation for the concluded method: (b) (4)

- Further the firm developed an accelerated (fast) in vitro release method for Doxorubicin Liposome Injection (increase the rotating speed to 12 rpm and temperature to 52 °C).

Dissolution Conditions:

Apparatus: Bottle rotating apparatus
Medium: Phosphate buffer, pH 6.4
Volume: 90 mL
RPM: 12
Temperature: 52 ± 0.5 °C
Time Point: 0.5, 1.5, 3, 5 and 7 hours

The % drug release is calculated by subtracting the residual assay (encapsulated drug) at every time point from the assay value of same liposomal batch.

In Vitro release data at ^(b)₍₄₎ and 12 rpm

Time (hr)	^(b) ₍₄₎ rpm	± S.D	12 rpm	± S.D
0.5	^(b) ₍₄₎	^(b) ₍₄₎	^(b) ₍₄₎	3.23
1.5	^(b) ₍₄₎	^(b) ₍₄₎	^(b) ₍₄₎	2.66
3	^(b) ₍₄₎	^(b) ₍₄₎	^(b) ₍₄₎	3.39
5	^(b) ₍₄₎	^(b) ₍₄₎	^(b) ₍₄₎	3.37
7	^(b) ₍₄₎	^(b) ₍₄₎	^(b) ₍₄₎	1.94



^(b)₍₄₎

The batches manufactured with (b) (4) (b) (4) were compared with the control batch. F2 values were less than 50, which indicate that the method used for in vitro release over 7 hrs is discriminatory. The results are given in below table:

Change type	Batch No	Standard condition	Change during batch preparation	F2 (similarity) value Limit 50-100
(b) (4)	10710477PF031	(b) (4)	(b) (4)	9.18
	10710477PF073			45.3
	10710477PF087			15.53
	10710477PF088			23.16

Based upon the above data, the firm concluded that the accelerated method by using bottle rotating apparatus seems to be suitable for in vitro release test for the routine quality control testing with more than two time points.

Comparative in vitro drug release testing results using the firm's proposed method

Batch # JK93496 (Sun's product)

Time (Hr)	6						6						Mean	SD	Min	Max	% CV
	T1-1	T1-2	T1-3	T1-4	T1-5	T1-6	T1-7	T1-8	T1-9	T1-10	T1-11	T1-12					
0.5	(b) (4)												8.00	1.25	(b) (4)		15.6267
1.5													20.07	2.91			14.48378
3													46.34	4.06			8.766584
5													69.67	3.39			4.863077
7													87.27	2.97			3.399853

Batch # 0910338 (RLD)

Time (Hr)	6						6						Mean	SD	Min	Max	% CV
	R1-1	R1-2	R1-3	R1-4	R1-5	R1-6	R1-7	R1-8	R1-9	R1-10	R1-11	R1-12					
0.5	(b) (4)												9.97	1.35	(b) (4)		13.49564
1.5													25.54	3.32			12.99904
3													52.56	3.65			6.944316
5													76.25	3.20			4.190402
7													94.67	3.02			3.192678

Each lot of test and RLD are tested on two different dates with 6 tubes of test and 6 tubes of reference on each date

- As the “Bottle Rotating Apparatus” is not an official compendial apparatus, in a telephone amendment, the DBI requested the firm to provide adequate information on the calibration of the instrument³. The review of the telephone amendment is as follows:

Review of Telephone Amendment

On May 10, 2012, the firm submitted its responses to the deficiency comments made by DBI through telephone request on May 3, 2012.

Deficiency: Please submit the model and manufacturer of the apparatus. Please also submit the standard operating procedure and detailed information concerning the calibration of the instrument.

Firm’s Response: Please note that as requested by the FDA model and manufacturer details for the Bottle Rotating Apparatus are provided below.

Manufacturer: (b) (4)
Model: Rotating Bottle Apparatus (b) (4)
(b) (4)

As per the information provided by the manufacturer the bottle rotating apparatus complies with US National Formulary XIV (Pg. No.: 985-986, General test "Timed - Release Tablets and Capsule-In Vitro Test Procedure").

Please also note that the standard operating procedure “QCI-157/02, Title: Operation and Calibration Procedure of Bottle Rotating Apparatus” containing detailed information regarding the calibration and operation of the apparatus has been provided herewith in Annexure 1. Operation manual from the manufacturer of the bottle rotating apparatus has also been provided herewith in Annexure 2.

Deficiency: Please provide the physical descriptions including size, shape, material composition and manufacturer of the 100 mL glass bottles used for in vitro drug release testing.

Firm’s Response: As per the information provided by the manufacturer the physical description, size, shape, material composition and manufacturer of the 100 mL glass bottles used for in vitro drug release testing is summarized below.

³ DARRTS: RAMSON, TERESA V 05/03/2012 VERBAL 05/04/2012 COR-ANDAIR-01(Advice/Information Request) Original-1 (Unknown) Archive

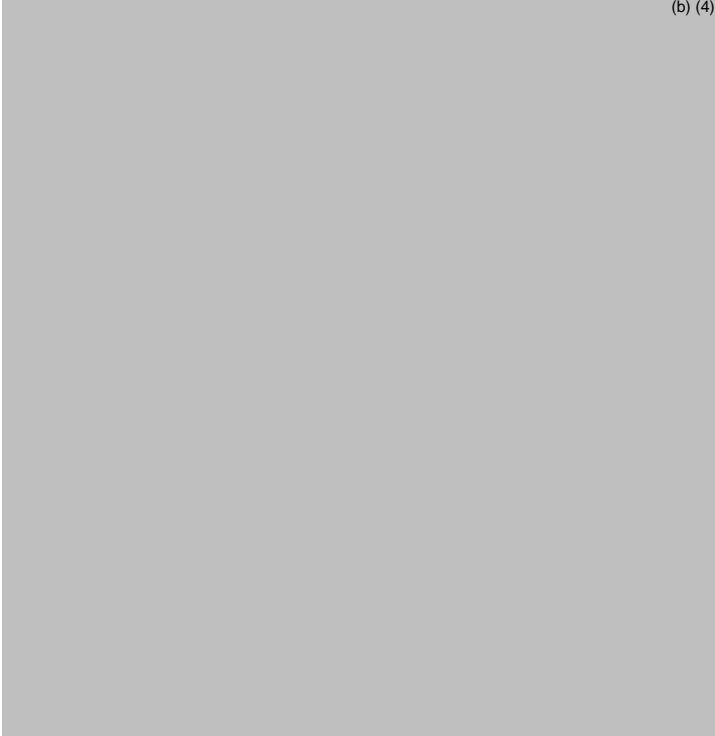
Description	Cylindrical transparent glass bottles with Cap with (b) (4) liner
Size	100 ml glass bottle with, -opening: 26.13 mm -total height: 142.1 mm -made of glass, 2 mm thick -bottom diameter: 35 mm
Shape	Cylindrical glass bottle
Material composition	Bottle is made of clear glass and caps include liners composed of (b) (4). Bottles and caps conform to US National Formulary XIV specifications
Manufacturer	(b) (4)

Deficiency: Please provide photographs of your apparatus and bottles

Firm's Response: As requested by the FDA photographs of the bottle rotating apparatus and cylindrical glass bottles are provided.



(b) (4)



Reviewer's Comments:

- The firm provided the SOP QCI-157/02 for Calibration Procedure, Title: Operation and Calibration Procedure of Bottle Rotating Apparatus. As per the SOP, the calibration should be performed for water bath temperature and speed of rotation for every 3 months.

Calibration procedure

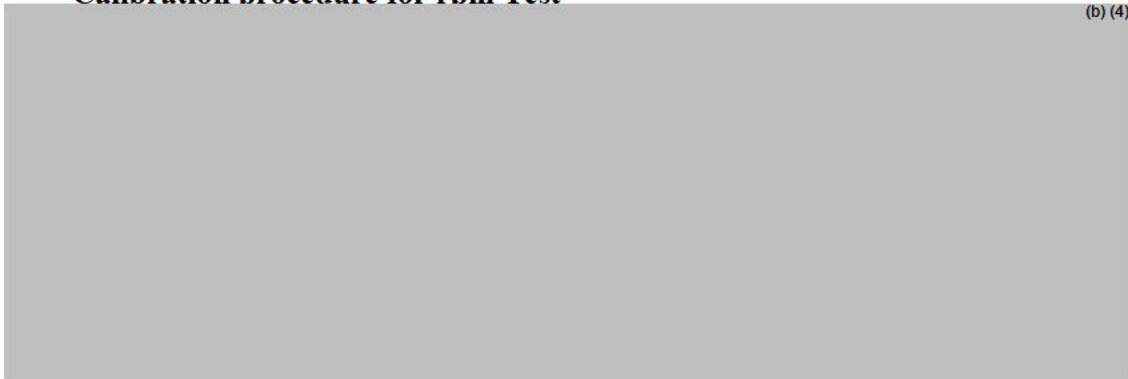
Calibration procedure for Temperature test:

(b) (4)



Calibration procedure for rpm Test

(b) (4)



Observation Table:

Temperature Test

S. No	Set Temperature	Observed temperature after stabilized	Limits
		Display of temperature indicator	
1	(b) (4)		(b) (4)
2			
3			

RPM Test

S. No	Set RPM	Observed rpm after stabilized	Limits
1	(b) (4)		(b) (4)
2			
3			

- The firm provided the manufacturer and model number of Bottle Rotating Apparatus. The firm also provided the physical dimensions of the 100 mL Glass Bottles used for in vitro drug release testing. Therefore the in vitro drug release testing of any future batches of the test product should be performed using the following apparatus:

(b) (4) **Bottle Rotating Apparatus** (b) (4)
(b) (4) **using 100 mL cylinder glass bottles** (b) (4)
with cap with (b) (4) **liner** (b) (4)

Analytical Method Validation for In Vitro Release Method:

Test preparation for IN VITRO release:

(b) (4)

The % drug release is calculated by subtracting the residual assay (encapsulated drug) at every time point from the assay value of same liposomal batch.

Instrumental Conditions:

Use a suitable High Performance Liquid Chromatograph (HPLC) with the following conditions.

Column:

(b) (4)

Flow rate:

Auto sampler Temperature:

Detector:

UV at 254 nm

Run time:

(b) (4)

Injection volume:

Dissolution Conditions:

Apparatus: Bottle rotating apparatus

Medium: Phosphate buffer, pH 6.4

Volume: 90 mL

RPM: 12

Temperature: 52 ± 0.5 °C

Time Point: 0.5, 1.5, 3, 5 and 7 hours

Calculation:

Calculate % release of Doxorubicin HCl at each time point using below mentioned formula,

(b) (4)

Over all comments on Method Validation: Linearity of doxorubicin is established in the range (b) (4) ppm. Based on the results of method validation, it can be concluded that method is precise, accurate, specific, linear and stability indicating. The method precision, reproducibility and robustness are established at all the sampling time points except at 30 minutes. At the initial time point (30 min), the variation of percent drug release is very high and thus the firm was unable to demonstrate the robustness and reproducibility of the method at this time point.

The firm's response to 4th deficiency is acceptable.

Deficiency Comment #5: In addition, please conduct the following in vitro drug release testing. Please note that this recommended method does not employ any dissolution apparatus.

The comparative testing should be conducted on the test and reference product, using one dosage unit (vial) (10 mL of 2 mg/mL) per replicate and six samples taken per unit for six different time points: Six samples of 1 mL of the vial content should be transferred to six separate glass tubes containing the medium of 98% fetal bovine serum with 80 mM NH₄Cl at pH 6.0, to obtain the final sample volume of 100 mL. The resulting drug concentration should be 20 microgram/mL of liposomal doxorubicin. These glass tubes should be incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome should be determined at the following six time points: 0 hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs. The testing should be replicated for 12 dosage vials per each test and the reference drug product.

The individual percent doxorubicin release data from each vial at each time point should be submitted, as well as the mean data from 12 vials at each time point for each product (% mean and % CV) over the period of 0 to 4 hours for the test and RLD from 12 dosage units.

Please submit a complete validation data and report for the above recommended test method.

Firm's Response to Deficiency #5: Please note that with regards to conducting in-vitro release testing as per above method, Sun had communicated with FDA on 21 February 12.

In mail dated 24 February FDA had suggested preliminary drug release studies described below on test product using the 4 different conditions:

- (i) With Option 1 medium (as described by Sun), at pH.7;
- (ii) With Option 1 medium (as described by Sun), but pH adjusted to pH 6.0 using hydrochloric acid;
- (iii) With Option 2 medium (as described by Sun), at pH 7.0; and
- (iv) With Option 2 medium (as described by Sun), but pH adjusted to pH 6.0 using hydrochloric acid.

For each of these 4 conditions, please use 6 units of the Test product only, and submit the preliminary testing results to the Division of Bioequivalence I (DBI) for evaluation. Based on the preliminary data submitted, if possible, the DBI will recommend the final drug release testing conditions, for which the official testing should be done using the available 10 units of the RLD and 12 units of the Test product.

On 7 March 12, Sun had provided data of this preliminary studies. On 8th March FDA had given following comments for this data:

Based on the preliminary results submitted by the firm, we have revised the previous recommended method as follows:

1. The sample size should be reduced from 100 mL to 3 mL, i.e., 30 microliter of the drug product should be added to 2.97 mL of the FBS containing 80 mM of ammonium chloride at pH 6.0 (equivalent to Sun's Medium 4).
2. Adjustment to pH 6.0 should be done during the reagent preparation and again after adding the drug product.
3. For each time point, a separate tube of sample should be used.
4. There should be no agitation during sample incubation. However, at the end of incubation, the sample tubes should be mixed well prior to removing each aliquot for further analysis.
5. At the end of incubation, the sample tubes should be placed on ice for at least 5 minutes before sample analysis.
6. The total free doxorubicin per time point sample should be measured at the end of each incubation period by heating the respective sample tube in waterbath at 72C for 30 minutes.
7. If this method is eventually determined by the Agency to be appropriate for Sun's product, more control of the FBS lot variability is necessary as the test product may fail established specifications due to such variability. Exploring different manufacturers of FBS is encouraged.
8. As mentioned in the ANDA deficiency letter, the firm should submit full analytical and dissolution method validation reports for its originally proposed in vitro release method (including individual data for all samples tested). Sun's method will still be considered and evaluated in comparison with the FDA-recommended method.
9. With the above modifications, if the drug release for the test product is still inadequate (with incomplete release at around 4-5 hours) at exactly pH 6.0, then pH

adjustment step may be omitted for achieving approximately (b) (4) % drug release within 4-5 hours (or equivalent to Medium 3). However, if it is found that, during this round of preliminary testing with procedure modifications, without pH adjustment to 6.0, the drug release is much greater than (b) (4) % in 4-5 hours, slightly lowering the pH may be necessary.

We recommend the firm conduct another round of preliminary testing as suggested above, using 6 units of the Test product only, and submit the second sets of preliminary results to the Division of Bioequivalence I (DBI) for evaluation. The DBI does not expect to recommend any additional significant modifications to the testing following this second round of testing, provided that complete release (about (b) (4) % within 4-5 hours) can be achieved based on the above recommended conditions.

On 12 March 12, Sun had provided data of above mentioned studies. On 12th March FDA had given following comments for this second set of preliminary data:

1. Based on the second set of preliminary data provided to us today, March 12, 2012, we recommend that the firm conduct the in vitro drug release testing for its ANDA using Sun's Medium 3 with pH adjusted to 6.5 +/- 0.1. The testing should be done using other testing conditions described in the firm's latest correspondence (i.e., in the attachment of its March 12, 2012 email), including the same sampling times. The firm should use 12 dosage units of the test product, and the available 10 dosage units of the RLD of the testing.
2. Along the individual and mean release results, the firm should provide a detailed analytical method validation report, and a detailed dissolution testing report for the recommended method.
3. As requested previously in the ANDA deficiency letter, the firm should submit full analytical and dissolution method validation reports for its originally proposed in vitro release method (including individual data for all samples tested). Sun's method will still be considered and evaluated in comparison with the FDA-recommended method.
4. Based on careful consideration of the data from both methods, the DBI will determine the most appropriate method and specifications for the test product.

Please note that final study has been conducted in accordance with FDA's mail dated March 12, and report containing results of this study has been provided herewith in section 5.3.1.3. Validation report for this test method has also been provided herewith in section 5.3.1.3.

Reviewer's Comments on Firm's Response #5: In the original submission, the firm submitted the comparative in vitro drug release results using its own proposed method. In the deficiency letter sent to the firm, the DBI asked the firm to conduct additional testing using FDA recommended method [DARRTS: RAMSON, TERESA V 02/16/2012 FAX 02/16/2012 COR-ANDA-01(Bio Incomplete Deficiencies) Original-1 (Unknown)]

Archive]. Subsequently, the firm requested DBI for additional guidance regarding the FDA-recommended in vitro drug release testing method given to the firm in the deficiency letter. Due to the expedited status of the ANDA based on the current drug shortage, the DBI responded to the firm's inquiry by email providing clarification on the method recommendation and asked the firm to conduct *preliminary* in vitro release testing using only the test product since the firm indicated that there was only a limited supply of the RLD available for testing (i.e., about 10 vial units). The *preliminary* data were submitted by email on March 7, 2012 and were reviewed by the DBI. Subsequently, based on the *preliminary* data submitted, the DBI provided additional details and suggested modifications of the recommended method. The DBI asked the firm to conduct additional *preliminary* testing based on the provided method details and suggested modifications of the method. The firm submitted the second set of *preliminary* data following the DBI's advice. The DBI reviewed the second set of *preliminary* data, and recommended the firm conduct its official in vitro testing on both test and reference product using *Sun's Medium 3 [2.97ml of 100% Fetal Bovine Serum (pH 7.10) containing 214 mg/ml Ammonium Chloride in water (pH 5.3), with pH adjusted to 6.5 +/- 0.1]. The firm should use 12 dosage units of the test product and the available 10 dosage units of the RLD of the testing"* [DARRTS: DANDAMUDI, SUMAN 04/03/2012 N/A 04/03/2012 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive].

In the current amendment, the firm submitted the comparative in vitro drug release results using the followings method:

In Vitro Release Conditions:

Apparatus: Circulating water bath

Temperature of bath: 47°C ± 0.5° C

Dissolution Medium: 98% Fetal Bovine Serum containing 80mM Ammonium chloride, pH 6.5

Time Points: 0, 0.5, 1, 2, 3, 4, 5 hrs

Preparation of Release Medium: [REDACTED] (b) (4)

Note: [REDACTED] (b) (4)

In Vitro Release Procedure: [REDACTED] (b) (4)



(b) (4)

Sample Processing:



(b) (4)

SPE Procedure:



(b) (4)

Chromatographic Conditions:

Use a suitable High Performance Liquid Chromatograph (HPLC) with the following conditions.

Column:



(b) (4)

Flow rate:

Auto sampler Temperature:

Detector:

UV at 254 nm

Run time:



(b) (4)

Injection volume: (b) (4)

Calculation:

Calculate % release of Doxorubicin HCl at each time point using below mentioned formula,



Product Name: Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL (Test Product)

Mfg Date: 02/2012

Batch No: JKL0863A

Time Point --- >	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
Vial No/Units							(b) (4)
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
MEAN	1.275	15.334	29.487	59.832	85.194	85.853	78.044
±S.D.	NA	0.3450	1.2003	1.8210	3.2317	2.9908	2.2773
%C.V.	NA	2.2	4.1	3.0	3.8	3.5	2.9
Min							(b) (4)
Max							

[Note: The test biobatch was expired, so the firm conducted in vitro drug release testing on a new test lot]

Product Name: Doxil® Liposome Injection, 2 mg/mL (Reference Product)
 Exp Date: 03/2012, Batch No: 1007992

Time Point --- >	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
Vial No/Units							
1							(b) (4)
2							
3							
4							
5							
6							
7							
8							
9							
10							
MEAN	1.480	17.315	32.636	61.712	77.689	79.404	74.689
±S.D.	NA	0.7235	1.0224	2.6092	2.8990	1.2725	1.6815
%C.V.	NA	4.2	3.1	4.2	3.7	1.6	2.3
Min							(b) (4)
Max							

[Note: The firm conducted in vitro drug release testing on expired reference lot, as the RLD is not available in the market].

Following this page, 4 Pages Withheld in Full as (b)(4)

4.4 In Vitro Drug Release Method

Firm's Proposed Method

Dissolution Conditions		Apparatus:	Bottle Rotating Apparatus								
		Sinker:	No								
		Speed of Rotation:	12 rpm								
		Medium:	USP phosphate buffer pH 6.4 (b) (4)								
		Volume:	90 mL								
		Temperature:	52°C								
Firm's Proposed Specifications		0.5 hr: NMT (b) (4)%, 1.5 hr: (b) (4)%, 3 hr: (b) (4)%, 5 hr: (b) (4)%, 7 hr: NLT (b) (4)%									
Dissolution Testing Site (Name, Address)		Sun Pharma Advanced Research Company Limited, Nima Compound, Tandalja, Vadodara-390012, Gujarat, India.									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units*		Collection Times (hr)					Study Report Location
						0.5	1.5	3	5	7	
DOX_IV R_US_20 10	12/14/20 10 and 12/24/20 10	Doxorubicin Hydrochloride Liposome Injection Batch # JK93496 Mfg date: Nov 2009	2 mg/mL Injection	12	Mean	8.00	20.07	46.34	69.67	87.27	Module# 5.3.1.3
					Range	(b) (4)					
					%CV	15.6	14.5	8.8	4.9	3.4	
		Doxil® Liposome Injection Batch # 0910338 Exp. date: Feb 2011	2 mg/mL Injection	12	Mean	9.97	25.54	52.56	76.25	94.67	
					Range	(b) (4)					
					%CV	13.5	13	6.9	4.2	3.20	

FDA-Recommended Method

Dissolution Conditions		Apparatus:	Circulating water bath										
		Sinker:	No										
		Speed of Rotation:	N/A										
		Medium:	98% Fetal Bovine Serum containing 80mM Ammonium chloride, pH 6.5										
		Volume:	3 mL										
		Temperature:	47°C										
Firm's Proposed Specifications		N/A											
Dissolution Testing Site (Name, Address)		Sun Pharma Advanced Research Company Limited, Nima Compound, Tandalja, Vadodara-390012, Gujarat, India.											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units*	Collection Times (hr)							Study Report Location	
					0	0.5	1	2	3	4	5		
In vitro BE_12_001	March 27, 2012	Doxorubicin Hydrochloride Liposome Injection Batch # JKL0863A Mfg date: Feb 2012	2 mg/mL Injection	12	Mean	1.275	15.334	29.48 7	59.832	85.194	85.85 3	78.04 4	Module# 5.3.1.3
					Range	(b) (4)							
					%CV	NA	2.2	4.1	3.0	3.8	3.5	2.9	
		Doxil® Liposome Injection Batch #1007992 Exp. date: March 2012	2 mg/mL Injection	12	Mean	1.480	17.315	32.63 6	61.712	77.689	79.40 4	74.68 9	
					Range	(b) (4)							
					%CV	NA	4.2	3.1	4.2	3.7	1.6	2.3	

Comparison of firm's proposed and FDA-recommended in vitro drug release methods

Firm's Proposed Method	FDA-recommend method
Apparatus: Bottle rotating apparatus Medium: Phosphate buffer, pH 6.4 Volume: 90 mL RPM: 12 Temperature: 52 ± 0.5 °C Time Point: 0.5, 1.5, 3, 5 and 7 hours	Apparatus: Circulating water bath Medium: 98% FBS containing 80 mM ammonium chloride, pH 6.5 Temperature: 47 ± 0.5 °C Time Point: 0, 0.5, 1, 2, 3, 4 and 5 hrs
Sample processing was done by (b) (4)	Sample processing was done using Solid Phase Extraction method using HLB cartridges
Doxorubicin was analyzed using HPLC with a UV detector at 254 nm	Doxorubicin was analyzed using HPLC with a UV detector at 254 nm
During the method validation, the firm could not demonstrate the robustness and reproducibility of the method at the initial time point (30 min) as the variation of percent drug release is very high at this time point.	During the method validation, the firm established the method precision and reproducibility for estimating the in vitro drug release. However the stability testing results indicated the degradation of doxorubicin in the FBS medium when stored for more than 2 hours
The test is conducted in 100 mL bottles with separate bottle for each time point and each vial using the Bottle Rotating Apparatus	The test is conducted in 5 mL glass tubes with separate test tube for each time point and each vial.
To the bottles containing release medium, drug product (b) (4) (b) (4) The testing is done in Bottle Rotating apparatus at a speed of 12 rpm and temperature of 52°C. At end of respective time points, sample is with drawn, processed and analyzed using HPLC.	The test tube containing release medium is placed on the stand and the stand is placed in the waterbath, where temperature is maintained at 47°C. To these tubes, drug product is added and mixed well by gentle shaking. The samples are incubated at 47°C without any agitation and at end of respective time points, sample is with drawn, processed and analyzed using HPLC.

Even though the “Bottle Rotating Apparatus” is not a compendial apparatus, if properly calibrated, the testing conditions can be uniformly maintained throughout the study. The speed of rotation and maintenance of temperature can be programmed thereby leading to less bias by the analyst.	The testing is done in glass test tubes with series of steps involved that may lead to the bias of the results in the hands of the analyst.
The drug is stable in release medium (USP Phosphate Buffer)	The drug degrades in the FBS medium if stored for more than 2 hours. In addition the method is susceptible to the slight pH changes and also to the change in the FBS lots. There is significant effect of pH on drug release. As the FBS does not have any buffering capacity, with the slight change in pH, percent of drug release is altered. In addition, when Sun has conducted the study using two different lots of FBS, there is difference in drug release profile (See the attachment). (b) (4) (b) (4)

Selection of in vitro drug release method for Doxorubicin Hydrochloride Liposomal Injection

The Division of Bioequivalence I accepts the firm's proposed method of using Bottle Rotating Apparatus for the in vitro drug release testing due to the following reasons:

- Doxorubicin is not stable in the release medium used in the FDA-recommended method.
- FDA-recommended method is sensitive to pH changes. As there is there is no buffer in the release medium and FBS being biological medium, the adjustment of pH is very critical. There is significant effect of pH on drug release.
- The in vitro drug release testing conducted with two different lots of FBS resulted in variation in the drug release profile. Therefore FBS supplier is critical to obtain accurate testing results using the FDA recommended method and change in the FBS lot may lead to failure of future batches.
- Because of the above stated problems associated with the FDA-recommended method, DBI accepts the firm's proposed method for their test product, Doxorubicin Hydrochloride Liposomal Injection, 2 mg/mL.

However since the Bottle Rotating Apparatus is not official compendial apparatus, the physical characteristics like size, shape and material composition has to be standardized to avoid any variability associated with the glass bottles.

In Vitro Drug Release Specifications:

The firm proposed specifications using their own method are too liberal for the test biolot. Therefore based on the data of the fresh biolot submitted, the DBI recommends the following specifications which are more appropriate for the test product. However, the DBI may consider changes in the specifications based on additional release data from any fresh production batches (with a minimum of 3) that have been found acceptable based on approved finished product specifications. Currently, there are multiple deficiencies cited by the OGD Division of Chemistry which has not approved the firm's proposed specifications and considers some of them too wide.

Firm's Proposed Specifications:

0.5 hr:	NMT	(b) (4) %
1.5 hr:	(b) (4)	%
3 hr:	(b) (4)	%
5 hr:	(b) (4)	%
7 hr:	NLT	(b) (4) %

DBI Recommended Specifications:

0.5 hr: NMT (b) (4) %
1.5 hr: (b) (4) %
3 hr: %
5 hr: %
7 hr: NLT (b) (4) %

4.5 Review of Science Team Consult

DB I through email correspondence has requested the OGD Science Team (ST) to provide comments on the BE review of Doxorubicin Hydrochloride Liposome Injection. The ST’s feedback has mainly been focused on the in vitro drug release testing method. Their comments and recommendations on both the firm’s proposed and FDA-recommended methods are provided in the Attachment Section.

ST’s Comments on Sun’s Proposed Method

Comment 1: Science team is concerned about (b) (4)
(b) (4)
(b) (4)
(b) (4). Therefore firm should be requested to provide more technical details and validation of their dissolution method (b) (4) if this method is to be employed.

Reviewer’s Comments: The article the ST references states that (b) (4)
(b) (4)
(b) (4)

(b) (4)
(b) (4)

The Science Team suggested that the firm should provide more technical details and validation of their dissolution method (b) (4). In the current amendment, the firm submitted the dissolution method validation report. Based on the results of method validation, it can be concluded that method is precise, accurate, specific, linear and stability indicating. The method precision, reproducibility and robustness are established at all the

sampling time points. The firm conducted the following studies to confirm the method robustness: (b) (4)

It is noted that the firm did not submit optimizing studies with the (b) (4) (proposed). However, compared with the release profile obtained for both test and RLD products using Sun's proposed method, the release profile obtained for the RLD product (b) (4) was much faster (e.g., at 3 hours, the drug from the RLD product was released at (b) (4)%) with Sun's method, and at 2 hours, the specification recommended (by the ONDQA chemist) for the RLD product (b) (4) is (b) (4)%, which is much greater. Therefore, the ST's concern that (b) (4) is not well founded.

Based on the dissolution data and method validation data, the DBI considers acceptable to (b) (4) in the firm's proposed dissolution medium. In addition, the dissolution method validation submitted by the firm regarding the firm's proposed method is adequate. However based on the ST's suggestion, a telephone request was made on 6/21/2012, asking the firm to provide justification for (b) (4)

[DARRTS: RAMSON, TERESA V 06/21/2012 VERBAL 06/21/2012 COR-ANDAIR-01(Advice/Information Request) Original-1 (Unknown) Archive]. On June 29, 2012, the firm submitted a telephone amendment providing the necessary data as requested by the DBI. Please see section 4.7 for the review of Telephone Amendment dated June 29, 2012.

Comment 2: As for the dissolution method using phosphate buffer without FBS, a literature publication suggested that it is not predictive of in-vivo performance of pegylated liposomal doxorubicin (even contrary to in-vivo performance), compared to phosphate buffer containing bovine serum albumin (BSA, a key component of FBS). Therefore firm should be requested to conduct further investigation of dissolution medium containing FBS or BSA.

Reviewer's Comments: The in-vitro drug release testing is not used to predict in vivo performance but as a quality control tool to monitor batch to batch consistency of the drug release from the product. In addition, as the FBS does not have any buffering capacity, with the slight change in pH, percent of drug release is altered. When Sun conducted the study using two different lots of FBS, there is difference in drug release profile. (b) (4) Therefore FBS supplier is critical to obtain accurate testing results using the FDA recommended method and change in the FBS lot may lead to failure of future batches. Therefore DBI accepts phosphate buffer without FBS as the release medium for in vitro drug release testing.

ST's Comments on FDA-Recommended Method

Comment 3: Sun indicated that doxorubicin was unstable in recommended dissolution medium 3 (pH 6.5, 47°C). Based on available Sun's data at 72°C and literature data better stability of doxorubicin at pH 6.0 is expected [at 72°C and pH 6.5, doxorubicin was less stable than at pH 6.0]. Thus, true difference between generic product and RLD beyond analytical method cannot be ruled out. To clarify, we recommend firm to provide the following data:

- 1) Determine the stability of doxorubicin in recommended release medium 2 (pH 6.0) [at 47C]
- 2) Perform comparative dissolution of RLD and generic in recommended release medium 2

Reviewer's Comments: (b) (4), the comparative dissolution testing should be conducted at 47°C and at pH 6.0. The DBI recommended the firm to conduct additional dissolution testing at 72°C only to measure the total free doxorubicin per time point sample (b) (4). The data indicated that doxorubicin was degrading at 72°C. The stability testing performed by the firm indicated the degradation of free doxorubicin in the FBS medium (pH 6.5 and 47°C) when stored for more than 2 hours.

The dissolution testing data showed that only 54% of the drug is released at 5 hrs in dissolution medium with pH adjusted to 6.0 (NDA medium). However in the dissolution medium, pH adjusted to 6.5, 85% of drug release is observed at 4 hrs. Based on this data, dissolution medium with pH adjusted to 6.5 was considered more appropriate for the test product.

Since the firm indicated that the quantity of the RLD product was limited and difficult for any additional comprehensive in vitro testing, the Science Team suggested correcting the degradation loss for the Sun's data before comparing with those of the RLD product (b) (4). However, any difference (after degradation correction) between Sun's product and (b) (4) the RLD product does not necessarily indicate that the two products did not have the same release profile, (b) (4)

In an attempt to document any comparative release testing results (b) (4) (b) (4) with the remaining (and possibly expired) RLD product quantity, the ST subsequently suggested that the firm provide any comparative results if at all possible. A telephone request was made on 6/25/2012, asking the firm to provide additional comparative in vitro testing data (b) (4) (98% FBS containing 80 mM ammonium chloride, pH 6.0, 47°C) and also stability testing data of drug substance in the FBS medium, pH 6.0 at 47°C [DARRTS: RAMSON, TERESA V

06/25/2012 VERBAL 06/25/2012 COR-ANDAIR-01(Advice/Information Request) Original-1 (Unknown) Archive]. On July 4, 2012, the firm submitted a telephone amendment providing the data as requested by the DBI. Please see section 4.8 for the review of Telephone Amendment dated July 4, 2012.

The DBI reviewer note that as doxorubicin is not stable in the release medium used (b) (4) (b) (4) Division of Bioequivalence I accepts the firm's proposed method of using Bottle Rotating Apparatus for the in vitro drug release testing.

4.6 Review of Telephone Amendment dated June 29, 2012

Deficiency Comment #1: The in vitro release testing conducted using your own proposed method, (b) (4) Please submit the following:

- Any reference such as scientific literature or your in-house studies to support the (b) (4)
- Optimization study for (b) (4)

Firm's Response to Deficiency 1: Please note that (b) (4) (b) (4) based on the following rationale:

(b) (4)

It is evident from the results that [REDACTED] (b) (4)
[REDACTED] of *in vitro* drug release.

Please also note that on page 62 of the product development report provided in section 3.2.P.2 of the submitted ANDA, study results indicating [REDACTED] (b) (4) has been provided.

Reviewer's Comments on Firm's Response #1: DB I through email correspondence has requested the OGD Science Team (ST) to provide comments on the BE review of Doxorubicin Hydrochloride Liposome Injection. The ST's feedback has mainly been focused on the *in vitro* drug release testing method (as the *in vivo* BE study had already been the focus of the first ST consult for the original BE review). The ST was concerned about [REDACTED] (b) (4)

[REDACTED]. Based on the ST's suggestion, a telephone request was made on 6/21/2012, asking the firm to provide justification for [REDACTED] (b) (4) [DARRTS: RAMSON, TERESA V 06/21/2012 VERBAL 06/21/2012 COR-ANDAIR-01(Advice/Information Request) Original-1 (Unknown) Archive]. In this telephone amendment dated 6/29/2012, the firm provided data showing the [REDACTED] (b) (4)

[REDACTED] their *in vitro* drug release testing studies using their own proposed method.

Deficiency Comment #2: *Validation data to demonstrate* [REDACTED] (b) (4)

Firm's Response to Deficiency 2: Please note that a study was performed to verify the [REDACTED] (b) (4)
[REDACTED] The drug release results for Doxorubicin liposome injection Batch No.: JKL3702 as per the above study are summarized in below graph.

4.7 Review of Telephone Amendment dated July 4, 2012

Deficiency Comment #1: *We are requesting additional comparative in vitro testing using one of our originally recommended methods (described below).*

*Apparatus: Circulating water bath
Medium: 98% FBS containing 80 mM ammonium chloride, pH 6.0
Temperature: 47 ± 0.5 °C
Volume: 3 mL
Time Point: 0, 0.5, 1, 2, 3, 4 and 5 hrs*

Procedure:

- 1. The sample size should be 3 mL, i.e., 30 μ L of the drug product should be added to 2.97 mL of the FBS containing 80 mM of ammonium chloride at pH 6.0.*
- 2. Adjustment to pH 6.0 should be done during the reagent preparation and again after adding the drug product.*
- 3. For each time point, a separate tube of sample should be used.*
- 4. There should be no agitation during sample incubation. However, at the end of incubation, the sample tubes should be mixed well prior to removing each aliquot for further analysis.*
- 5. At the end of incubation, the sample tubes should be placed on ice for at least 5 minutes before sample analysis.*

We are aware that you have limited supply of the RLD product and these lots might have been expired at this time. However it is important that we obtain the comparative profile of two products using this method for our information purpose.

Firm's Response to Deficiency 1: Please note that the study report containing the results of in vitro testing of test and reference product as per above FDA recommended method has been provided herewith in section 5.3.1.3.

Reviewer's Comments on Firm's Response #1: To obtain additional information on comparative in vitro drug release profiles (b) (4) as a part of the current FDA-recommended in vitro comparative characterization of the two products belonging to this special dosage form, the ST suggested that the firm provide a comparative in vitro drug release testing using the (b) (4) recommended method (98% FBS containing 80 mM ammonium chloride, pH 6.0 at 47 ± 0.5 °C), which it did not provide previously due to the concern that the limited available quantity of the RLD product was used for unnecessary testing (given that the firm found the drug was not stable under the (b) (4) testing conditions). In the telephone request 6/25/2012, the firm was asked to provide additional comparative in vitro testing data (b) (4) [DARRTS: RAMSON, TERESA V 06/25/2012 VERBAL 06/25/2012 COR-ANDAIR-01(Advice/Information Request) Original-1 (Unknown) Archive].

In this telephone amendment dated July 4, 2012, the firm submitted the comparative in vitro study of Doxorubicin Hydrochloride Liposomal Injection in 98% FBS, pH 6.0 at 47° C using 12 units of test product and 10 units of reference product

Product Name: Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL (Test Product)
Mfg Date: 02/2012
Batch No: JKL0863A

Time Point -->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
Vial No/Units							
1	BQL	(b) (4)					
2	BQL						
3	BQL						
4	BQL						
5	BQL						
6	BQL						
7	BQL						
8	BQL						
9	BQL						
10	BQL						
11	BQL						
12	BQL						
MEAN	NA	7.455	14.119	27.748	41.161	53.512	63.048
±S.D.	NA	0.5301	0.9385	1.3609	3.3492	5.3093	6.7892
%C.V.	NA	7.1	6.6	4.9	8.1	9.9	10.8

[Note: The test biobatch was expired, so the firm conducted in vitro drug release testing on a new test lot]

Product Name: Doxil® Liposome Injection, 2 mg/mL (Reference Product)
Exp Date: 03/2012, Batch No: 1007992

Time Point -->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
Vial No/Units							
1	BQL	(b) (4)					
2	BQL						
3	BQL						
4	BQL						
5	BQL						
6	BQL						
7	BQL						
8	BQL						
9	BQL						
10	BQL						
MEAN	NA	9.724	16.731	31.137	43.799	56.677	61.505
±S.D.	NA	0.7459	1.4300	2.5853	3.3181	5.8425	3.4019
%C.V.	NA	7.7	8.5	8.3	7.6	10.3	5.5

[Note: The firm conducted in vitro drug release testing on an expired reference lot, as the RLD is not available in the market. This RLD lot is not same as the biostudy RLD lot].

The above results indicated that both test and reference products had comparably and significantly slower and incomplete release of the drug (b) (4)

However, since both the test and RLD lots showed comparable release profiles (b) (4), it appeared that the observed difference in the release profiles of the RLD product (b) (4) and ANDA, respectively, may be due to (b) (4) rather than any difference between the test and RLD formulations.

As mentioned above, regardless of the differences observed (b) (4), the in vitro drug release profile of test and reference products in the current ANDA submission were similar.

Deficiency Comment #2: *In the amendment dated April 9, 2012, you have submitted the stability testing results of doxorubicin drug substance in FBS medium, pH 6.5 at 47°C. Please conduct additional stability testing study of drug substance in the FBS medium (98% FBS containing 80 mM ammonium chloride), pH 6.0 at 47°C.*

Firm's Response to Deficiency 2: Please note that as recommended by the Agency, the stability study of drug substance in FBS medium, pH 6.0 at 47°C, has been performed. The results of this study have been summarized in appendix I of the study report provided herewith in section 5.3.1.3.

Reviewer's Comments on Firm's Response #2: One of the ST's concerns was that "Based on available Sun's data at 72°C and literature data, better stability of doxorubicin at pH 6.0 is expected [at 72°C and pH 6.5, doxorubicin was less stable than at pH 6.0)". Therefore per the ST's suggestion the firm was asked to submit the stability data of doxorubicin in FBS medium at pH6.0.

In this Telephone Amendment, dated July 4, 2012, the firm submitted stability results of in FBS medium at pH 6.0. The recovery of LQC and HQC prepared in FBS medium was compared with the recovery of LQC and HQC injected during the sequence.

% Recovery of QC samples calculated using the following formula:

$$\% \text{ Recovery of QC} = \frac{AT}{AS} \times \frac{WS}{\text{Dilution}} \times \frac{\text{Dilution}}{WT} \times 100$$

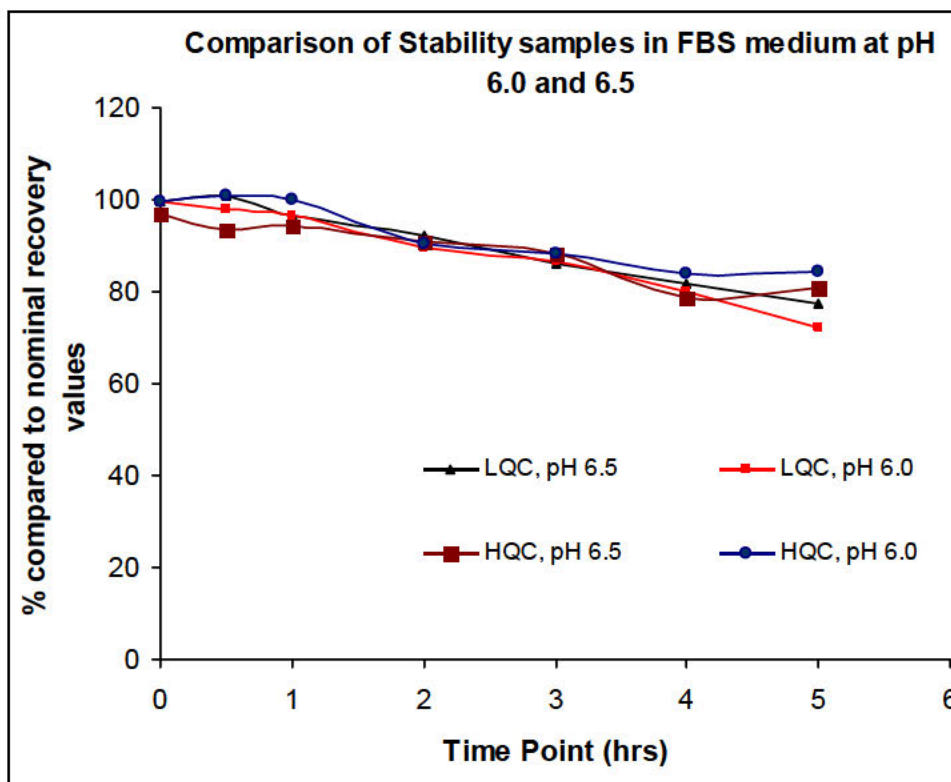
Where:

AT= Area count of doxorubicin peak in test preparation
AS= Average area count of doxorubicin peak in standard preparation
WS= Weight of doxorubicin WS in mg
WT= Weight of doxorubicin hydrochloride WS in mg for QC preparation
For both LQC and HQC samples, more than 10% decrease in recovery is observed after 2 hr storage at 47° C in FBS medium. More than 15% decrease in recovery is observed at 4 hr and 5 hrs storage of the samples. Therefore as the storage period in FBS medium increases, the % recovery of doxorubicin is decreasing. This indicates degradation of doxorubicin at 47° C in FBS medium, pH 6.0 after 1 hr storage time.

	QC sample	Time Point in Hr	Stability QC	Routine QC	Difference	% Difference
Mean% Recovery	LQC	0	102.275	102.526	-0.251	-0.24
		0.5	103.280	102.526	0.754	0.74
		1	99.075	102.526	-3.451	-3.37
		2	94.635	102.526	-7.891	-7.70
		3	88.170	102.526	-14.356	-14.00
		4	83.730	102.526	-18.796	-18.33
		5	79.425	102.526	-23.101	-22.53
	HQC	0	92.095	95.045	-2.950	-3.10
		0.5	88.960	95.045	-6.085	-6.40
		1	89.675	95.045	-5.370	-5.65
		2	86.280	95.045	-8.765	-9.22
		3	83.830	95.045	-11.215	-11.80
		4	75.000	95.045	-20.045	-21.09
		6	76.755	95.045	-18.290	-19.24

The reviewer compared the stability data of doxorubicin in FBS medium at Ph 6.0 and 6.5 for both LQC and HQC samples.

	QC sample	Time Point in Hr	Recovery Values as % of Nominal Values	
			pH 6.5	pH 6.0
Mean% Recovery	LQC	0	99.76	99.59
		0.5	100.74	97.72
		1	96.63	96.46
		2	92.30	89.77
		3	86.00	86.60
		4	81.67	80.11
		5	77.47	81.60
	HQC	0	96.90	99.38
		0.5	93.60	101.04
		1	94.35	99.81
		2	90.78	90.39
		3	88.20	88.15
		4	78.91	83.72
		6	80.76	84.22



Based on the above results, better stability of doxorubicin was not observed in FBS medium at pH 6.0. The stability results indicated that the drug degraded in the FBS medium if stored beyond 2 hrs at both pH 6.0 and 6.5.

4.8 Importation of Sun's Lots

- Temporary importation of foreign drugs is considered only in cases when there is a shortage of an approved U.S. drug that is critical to patients.
- In response to the Doxil shortage, FDA is temporarily importing Sun's product, Lipidox (Doxorubicin Hydrochloride Liposomal) Injection to the United States.
- Before the importation, Lipidox is evaluated by different divisions of NDA and ANDA to ensure that does not pose any obvious safety and quality issues.
- Till date, COA of 23 lots of Sun's product, Lipidox has been evaluated for importation (not for approval). Therefore the reviewer put together the table for the in vitro drug release data from the 23 lots that were imported till to date (Please see attachments).
- The in vitro drug release specifications currently recommended by the DBI were based on the biolot. The DBI makes note of the imported lots that did not meet the DBI-recommended specifications. (Please see attachments) Until the finished product specifications are established for Sun's product, these imported lots cannot be evaluated for their acceptability and are not considered valid to be used in setting the in vitro release specifications. Currently, there are multiple deficiencies cited by the OGD Division of Chemistry which has not approved the firm's proposed specifications and considers some of them too wide.

4.9 Deficiency Comment

The in vitro drug release testing using firm's own proposed method with Bottle Rotating Apparatus is acceptable. Based on the data submitted for the test lot used in the in vivo bioequivalence study, the DBI has recommended appropriate specifications for the test product. The firm should acknowledge the acceptance of the following method and specifications.

The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4) (b) (4) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus,

effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr: NMT (b) (4) %
 1.5 hr: (b) (4) %
 3 hr: %
 5 hr: %
 7 hr: NLT (b) (4) %

4.10 Recommendations

1. The Division of Bioequivalence tentatively accepts the fed BE study (C10112) conducted by the Sun Pharma Global FZE. on its Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL, lot # JK93496A, comparing it to Ortho Biotech’s Doxil® Liposomal Injection, 2 mg/mL, lot # 0907642.
2. The in vitro equivalence study (Liposome Size Distribution) submitted for Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL, by Sun Pharma Global FZE, comparing it to Doxil® Liposomal Injection, 2 mg/mL, manufactured by Ortho Biotech, is tentatively acceptable.
3. The firm’s *in vitro* drug release testing is incomplete. The firm should acknowledge the following method and specification.

Apparatus	Bottle Rotating Apparatus
Speed	12 rpm
Medium	Phosphate Buffer, pH 6.4
Volume	90 mL
Temperature	52° C
DB-recommended specifications	0.5 hr: NMT (b) (4) % 1.5 hr: (b) (4) % 3 hr: % 5 hr: % 7 hr: NLT (b) (4) %

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4)) using 100 mL cylinder glass bottles ((b) (4)) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure

and the analytical method should be as specified in the SOP QCI-157/02 for Calibration Procedure, Title: Operation and Calibration Procedure of Bottle Rotating Apparatus (effective date 01/25/2011), SOP for In Vitro testing, Title: Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 4/3/2012⁴), respectively.

4.11 Comments for Other OGD Disciplines

Discipline	Comment
OSI	Clinical sites: NRR Hospital, Bangalore: A new site OSI inspection was requested for this clinical site on February 16, 2012 and is still pending the outcome of the request. Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu: A new-site OSI inspection will be requested for this clinical site. Analytical site: A for-cause Office of Scientific Investigations (OSI) inspection was requested for the analytical site of ANDA 090886 on May 20, 2010 and is still pending the outcome of the request. In vitro testing site: A routine OSI inspection was requested for this site on February 16, 2012 and is still pending the outcome of the request

⁴ Even though the in vitro testing is performed before the effective date of this SOP, the same procedure was followed as outlined in this SOP

4.12 Attachments

Reference: FDA BE Query on Doxorubicin Liposomes, 2mg/ml, Dated 17th February 2012, Point No: 5

FDA correspondence Dated 24th February 2012

Since the availability of the RLD is limited, we recommend the firm conduct a preliminary drug release study using the 4 different conditions described below:

1. With Option 1 medium (as described by Sun), at pH.7; -Medium1
2. With Option 1 medium (as described by Sun), but pH adjusted to pH 6.0 using hydrochloric acid; -Medium2
3. With Option 2 medium (as described by Sun), at pH 7.0; and -Medium3
4. With Option 2 medium (as described by Sun), but pH adjusted to pH 6.0 using hydrochloric acid.-Medium4

For each of these 4 conditions, please use 6 units of the Test product only, and submit the preliminary testing results to the Division of Bioequivalence I (DBI) for evaluation.

Based on the preliminary data submitted, if possible, the DBI will recommend the final drug release testing conditions, for which the official testing should be done using the available 10 units of the RLD and 12 units of the Test product.

Sun Response:

As per the FDA correspondence in vitro drug release study was conducted by using following four mediums.

Medium 1: 98% Fetal Bovine Serum (FBS) with 2 ml 80mM Ammonium Chloride. Take 98 ml of FBS in a beaker and add 2 ml of 80 mM ammonium Chloride into it, mix well. (Resultant pH of medium - 6.86)

Medium 2: 98% Fetal Bovine Serum (FBS) with 2ml 80mM Ammonium Chloride. Take 98 ml of FBS in a beaker and add 2 ml of 80 mM ammonium Chloride into it, mix well. Adjusted the pH to 6.0 with 5M HCl.

Medium 3: 98% Fetal Bovine Serum(FBS) with 2ml 4M Ammonium Chloride. Take 98 ml of FBS in a beaker and add 2 ml of 4M ammonium Chloride into it, mix well. (Resultant pH of medium - 6.69)

Medium 4: 98% Fetal Bovine Serum(FBS) with 2ml 4M Ammonium Chloride. Take 98 ml of FBS in a beaker and add 2 ml of 4M ammonium Chloride into it, mix well. Adjusted the pH to 6.0 with 5M HCl

For each of these four medium, six vials of Doxorubicin Liposomes, 2mg/ml, were taken and below procedure suggested by agency was followed.

“Six samples of 1 ml of the vial content was transferred to six separate glass tubes containing the medium to obtain the final sample volume of 100 ml. These glass tubes were incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome was determined at the following six time points; 0hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs.

The individual percent doxorubicin release data from each vial at each time, as well as the % mean with % CV data from 06 vials at each time over the period of 0 to 4 hours for all the four medium is compiled in below four tables. (Table 1, Table 2, Table 3, Table 4)

Note: Whole study has been performed using Doxorubicin Liposomes, 2mg/ml, 25 ml, Batch No: JKL0863A

Table 1. % Release of Doxorubicin in Medium 1 (FBS Lot used: 1082735)

Vial	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
	Tube No.						
Vial 1	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
Vial 2	1						
	2						
	3						
	4						
	5						
	6						
Vial 3	1						
	2						
	3						
	4						
	5						
	6						
Vial 4	1						
	2						
	3						

	4	(b) (4)											
	5												
	6												
Vial 5	1												
	2												
	3												
	4												
	5												
	6												
Vial 6	1												
	2												
	3												
	4												
	5												
	6												
Mean								1.0908	1.4732	2.0125	2.8572	3.9216	4.4849
±S.D.								0.0651	0.1095	0.0957	0.1586	0.2425	0.1930
% CV								6.0	7.4	4.8	5.6	6.2	4.3

Table 2. % Release of Doxorubicin in Medium 2 (FBS Lot used: 1028022)

Vial	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
	Tube No.	(b) (4)					
Vial 1	1						
	2						
	3						
	4						
	5						
	6						
Vial 2	1						
	2						
	3						
	4						
	5						
	6						
Vial 3	1						
	2						
	3						

	4	(b) (4)					
	5						
	6						
Vial 4	1						
	2						
	3						
	4						
	5						
	6						
Vial 5	1						
	2						
	3						
	4						
	5						
	6						
Vial 6	1						
	2						
	3						
	4						
	5						
	6						
	Mean	1.0724	1.1571	1.2309	1.4493	1.6081	1.8178
	±S.D	0.0983	0.1255	0.0939	0.0936	0.1007	0.1087
	% C.V.	9.2	10.8	7.6	6.5	6.3	6.0

Table 3. % Release of Doxorubicin in Medium 3 (FBS Lot used: 1082735)

Vial	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
	Tube No.	(b) (4)					
Vial 1	1						
	2						
	3						
	4						
	5						
	6						
Vial 2	1						
	2						
	3						

	4	(b) (4)					
	5						
	6						
Vial 3	1						
	2						
	3						
	4						
	5						
	6						
Vial 4	1						
	2						
	3						
	4						
	5						
	6						
Vial 5	1						
	2						
	3						
	4						
	5						
	6						
Vial 6	1						
	2						
	3						
	4						
	5						
	6						
Mean		1.3416	10.4594	20.1938	40.2175	61.4308	69.6519
±S.D		0.2578	0.7417	1.6662	2.8259	4.1229	3.6362
% C.V.		19.2	7.1	8.3	7.0	6.7	5.2

Table 4. % Release of Doxorubicin in Medium 4 (FBS Lot used: 1028022)

Vial	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
	Tube No.						
Vial 1	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
Vial 2	1						
	2						
	3						
	4						
	5						
	6						
Vial 3	1						
	2						
	3						
	4						
	5						
	6						
Vial 4	1						
	2						
	3						
	4						
	5						
	6						
Vial 5	1						
	2						
	3						
	4						
	5						
	6						
Vial 6	1						
	2						
	3						
	4						
	5						

	6	(b) (4)					
Mean	1.3247	4.7208	8.2759	16.3874	24.2866	32.2961	
±S.D	0.1833	0.2736	0.5079	1.0183	1.5114	2.0458	
% CV	13.8	5.8	6.1	6.2	6.2	6.3	

From the above data obtained, there is significant difference in the medium 4 where pH is adjusted to 6.0 with its parent medium 3. This significant difference may be due to change in pH or may be due to change in FBS lot, as we used different lot of FBS for preparation of Medium 4 (1082022)

To confirm this, we planned following two experiments simultaneously

- In vitro release in Medium 4 using FBS lot 1082735, same as medium 3.
- In vitro release in Medium 3 using two different lots of FBS (1028022 & 953873)

I) In vitro release in Medium 4 using FBS lot 1082735, same as medium 3.

We planned above mentioned experiment in one tube from two different vials. Results for the same are given in Table no 5.

Table 5. % Release of Doxorubicin in Medium 4 (FBS Lot used: 1082735)

Time Point	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
Vial No	(b) (4)					
1	(b) (4)					
2	(b) (4)					
MEAN	1.44	4.03	7.49	13.83	18.52	24.04
±S.D.	0.19	0.26	0.47	0.71	0.71	0.58
%C.V.	13.3	6.5	6.2	5.1	3.8	2.4

In vitro release in Medium 3 using two different lots of FBS (1028022 & 953873)

We have conducted the drug release study using medium 3 (better drug release profile among the four different medium) with 2 additional lots of FBS (Lot 1028022 and Lot 953873). The drug release was performed in one tube each from 6 vials of drug product for both the lots. The drug release data using both the lots of FBS in medium 3 is as follows:

Table 6. % Release of Doxorubicin in Medium 3 (FBS Lot used: 1028022)

Time Point	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
Vial No	(b) (4)					
1						
2						
3						
4						
5						
6						
MEAN	1.662	14.550	27.784	54.114	73.679	81.391
±S.D. %C.V.	0.116 7.0	0.783 5.4	0.812 2.9	1.913 3.5	2.305 3.1	1.859 2.3

Table 7. % Release of Doxorubicin in Medium 3 (FBS Lot used: 953873)

Time Point	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
Vial No	(b) (4)					
1						
2						
3						
4						
5						
6						
MEAN	1.367	17.774	34.222	64.995	83.924	80.352
±S.D.	0.060	0.684	0.992	1.244	0.738	1.380
%C.V.	4.4	3.9	2.9	1.9	0.9	1.7

Drug release data from the table no 5, we conclude that there is significant effect of HCl or pH on drug release.

From data of drug release of table no 3, 6 and 7, we conclude that there is difference in drug release profile while using different lots of FBS.

OGD SCIENCE STAFF CONSULT REVIEW

To: **Hoainhon N Caramenico**
Deputy Director, Division of Bioequivalence I, OGD

Re: **ANDA 203263**

Consult No: **ANDA 203263**

Drug Product: **Doxorubicin HCl Liposome Injection**
2 mg/ml, 10 ml and 25 ml

Sponsor: **Sun Pharma Global FZE**

Original Submission: **December 28, 2009 (Supplement Original)**

Date of Consult Request: **May 21, 2012**

Date of Review: **May 25, 2012**

Consultant: **Wenlei Jiang, Ph.D.**
Science Staff, OGD

Robert Lionberger, Ph.D.
Science Staff, OGD

Through: **Lawrence Yu, Ph.D.**
Deputy Director for Science and Chemistry, OGD

Reason for Consultation

DBI requests Science Staff to comment on the BE review of ANDA 203263.

Executive Summary

Sun Pharm's Doxorubicin HCl liposome has the same formulation composition and manufacturing process as those of RLD. However, (b) (4)

(b) (4)

product. Sun proposed a dissolution method using phosphate buffer (b) (4), and obtained comparative dissolution profiles between RLD and generic with this method. DBI plans to accept this proposed dissolution method.

In this document, Science Staff focused on review of (b) (4) dissolution methods, and suggested to request the firm to provide justification of dissolution difference

(b) (4)
In addition, (b) (4)
Therefore, Sun should be requested to provide more technical details and validation of their dissolution method (b) (4).

In addition, literature (b) (4) data suggest that the addition of fetal bovine serum (FBS) or bovine serum albumin (a key component in FBS) in the dissolution medium have more in-vivo relevance for pegylated liposome products. Science staff suggested the firm conducts further investigation of dissolution medium containing FBS or BSA.

Background Summary

NDA dissolution method summary

The in-vitro dissolution method of doxorubicin HCl liposome in the NDA has evolved since approval. NDA applicant initially developed the following dissolution method 1⁵:

Method 1:

Dissolution medium: 2.0 M Ammonium Chloride, 0.2 M Histidine Solution, pH 6.5

Temperature: 52 ± 0.2°C.

Sample determination: **within one hour of completing sample incubation**, released and encapsulated drug content were separated with size exclusion chromatograph and doxorubicin content was measured by UV spectroscopy at 480 nm.

Release% = Encapsulated drug% prior to release study – Encapsulated drug% at different time points

Specification: The acceptance criteria require that the release at 0.5 hour time point to be no more than (NMT) (b) (4)%, and that the release at the 3 hr time point to be no less than (NLT) (b) (4)%.

In vitro drug release results obtained with this method were found to be inconsistent with the relative pharmacokinetic profiles of DOXIL® and its formulation variants. (b) (4)

⁵ NDA 50718 Biopharm Rev. 1995

⁶ NDA 50718

(b) (4)

(b) (4)

Sun Pharma dissolution method summary

Sun Pharma explored many dissolution methods such as [REDACTED] (b) (4)
Here only the major dissolution methods are listed. The comparative dissolution testing using the following method was first submitted to OGD:

Apparatus: Bottle Rotating Apparatus

Speed of Rotation: 12 rpm

Medium: USP phosphate buffer pH 6.4 [REDACTED] (b) (4)

Volume: 90 mL

Temperature: 52°C

Time point: 0.5, 1.5, 3, 5, and 7 hr.

Dissolution Conditions		Apparatus:	Bottle Rotating Apparatus								
		Sinker:	No								
		Speed of Rotation:	12 rpm								
		Medium:	USP phosphate buffer: pH 6.4 (b) (4)								
		Volume:	90 mL								
		Temperature:	52°C								
Firm's Proposed Specifications		0.5 hr: NMT (b) (4)%, 1.5 hr: (b) (4)%, 3 hr: (b) (4)%, 5 hr: (b) (4)%, 7 hr: NLT (b) (4)%									
Dissolution Testing Site (Name, Address)		Sua Pharma Advanced Research Company Limited, Nima Compound, Taudalja, Vadodra-390012, Gujarat, India.									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units*	Collection Times (hr)					Study Report Location	
					0.5	1.5	3	5	7		
DOX_IV R_US_20 10	12/14/2010 and 12/24/2010	Doxerubicin Hydrochloride Liposome Injection Batch # JK93496 Mfg date: Nov 2009	2 mg/mL Injection	12	Mean	8.00	20.07	46.34	69.67	87.27	Module# 5.3.1.3
					Range	(b) (4)					
					%CV	15.6	14.5	8.8	4.9	3.4	
		Doxil® Liposome Injection Batch # 0910338 Exp. date: Feb 2011	2 mg/mL Injection	12	Mean	9.97	25.54	52.56	76.25	94.67	
					Range	(b) (4)					
					%CV	13.5	13	6.9	4.2	3.20	

* Each lot of Test and Reference were tested on two different dates with 6 tubes of test and 6 tubes of reference on each date

During the ANDA 203263 review process, OGD recommended the following dissolution methods to Sun Pharma.

Recommendation 1¹⁰ (02/16/2012 BE general review):

Medium: 98% FBS containing 80 mM ammonium chloride, pH 6.0

Temperature: 47 ± 0.5 °C

Time Point: 0, 0.5, 1, 2, 3, and 4 hrs

Volume: 1 ml of the test product in dissolution medium to obtain final sample volume of 100 ml, resulting drug concentration 20 µg/ml.

Sun conducted multiple dissolution studies using different media (details in 04/02/2012 BE review, however unclear about rotation speed and detection method). Table below summarized the data obtained from FDA recommended method 1.

¹⁰ ANDA 203263 BE Rev. 02/16/2012

Table 2. % release of doxorubicin in 98% FBS containing 80 mM ammonium chloride, pH 6.0
A: FBS lot 1082375

Time Point	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
Vial No						
1	(b) (4)					
2						
MEAN	1.44	4.03	7.49	13.83	18.52	24.04
±S.D.	0.19	0.26	0.47	0.71	0.71	0.58
%C.V.	13.3	6.5	6.2	5.1	3.8	2.4

Table 3. % release of doxorubicin in 98% FBS containing 80 mM ammonium chloride, pH 6.0
B: FBS lot 1028022

Vial	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
	Tube No.						
Mean		1.3247	4.7208	8.2759	16.3874	24.2866	32.2961
±S.D		0.1833	0.2736	0.5079	1.0183	1.5114	2.0458
% CV		13.8	5.8	6.1	6.2	6.2	6.3

Sun's product has significantly slower and incomplete release from the RLD in a dissolution medium very similar to that in RLD. Sun also performed dissolution studies in the medium with pH of 6.69 (98% FBS containing 80 mM ammonium chloride, resultant pH 6.69, no further pH adjustment), and a much faster release was observed (Table 4). In addition, Sun observed FBS lots affected dissolution data.

Table 4. % release of doxorubicin in 98% FBS containing 80 mM ammonium chloride, pH 6.69, FBS lot 1028022

Time Point	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
Vial No						
1	(b) (4)					
2						
3						
4						
5						
6						
MEAN	1.662	14.550	27.784	54.114	73.679	81.391
±S.D.	0.116	0.783	0.812	1.913	2.305	1.859
%C.V.	7.0	5.4	2.9	3.5	3.1	2.3

Based on the preliminary results submitted by the firm, DBI recommended the following dissolution method.

Recommendation 2¹¹ (03/08/12, DBI's email response)

- Medium: 98% FBS containing 80 mM ammonium chloride, pH 6.0
 Temperature: 47 ± 0.5 °C
 Time Point: 0, 0.5, 1, 2, 3, 4 and 5 hrs
 Volume: 30 µl of the test product added to 2.97 ml of dissolution medium
 Others:
- a. Adjustment to pH 6.0 should be done during the reagent preparation and again after adding the drug product.
 - b. For each time point, a separate tube of sample should be used.
 - c. There should be no agitation during sample incubation. However, at the end of incubation, the sample tubes should be mixed well prior to removing each aliquot for further analysis.
 - d. At the end of incubation, the sample tubes should be placed on ice for at least 5 minutes before sample analysis.
 - e. The total free doxorubicin per time point sample should be measured at the end of each incubation period by heating the respective sample tube in water bath at 72° C for 30 minutes.

¹¹ ANDA 203263 Telephone amendment BE review. 04/03/2012

Liposomal doxorubicin and free doxorubicin were separated with solid phase Extraction using (b) (4) HLB (1 cc) cartridges. Drug released in FBS in the form of free drug (not encapsulated in liposomes) was determined by HPLC-UV method. Sun conducted dissolution tests with recommended method 2 and found the release may be incomplete (Table 5). However, compared to Table 2 and 3 (same dissolution medium), faster release was observed, possibly due to smaller dissolution volume?

Sun further conducted dissolution tests with recommended method 2 but adjusting the pH to 6.5 and the data are shown in Table 6. At pH 6.5, doxorubicin has faster release compared to pH 6.0. However, doxorubicin has less stability at pH 6.5 than at pH 6.0 (based on data at 72°C), which is consistent with literature pH stability of doxorubicin.

Table 5. % release of doxorubicin with recommended method 2

Temperature	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
	Vial No/Unit No							
47°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	1.358	7.364	12.407	22.905	33.121	42.388	54.637
	±S.D.	0.146	0.294	0.443	0.822	0.644	0.806	5.618
	%C.V.	10.7	4.0	3.6	3.6	1.9	1.9	10.3
72°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	77.154	78.297	78.382	80.335	75.045	75.172	71.040
	±S.D.	2.528	2.792	1.519	2.317	2.148	1.769	1.910
	%C.V.	3.3	3.6	1.9	2.9	2.9	2.4	2.7

Table 6. % release of doxorubicin with recommended method 2 but with a slightly different pH (pH 6.5±0.1)

Temperature	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
	Vial No/Units							
47°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	1.25	14.24	26.56	51.66	73.43	85.13	80.08
	±S.D.	0.16	0.66	1.31	1.97	1.5	3.14	1.7
	%C.V.	12.8	4.6	4.9	3.8	2.0	3.7	2.1
72°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	67.34	68.04	65.36	65.18	66.11	63.93	59.04
	±S.D.	0.98	0.69	1.08	1.62	3.32	1.28	1.13
	%C.V.	1.5	1.0	1.7	2.5	5.0	2.0	1.9

Based on these preliminary dissolution data, OGD recommended the following dissolution method.

Recommendation 3¹¹ (DBI's Email response 03/12/2012):

- Apparatus: Circulating water bath
- Medium: 98% FBS containing 80 mM ammonium chloride, pH 6.5
- Temperature: 47 ± 0.5 °C
- Time Point: 0, 0.5, 1, 2, 3, 4, and 5 hrs
- Volume: 30 µl of the test product added to 2.97 ml of dissolution medium
- Others: Remain the same as in recommendation 2

Sun further conducted comparative dissolution on RLD and ANDA product, and the data are shown in Table 7. Sun concluded that the test and RLD had comparable dissolution at recommended method 3 (pH 6.5).

Table 7. Comparative dissolution data of test and RLD in recommended method 3.

% Drug Release in 98% Fetal Bovine Serum								
Time Point (Hrs)▶		0	0.5	1	2	3	4	5
Mean	Test	1.275	15.334	29.487	59.832	85.194	85.853	78.044
	Reference	1.480	17.315	32.636	61.712	77.689	79.404	74.689
±S.D.	Test	NA*	0.3450	1.2003	1.8210	3.2317	2.9908	2.2773
	Reference	NA*	0.7235	1.0224	2.6092	2.8990	1.2725	1.6815
% C.V.	Test	NA*	2.2	4.1	3.0	3.8	3.5	2.9
	Reference	NA*	4.2	3.1	4.2	3.7	1.6	2.3

However, Sun commented that doxorubicin is not stable in the release medium used in the FDA- recommended method 3 (pH 6.5). In addition, change in FBS lots resulted in variation in the in vitro drug release profile. Therefore, Sun proposed to use its originally proposed method

Apparatus: Bottle Rotating Apparatus (100 ml)

Speed of Rotation: 12 rpm

Medium: USP phosphate buffer pH 6.4 (b) (4)

Volume: 90 mL

Temperature: 52°C

Time point: 0.5, 1.5, 3, 5, and 7 hr.

DBI plans to accept this dissolution method and proposed the following specification limits:

0.5 hr: NMT (b) (4) %
 1.5 hr: (b) (4) %
 3 hr: %
 5 hr: %
 7 hr: NLT (b) (4) %

Discussion

Sun Pharm's doxorubicin HCl liposome has the same formulation composition and manufacturing process as those of RLD. However, Sun's liposome product has much slower dissolution (b) (4) (OGD recommended method 2). As this is a first generic of a complex liposome product, the Science Staff suggests the firm provide justifications of this difference before accepting Sun's proposed method.

Sun indicated that doxorubicin was unstable in recommended dissolution medium 3 (pH 6.5). Based on available Sun's data (Table 5 and 6, data at 72°C) and literature data¹² (Fig 4), better stability of doxorubicin at pH 6.0 is expected. Thus, true difference between generic product and RLD beyond analytical method cannot be ruled out. To clarify, we recommend Sun to provide the following data:

1. Determine the stability of doxorubicin in recommended release medium 2
2. Perform comparative dissolution of RLD and generic in recommended release medium 2

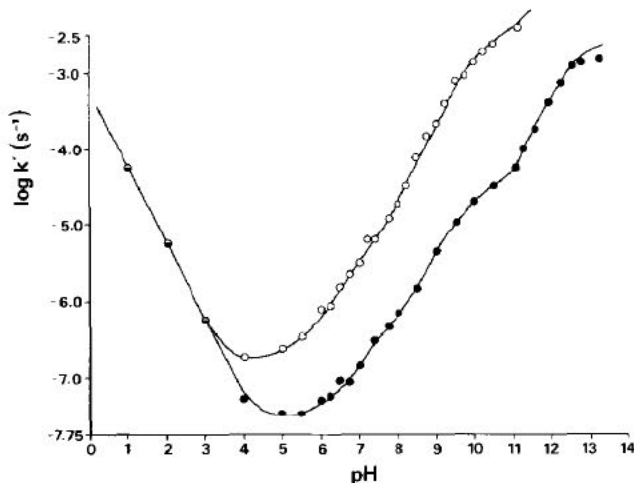


Fig. 3. Log k' -pH profiles for doxorubicin (○) and daunorubicin (●) degradation at 50°C, corrected for buffer and ionic strength influences.

As for the dissolution method using phosphate buffer without FBS, a literature publication suggested that it is not predictive of in-vivo performance of pegylated liposomal doxorubicin (even contrary to in-vivo performance), compared to phosphate buffer containing bovine serum albumin (BSA, a key component of FBS)¹³. (b) (4)

¹² J. H. Benjinen et al. Aspects of the degradation kinetics of doxorubicin in aqueous solution. *Int J. Pharm.* 32: 123-131(1986)

¹³ A. Hioki et al. Development of an in Vitro Drug Release Assay of PEGylated Liposome Using Bovine Serum Albumin and High Temperature. *Biol. Pharm. Bull.* 33: 1466—1470 (2010)

Another concern with Sun's phosphate buffer dissolution method is

(b) (4)

(b) (4)

(b) (4) More validation work on dissolution method should be provided.

Conclusions

1. Sun Pharm's Doxorubicin HCl liposome has the same formulation composition and manufacturing process as those of RLD. However, Sun's liposome product has much slower dissolution (b) (4). Sun was not aware of this difference, thus no justification was provided.
2. Sun's proposed dissolution medium of phosphate buffer without FBS may not have in-vivo relevance. In addition (b) (4)

Recommendations

1. Request Sun to provide the stability of doxorubicin in 98% FBS containing 80 mM ammonium chloride (pH 6.0) and comparative dissolution data of RLD and generic in this dissolution medium. (b) (4)

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(b) (4)

. Sun's dissolution report.

(b) (4)

2. Request Sun to provide more technical details and validation of their dissolution method [REDACTED] ^{(b)(4)} if this method is to be employed.
3. Request Sun to conduct further investigation of dissolution medium containing FBS or BSA.

BIOEQUIVALENCE DEFICIENCY

ANDA: 203263
APPLICANT: Sun Pharma Global FZE
DRUG PRODUCT: Doxorubicin Hydrochloride Injection,
Liposomal, 2 mg/mL (10 mL and 25 mL)

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledge on the cover sheet.

The following deficiency has been identified:

The in vitro drug release testing using your proposed method with Bottle Rotating Apparatus is acceptable. Based on the data submitted for the test lot used in the in vivo bioequivalence study, the DBI has recommended appropriate specifications for the test product. Please acknowledge your acceptance of the following method and specifications:

The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus ((b) (4)) using 100 mL cylinder glass bottles ((b) (4)) with cap with (b) (4) liner ((b) (4)). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in your SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr:	NMT	(b) (4) %
1.5 hr:		(b) (4) %
3 hr:		%
5 hr:		%
7 hr:	NLT	(b) (4) %

Please note the following:

1. You may request revision of the above FDA-recommended release specifications by submitting additional in vitro release data from fresh test lots, for which the validation has been reviewed and accepted by the Division of Chemistry, Office of Generic Drugs (OGD): The Manufacturing, Chemistry and Controls (CMD) records for these test lots should be submitted to the chemistry review division, and demonstrate that they are manufactured under the same approved manufacturing site, conditions, specifications, controls, and are pharmaceutically equivalent to the test lot used in the bioequivalence study. We note that at the present time, the evaluation of the proposed finished product specifications for the test product by the OGD chemistry division is ongoing.

2. Due to the reported limited availability of the reference listed drug (RLD) product, Doxil[®], the Agency has not requested a complete comparative characterization of the in vitro release profile for the test versus the RLD product at this time. However, if and when the RLD product becomes available, additional comparative characterization testing may be requested by the Agency, as appropriate, to obtain more complete information on the in vitro release of the test product, as compared with the reference product.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

ANDA: 203263

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
17427	4/9/2012	Other (REGULAR)	Study Amendment	1	1
17427	6/16/2011	Other (REGULAR)	Consult Response Review (Clinical Division)	1	1
17427	4/9/2012	Other (REGULAR)	Consult Response Review (Science Team)	1	1
17427	7/4/2012	Other (REGULAR)	Study Amendment	1	1
				Total:	4

*Note: The reviewer did not document the productivity credit for the review of the clinical consult response during the review of the original submission. Therefore it is documented in this amendment. Also, due to the expedite status of the ANDA, several telephone requests were made which would normally be done by written communication (i.e., letter). Consequently, some of these “telephone amendments” contained new in vitro testing data for review, and therefore, an additional study amendment credit is documented.

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

/s/

SUMAN DANDAMUDI
07/19/2012

SHRINIWAS G NERURKAR
07/19/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/20/2012

DIVISION OF BIOEQUIVALENCE REVIEW OF AN AMENDMENT

ANDA No.	203263		
Drug Product Name	Doxorubicin hydrochloride Liposome Injection		
Strength(s)	2 mg/mL, 10 mL and 25 mL		
Applicant Name	Sun Pharma Global FZE		
Address	Office # 43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U.A.E		
Applicant's Point of Contact	Robert Kurkiewicz Sun Pharmaceutical industries Ltd. (C/O Caraco) 1150 Elijah Mccoy Drive, Detroit, MI 48202		
Contact's Telephone Number	313-556-4105		
Contact's Fax Number	248-926-0231		
Original Submission Date(s)	June 16, 2011		
Submission Date(s) of Amendment(s) Under Review	March 07, 2012 (Telephone Amendment)		
Reviewer	Suman Dandamudi Ph.D		
Study Number (s)	PKD_09_030	DOX/003/08	FDD-02/10-11/001
Study Type (s)	Fed	Pilot Fed	In-Vitro
Strength (s)	2 mg/mL	2 mg/mL	2 mg/mL
Clinical Site-1	MNJ Institute of Oncology & Regional Cancer Centre		
Clinical Site-1 Address	Red Hills, Hyderabad- 500 004, India		
Clinical Site-2	Kailash Cancer Hospital & Research Centre		
Clinical Site-2 Address	Goraj, Vadodara- 391760, India		
Clinical Site-3	Dr. G. Vishwanathan Speciality Hospitals		
Clinical Site-3 Address	#27, Babu road, Trichy, Tamilnadu- 620 008, India		
Clinical Site-4	Dr. Kamakshi Memorial Hospital		
Clinical Site-4 Address	No.1, Radial Road, Palikaranai, Chennai- 600 100, India		
Clinical Site-5	NRR Hospital		
Clinical Site-5 Address	Chikkasandra, Bangalore- 560090 (India)		
Analytical Site (fed study)	Sun Pharmaceutical Industries Ltd.,		
Analytical Site Address (fed study)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India		
Analytical Site	Sun Pharmaceutical Industries Ltd.,		
Analytical Site Address	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India		
REVIEW RESULT	INADEQUATE		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	DISSOLUTION	2 MG/ML	INADEQUATE
1	FED STUDY	2 MG/ML	INADEQUATE

1. EXECUTIVE SUMMARY

Sun Pharma submitted has submitted ANDA 203263 for its test product, Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL. The submission references NDA 050718, Doxil® (Doxorubicin Hydrochloride) Liposomal Injection, 2 mg/mL from Ortho Biotech. The DBI had previously reviewed the original submission and issued a deficiency letter to the firm.

The firm in the current amendment, dated March 7, 2012, submitted its partial response to one of the deficiency comments made by the Division of Bioequivalence I (DBI) in the letter dated February 16, 2012. The same response was sent on the same date to the DBI through email. The DBI had reviewed the set of the preliminary in vitro drug release testing data submitted in the March 7, 2012 email (which is the same as given in the current amendment), and provided its comments to the firm through email correspondence on March 8, 2012. This DBI email correspondence is attached in the current review document.

Subsequently, in response to the DBI's March 8, 2012 email comments, the firm submitted additional preliminary in vitro drug release testing data in an email dated March 12, 2012. The DBI reviewed the second set of the preliminary data and recommended the firm to conduct its full in vitro drug release testing on both the test and reference product using the following method: *"Sun's Medium 3 [98 ml of 100% Fetal Bovine Serum (pH 7.10) + 2 ml of 214 mg/ml Ammonium Chloride in water (pH 5.3), with pH adjusted to 6.5 +/- 0.1]. The firm should use 12 dosage units of the test product and the available 10 dosage units of the RLD of the testing"*. The firm was also asked to submit full analytical and dissolution method validation reports for its originally proposed in vitro release method as well as the most recently recommended method. Based on the careful consideration of the data from the firm's proposed and FDA recommended methods, the DBI will determine the most appropriate method and specifications for the test product. The latest DBI email dated March 12, 2012, including the above recommendations, is also attached in the current review document.

Since the DBI had already responded by email to the firm's emails containing submissions of preliminary in vitro drug release testing data, no additional communication to the firm is necessary at this time.

Therefore the firm should submit the comparative in vitro drug release testing results based on the latest DBI recommendations made on March 12, 2012. I In addition the firm also should submit its responses to the other deficiency comments made by the DBI in the letter dated Feb 16, 2012.

The application is **incomplete**.

2. TABLE OF CONTENTS

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3. BACKGROUND

The DBI has previously reviewed the original submission of the current ANDA and issued a deficiency letter to the firm on February 16, 2012. Subsequently, the firm contacted the Project Manager Teresa Ramson of the division and inquired additional guidance from the division regarding the FDA-recommended in vitro drug release testing method given to the firm in the deficiency letter. Due to the expedited status of the ANDA based on the current drug shortage, the DBI responded to the firm’s inquiry by email providing clarification on the method recommendation and asked the firm to conduct *preliminary* in vitro release testing using only the test product since the firm indicated that there was only a limited supply of the RLD available for testing (i.e., about 10 vial units). The *preliminary* data were submitted by email on March 7, 2012 and were reviewed by the DBI. Subsequently, based on the *preliminary* data submitted, the DBI provided additional details and suggested modifications of the recommended method. The DBI asked the firm to conduct additional *preliminary* testing based on the provided method details and suggested modifications of the method. The firm submitted the second set of *preliminary* data following the DBI’s advice. The DBI reviewed the second set of *preliminary* data, and recommended the firm conduct its official in vitro testing on both test and reference product using one of the procedures used in the *preliminary* testing.

The current amendment only included the first set of *preliminary* data.

4. REVIEW OF SUBMISSION

Deficiency Comment 5 From the DBI Letter Dated 02/16/2012 (Concerning the DBI Recommendation for Additional In Vitro Drug Release Testing Using the FDA Method): The comparative testing should be conducted on the test and reference product, using one dosage unit (vial) (10 mL of 2 mg/mL) per replicate and six samples taken per unit for six different time points: six samples of 1 mL of the vial content should be

transferred to six separate glass tubes containing the medium of 98% fetal bovine serum with 80 mM NH₄Cl at pH 6.0, to obtain the final sample volume of 100 mL. The resultant drug concentration should be 20 µg/mL of liposomal doxorubicin. The glass tubes should be incubated at 47 C without agitation. From these six glass tubes the amount of doxorubicin released from the liposome should be determined at the following six time points: 0 hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs. The testing should be replicated for 12 dosage vials per each test and the reference drug product.

The individual percent doxorubicin release data from each vial at each time point should be submitted, as well as the mean data from 12 vials at each time point for each product (% mean and % CV) over the period of 0 to 4 hours for the test and RLD from 12 dosage units.

Firm's Email Question Concerning the Above Deficiency (Sent 02/21/0212)

Sun Pharma has two questions concerning the recent BE deficiency.

1. Currently we have 10 vials of RLD 25ml. We do not have any stock of 10ml. For the current BE deficiency, FDA asked for 12 units to be used, however instead of using 12 units can we complete the study using 10 units(available with us) because non availability of RLD.

2A. In query no 5, FDA has asked for in-vitro release test. The medium specified is 98 % fetal bovine serum with 80mM NH₄Cl at pH 6.0

2B. Sun has prepared fetal bovine serum using following two methods, however in both cases the resultant pH is around 7.0

Option1

98 ml of 100% Fetal Bovine Serum (pH 7.10) + 2 ml of 80 mM Ammonium Chloride in water (pH 5.71) , pH of resulting final solution is 7.0.

Note: Ammonium Chloride in final solution is 1.6 mM

Option 2

98 ml of 100% Fetal Bovine Serum (pH 7.10) + 2 ml of 214 mg/ml Ammonium Chloride in water (pH 5.3), pH of resulting final solution is 7.0.

Note: Ammonium Chloride in final solution is 80 mM

3. In both the options pH of medium specified by FDA (PH 6.0) is not achieved, please provide clarification on composition of medium to be used for the study and whether any one of the above options are suitable for conducting this study.

DBI's Response to the Firm's 02/21/2012 Email Question (Sent 02/24/2012):

Since the availability of the RLD is limited, we recommend the firm conduct a preliminary drug release study using the 4 different conditions described below:

- i. With Option 1 medium (as described by Sun), at pH.7; -Medium1
- ii. With Option 1 medium (as described by Sun), but pH adjusted to pH 6.0 using hydrochloric acid; -Medium2
- iii. With Option 2 medium (as described by Sun), at pH 7.0; and -Medium3
- iv. With Option 2 medium (as described by Sun), but pH adjusted to pH 6.0 using hydrochloric acid.-Medium4

For each of these 4 conditions, please use 6 units of the Test product only, and submit the preliminary testing results to the Division of Bioequivalence I (DBI) for evaluation.

Based on the preliminary data submitted, if possible, the DBI will recommend the final drug release testing conditions, for which the official testing should be done using the available 10 units of the RLD and 12 units of the Test product.

Firm's Subsequent Response to the DBI's 02/14/2012 Email Comments (Sent 03/07/2012) – Content of the Current ANDA Amendment:

As per the FDA correspondence in vitro drug release study was conducted by using following four mediums.

Medium 1: 98% Fetal Bovine Serum (FBS) with 2ml 80mM Ammonium Chloride. Take 98 ml of FBS in a beaker and add 2 ml of 80 mM ammonium Chloride into it, mix well. (Resultant pH of medium - 6.86).

Medium 2: 98% Fetal Bovine Serum (FBS) with 2ml 80mM Ammonium Chloride. Take 98 ml of FBS in a beaker and add 2 ml of 80 mM ammonium Chloride into it, mix well. Adjusted the pH to 6.0 with 5M HCl.

Medium 3: 98% Fetal Bovine Serum (FBS) with 2ml 4M Ammonium Chloride. Take 98 ml of FBS in a beaker and add 2 ml of 4M ammonium Chloride into it, mix well. (Resultant pH of medium - 6.69).

Medium 4: 98% Fetal Bovine Serum (FBS) with 2ml 4M Ammonium Chloride. Take 98 ml of FBS in a beaker and add 2 ml of 4M ammonium Chloride into it, mix well. Adjusted the pH to 6.0 with 5M HCl.

For each of these four medium, six vials of Doxorubicin Liposomes, 2mg/ml, were taken and below procedure suggested by agency was followed.

“Six samples of 1 ml of the vial content were transferred to six separate glass tubes containing the medium to obtain the final sample volume of 100 ml. These glass tubes were incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome was determined at the following six time points; 0hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs.

The individual percent doxorubicin release data from each vial at each time, as well as the % mean with % CV data from 06 vials at each time over the period of 0 to 4 hours for all the four medium is compiled in below four tables. (Table 1, Table 2, Table 3, Table 4)

Note: Whole study has been performed using Doxorubicin Liposomes, 2mg/ml, 25 ml, Batch No: JKL0863A.

Table 1. % Release of Doxorubicin in Medium 1 (FBS Lot used: 1082735)

Vial	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
	Tube No.						
Vial 1	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
Vial 2	1						
	2						
	3						
	4						
	5						
	6						
Vial 3	1						
	2						
	3						
	4						
	5						
	6						
Vial 4	1						
	2						
	3						
	4						
	5						
	6						

Vial 5	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
Vial 6	1						
	2						
	3						
	4						
	5						
	6						
Mean		1.0908	1.4732	2.0125	2.8572	3.9216	4.4849
±S.D.		0.0651	0.1095	0.0957	0.1586	0.2425	0.1930
% CV		6.0	7.4	4.8	5.6	6.2	4.3

Table 2. % Release of Doxorubicin in Medium 2 (FBS Lot used: 1028022)

Vial	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
	Tube No.	(b) (4)					
Vial 1	1						
	2						
	3						
	4						
	5						
	6						
Vial 2	1						
	2						
	3						
	4						
	5						
	6						
Vial 3	1						
	2						
	3						
	4						
	5						
	6						

Vial 4	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
Vial 5	1						
	2						
	3						
	4						
	5						
	6						
Vial 6	1						
	2						
	3						
	4						
	5						
	6						
Mean		1.0724	1.1571	1.2309	1.4493	1.6081	1.8178
±S.D		0.0983	0.1255	0.0939	0.0936	0.1007	0.1087
% C.V.		9.2	10.8	7.6	6.5	6.3	6.0

Table 3. % Release of Doxorubicin in Medium 3 (FBS Lot used: 1082735)

Vial	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
	Tube No.						
Vial 1	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
Vial 2	1						
	2						
	3						
	4						
	5						
	6						

Vial 3	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
Vial 4	1						
	2						
	3						
	4						
	5						
	6						
Vial 5	1						
	2						
	3						
	4						
	5						
	6						
Vial 6	1						
	2						
	3						
	4						
	5						
	6						
Mean		1.3416	10.4594	20.1938	40.2175	61.4308	69.6519
±S.D		0.2578	0.7417	1.6662	2.8259	4.1229	3.6362
% C.V.		19.2	7.1	8.3	7.0	6.7	5.2

Table 4. % Release of Doxorubicin in Medium 4 (FBS Lot used: 1028022)

Vial	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
	Tube No.	(b) (4)					
Vial 1	1						
	2						
	3						
	4						
	5						
	6						

Vial 2	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
Vial 3	1						
	2						
	3						
	4						
	5						
	6						
Vial 4	1						
	2						
	3						
	4						
	5						
	6						
Vial 5	1						
	2						
	3						
	4						
	5						
	6						
Vial 6	1						
	2						
	3						
	4						
	5						
	6						
Mean	1.3247	4.7208	8.2759	16.3874	24.2866	32.2961	
±S.D	0.1833	0.2736	0.5079	1.0183	1.5114	2.0458	
% CV	13.8	5.8	6.1	6.2	6.2	6.3	

From the above data obtained, there is significant difference in the medium 4 where pH is adjusted to 6.0 with its parent medium 3. This significant difference may be due to change in pH or may be due to change in FBS lot, as we used different lot of FBS for preparation of Medium 4(1082022).

To confirm this, we planned following two experiments simultaneously

- I. In vitro release in Medium 4 using FBS lot 1082735, same as medium 3.
- II. In vitro release in Medium 3 using two different lots of FBS (1028022 & 953873)

I. In vitro release in Medium 4 using FBS lot 1082735, same as medium 3.

We planned above mentioned experiment in one tube from two different vials. Results for the same are given in Table no 5.

Table 5. % Release of Doxorubicin in Medium 4 (FBS Lot used: 1082735)

Time Point	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
Vial No						
1	(b) (4)					
2						
MEAN	1.44	4.03	7.49	13.83	18.52	24.04
±S.D.	0.19	0.26	0.47	0.71	0.71	0.58
%C.V.	13.3	6.5	6.2	5.1	3.8	2.4

II. In vitro release in Medium 3 using two different lots of FBS (1028022 & 953873)

We have conducted the drug release study using medium 3 (better drug release profile among the four different medium) with 2 additional lots of FBS (Lot 1028022 and Lot 953873). The drug release was performed in one tube each from 6 vials of drug product for both the lots. The drug release data using both the lots of FBS in medium 3 is as follows:

Table 6. % Release of Doxorubicin in Medium 3 (FBS Lot used: 1028022)

Time Point	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
Vial No						
1	(b) (4)					
2						
3						
4						
5						
6						
MEAN	1.662	14.550	27.784	54.114	73.679	81.391
±S.D.	0.116	0.783	0.812	1.913	2.305	1.859
%C.V.	7.0	5.4	2.9	3.5	3.1	2.3

Table 7. % Release of Doxorubicin in Medium 3 (FBS Lot used: 953873)

Time Point	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr
Vial No	(b) (4)					
1						
2						
3						
4						
5						
6						
MEAN	1.367	17.774	34.222	64.995	83.924	80.352
±S.D.	0.060	0.684	0.992	1.244	0.738	1.380
%C.V.	4.4	3.9	2.9	1.9	0.9	1.7

Drug release data from the table no 5, we conclude that there is significant effect of HCl or pH on drug release.

From data of drug release of table no 3, 6 and 7, we conclude that there is difference in drug release profile while using different lots of FBS.

Since we have sufficient quantity of FBS lot no 953873, Sun will perform the comparative drug release study using FBS lot no 953873, in medium which will be suggested by FDA

DBI's Email Response to the Firm's 03/07/2012 First Set of Preliminary Data Above (Sent 03/08/2012)

Based on the preliminary results submitted by the firm, we have revised the previous recommended method as follows:

1. The sample size should be reduced from 100 mL to 3 mL, i.e., 30 microliter of the drug product should be added to 2.97 mL of the FBS containing 80 mM of ammonium chloride at pH 6.0 (equivalent to Sun's Medium 4).
2. Adjustment to pH 6.0 should be done during the reagent preparation and again after adding the drug product.
3. For each time point, a separate tube of sample should be used.
4. There should be no agitation during sample incubation. However, at the end of incubation, the sample tubes should be mixed well prior to removing each aliquot for further analysis.
5. At the end of incubation, the sample tubes should be placed on ice for at least 5 minutes before sample analysis.
5. The total free doxorubicin per time point sample should be measured at the end of each incubation period by heating the respective sample tube in water bath at 72° C for 30 minutes.

6. If this method is eventually determined by the Agency to be appropriate for Sun's product, more control of the FBS lot variability is necessary as the test product may fail established specifications due to such variability. Exploring different manufacturers of FBS is encouraged.

7. As mentioned in the ANDA deficiency letter, the firm should submit full analytical and dissolution method validation reports for its originally proposed in vitro release method (including individual data for all samples tested). Sun's method will still be considered and evaluated in comparison with the FDA-recommended method.

8. With the above modifications, if the drug release for the test product is still inadequate (with incomplete release at around 4-5 hours) at exactly pH 6.0, then pH adjustment step may be omitted for achieving approximately (b)(4)% drug release within 4-5 hours (or equivalent to Medium 3). However, if it is found that, during this round of preliminary testing with procedure modifications, without pH adjustment to 6.0, the drug release is much greater than (b)(4)% in 4-5 hours, slightly lowering the pH may be necessary.

We recommend the firm conduct another round of preliminary testing as suggested above, using 6 units of the Test product only, and submit the second sets of preliminary results to the Division of Bioequivalence I (DBI) for evaluation. The DBI does not expect to recommend any additional significant modifications to the testing following this second round of testing, provided that complete release (about (b)(4)% within 4-5 hours) can be achieved based on the above recommended conditions.

Firm's Email Submission of the Second Set of *Preliminary* Data (Sent 03/12/2012)

Above revised recommended sample size i.e. 30 microliter of drug product in 2.97 ml of FBS was adopted for all the experiments. The six vials/units of drug product, Doxorubicin Liposome 2 mg/ml, 25ml (Batch No. JKL0863) has been used in all the below experiments.

Experiment No. 1:

Experiment 1 was performed by using Sun's Medium 4 and the pH was adjusted during reagent preparation and again after addition of drug product to 6.0. For each time point a separate tube has been used. The release performed with no agitation during the incubation at 47°C and the sample tubes were gently shaken prior to withdrawal of aliquot for the analysis. Each sample tube after incubation at 47°C and withdrawal of aliquot of respective time points was subjected to 72°C for 30 minutes. At each time point the sample tubes were placed in ice for 5 minutes before the analysis at incubation temperature i.e. 47°C and 72°C. The drug release in Sun's Medium-4 has been performed and data is given in Table-01.

Table-01: % Drug release in Sun's Medium 4 (pH adjusted during reagent preparation and after drug addition at 6.0)

Temperature	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
	Vial No/Unit No							
47°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	1.358	7.364	12.407	22.905	33.121	42.388	54.637
	±S.D.	0.146	0.294	0.443	0.822	0.644	0.806	5.618
	%C.V.	10.7	4.0	3.6	3.6	1.9	1.9	10.3
72°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	77.154	78.297	78.382	80.335	75.045	75.172	71.040
	±S.D.	2.528	2.792	1.519	2.317	2.148	1.769	1.910
	%C.V.	3.3	3.6	1.9	2.9	2.9	2.4	2.7

The above study results shows that approximate 54% of the drug release is obtained up to 5 hrs, when samples were incubated at 47°C, therefore another experiment was planned.

Experiment No.:2

Experiment 2 was performed in Sun's Medium 3 with the same procedure adopted in Experiment No.1. The data of drug release in Sun's Medium3 is given in Table-02.

Table-02: % Drug release in Sun's Medium 3

Temperature	Time Point --->	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
	Vial No/Unit No							
47°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	1.157	22.642	43.960	80.218	91.751	85.524	80.761
	±S.D.	0.062	1.046	0.329	3.234	1.484	1.152	2.205
	%C.V.	5.4	4.6	0.7	4.0	1.6	1.3	2.7
72°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	77.482	70.924	72.662	67.989	66.273	58.852	54.641
	±S.D.	2.071	1.307	0.771	1.847	1.516	1.368	0.411

Drug release in Sun's medium 3 shows much faster drug release, about 91 % within 3 hrs whereas after 4 and 5 hrs drop in drug release is observed, which may be because of degradation, therefore as per FDA's recommendation to achieve the desired drug release (Approximate (b) (4) % within 4-5 hours), we have taken the trials with lowering the pH of Sun's Medium3 and found that Sun's Medium 3 with pH around 6.5±0.1 (before addition of drug product) shows desired drug release i.e. approximately (b) (4) % drug release within 4- 5 hours (Refer Table-03).

Table-03: % Drug release in Sun's Medium 3 with pH 6.5 ± 0.1

Temperature	Time Point --- >	0 Hr	0.5 Hr	1 Hr	2 Hr	3 Hr	4 Hr	5 Hr
	Vial No/Units							
47°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	1.25	14.24	26.56	51.66	73.43	85.13	80.08
	±S.D.	0.16	0.66	1.31	1.97	1.5	3.14	1.7
	%C.V.	12.8	4.6	4.9	3.8	2.0	3.7	2.1
72°C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	MEAN	67.34	68.04	65.36	65.18	66.11	63.93	59.04
	±S.D.	0.98	0.69	1.08	1.62	3.32	1.28	1.13
	%C.V.	1.5	1.0	1.7	2.5	5.0	2.0	1.9

As shown in Table-03, the desired drug release profile is achieved up to 4 hrs and then the release drops at 5 hrs. Therefore the drug release in Sun's Medium3 at pH around 6.5±0.1 up to 4 hrs is seems to be suitable to perform comparative testing on the Test and Reference product.

DBI's Email Response to the Firm's 03/12/2012 Second Set of Preliminary Data Above (Sent 03/12/2012)

1. Based on the second set of preliminary data provided to us today, March 12, 2012, we recommend that the firm conduct the in vitro drug release testing for its ANDA using Sun's Medium 3 with pH adjusted to 6.5 +/- 0.1. The testing should be done using other testing conditions described in the firm's latest correspondence (i.e., in the attachment of its March 12, 2012 email), including the same sampling times. The firm should use 12 dosage units of the test product, and the available 10 dosage units of the RLD of the testing.
2. Along with the individual and mean release results, the firm should provide a detailed analytical method validation report, and a detailed dissolution testing report for the recommended method.
3. As requested previously in the ANDA deficiency letter, the firm should submit full analytical and dissolution method validation reports for its originally proposed in vitro release method (including individual data for all samples tested). Sun's method will still be considered and evaluated in comparison with the FDA-recommended method.

4. Based on careful consideration of the data from both methods, the DBI will determine the most appropriate method and specifications for the test product.

5. RECOMMENDATION

Since the DBI had already responded to the firm's emails listed above, including the 03/07/2012 email containing the exact content provided in the current amendment, the DBI does not conduct additional review of the preliminary data at this time. No additional communication to the firm is deemed necessary.

Attachments:

Email Correspondence between DBI and Sun Pharma

From: Ramson, Teresa
Sent: Monday, March 12, 2012 3:27 PM
To: 'Robert.Kurkiewicz@caraco.com'
Subject: RE: BE-Defi Doxorubicin HCl liposome Inj. ANDA 203263

1. Based on the second set of preliminary data provided to us today, March 12, 2012, we recommend that the firm conduct the in vitro drug release testing for its ANDA using Sun's Medium 3 with pH adjusted to 6.5 +/- 0.1. The testing should be done using other testing conditions described in the firm's latest correspondence (i.e., in the attachment of its March 12, 2012 email), including the same sampling times. The firm should use 12 dosage units of the test product, and the available 10 dosage units of the RLD of the testing.
2. Along the individual and mean release results, the firm should provide a detailed analytical method validation report, and a detailed dissolution testing report for the recommended method.
3. As requested previously in the ANDA deficiency letter, the firm should submit full analytical and dissolution method validation reports for its originally proposed in vitro release method (including individual data for all samples tested). Sun's method will still be considered and evaluated in comparison with the FDA-recommended method.
4. Based on careful consideration of the data from both methods, the DBI will determine the most appropriate method and specifications for the test product.

Thanks,

Teresa

From: Robert.Kurkiewicz@caraco.com [mailto:Robert.Kurkiewicz@caraco.com] **On Behalf Of** RobertKurkiewicz/Caraco%CARACO@CARACO.COM
Sent: Monday, March 12, 2012 10:05 AM
To: Ramson, Teresa; Chuh, Esther
Subject: Fw: BE-Defi Doxorubicin HCl liposome Inj. ANDA 203263

----- Forwarded by Robert Kurkiewicz/CARACO on 03/12/2012 10:00 AM -----

Date: 03/12/2012 09:48 AM
Subject: Re: Fw: BE-Defi Doxorubicin HCl liposome Inj. ANDA 203263

Please find attached results of studies conducted in accordance with below mail.

The method validation report for Sun originally proposed in-vitro release test has been provided in original ANDA in section 3.2.P.5.3 (file name 'In vitro release analytical method validation report').

Please provide final method for performing comparative in-vitro release testing on priority owing to nearing expiry of RLD samples.

Thanks,

Bob

Robert Kurkiewicz
US Agent
Sun Pharmaceutical Industries, Ltd.
C/O Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Dr.
Detroit, MI 48202
313-556-4105
Fax 248-926-0231

From: RobertKurkiewicz/Caraco@CARACO
To: Abhay Muthal/REGULATORY AFFAIRS/TANDALJA/SPIL@SPIL, Nayna Daptardar/REGULATORY AFFAIRS/TANDALJA/SPIL@SPIL, Vipul Doshi/CQ/TANDALJA/SPIL@SPIL, GP Singh Sachdeva/Sales and Marketing/CARACO@CARACO
Date: 08/03/2012 11:11 PM
Subject: Fw: BE-Defi Doxorubicin HCl liposome Inj. ANDA 203263
Sent by: Robert Kurkiewicz@CARACO

----- Forwarded by Robert Kurkiewicz/CARACO on 03/08/2012 12:33 PM -----

From: "Ramson, Teresa" <Teresa.Ramson@fda.hhs.gov>
To: ""Robert.Kurkiewicz@Caraco.com"" <Robert.Kurkiewicz@Caraco.com>
Cc: "Chuh, Esther" <Esther.Chuh@fda.hhs.gov>
Date: 03/08/2012 12:29 PM
Subject: RE: BE-Defi Doxorubicin HCl liposome Inj. ANDA 203263
Hello Mr. Kurkiewicz,

Based on the preliminary results submitted by the firm, we have revised the previous recommended method as follows:

1. The sample size should be reduced from 100 mL to 3 mL, i.e., 30 microliter of the drug product should be added to 2.97 mL of the FBS containing 80 mM of ammonium chloride at pH 6.0 (equivalent to Sun's Medium 4).
2. Adjustment to pH 6.0 should be done during the reagent preparation and again after adding the drug product.
3. For each time point, a separate tube of sample should be used.
4. There should be no agitation during sample incubation. However, at the end of incubation, the sample tubes should be mixed well prior to removing each aliquot for further analysis.
5. At the end of incubation, the sample tubes should be placed on ice for at least 5 minutes before sample analysis.
5. The total free doxorubicin per time point sample should be measured at the end of each incubation period by heating the respective sample tube in water bath at 72C for 30 minutes.
6. If this method is eventually determined by the Agency to be appropriate for Sun's product, more control of the FBS lot variability is necessary as the test product may fail established specifications due to such variability. Exploring different manufacturers of FBS is encouraged.
7. As mentioned in the ANDA deficiency letter, the firm should submit full analytical and

dissolution method validation reports for its originally proposed in vitro release method (including individual data for all samples tested). Sun's method will still be considered and evaluated in comparison with the FDA-recommended method.

8. With the above modifications, if the drug release for the test product is still inadequate (with incomplete release at around 4-5 hours) at exactly pH 6.0, then pH adjustment step may be omitted for achieving approximately (b) (4) % drug release within 4-5 hours (or equivalent to Medium 3). However, if it is found that, during this round of preliminary testing with procedure modifications, without pH adjustment to 6.0, the drug release is much greater than (b) (4) % in 4-5 hours, slightly lowering the pH may be necessary.

We recommend the firm conduct another round of preliminary testing as suggested above, using 6 units of the Test product only, and submit the second sets of preliminary results to the Division of Bioequivalence I (DBI) for evaluation. The DBI does not expect to recommend any additional significant modifications to the testing following this second round of testing, provided that complete release (about (b) (4) % within 4-5 hours) can be achieved based on the above recommended conditions.

Thanks,
Teresa

From: Robert.Kurkiewicz@caraco.com [<mailto:Robert.Kurkiewicz@caraco.com>] On Behalf Of RobertKurkiewicz/Caraco%CARACO@CARACO.COM
Sent: Wednesday, March 07, 2012 9:13 AM
To: Ramson, Teresa; Chuh, Esther
Subject: Fw: BE-Defi Doxorubicin HCl liposome Inj. ANDA 203263

Please find attached report of preliminary study conducted in accordance with following mail from FDA. We will submit this data officially as a telephone amendment.

Please provide feedback on media to be used for final study on priority, as RLD samples on which this study is to be done are having expiry date of March 2012.

----- Forwarded by Robert Kurkiewicz/CARACO on 02/24/2012 11:26 AM -----

From: "Ramson, Teresa" <Teresa.Ramson@fda.hhs.gov>
To: "'Robert.Kurkiewicz@Caraco.com'" <Robert.Kurkiewicz@Caraco.com>, "Chuh, Esther" <Esther.Chuh@fda.hhs.gov>
Date: 02/24/2012 11:09 AM
Subject: RE: BE-Def Doxorubicin HCl liposome Inj. ANDA 203263

Hello Mr. Kurkiewicz,

Please be informed of the following:

Since the availability of the RLD is limited, we recommend the firm conduct a *preliminary* drug release study using the 4 different conditions described below:

- (i) With Option 1 medium (as described by Sun), at pH.7;
- (ii) With Option 1 medium (as described by Sun), but pH adjusted to pH 6.0 using hydrochloric acid;
- (iii) With Option 2 medium (as described by Sun), at pH 7.0; and
- (iv) With Option 2 medium (as described by Sun), but pH adjusted to pH 6.0 using hydrochloric acid.

For each of these 4 conditions, please use 6 units of the Test product only, and submit the preliminary testing results to the Division of Bioequivalence I (DBI) for evaluation. Based on the preliminary data submitted, if possible, the DBI will recommend the final drug release testing conditions, for which the official testing should be done using the available 10 units of the RLD and 12 units of the Test product.

Teresa

From: Robert.Kurkiewicz@caraco.com [<mailto:Robert.Kurkiewicz@caraco.com>] **On Behalf Of** RobertKurkiewicz/Caraco%CARACO@CARACO.COM
Sent: Tuesday, February 21, 2012 11:42 AM
To: Chuh, Esther; Ramson, Teresa
Subject: BE-Defi Doxorubicin HCl liposome Inj. ANDA 203263

Sun Pharma has two questions concerning the recent BE deficiency.

1. Currently we have 10 vials of RLD 25ml. We do not have any stock of 10ml. For the current BE deficiency, FDA asked for 12 units to be used, however instead of using 12 units can we complete the study using 10 units(available with us) because non availability of RLD.

2.

A. In query no 5, FDA has asked for in-vitro release test. The medium specified is 98 % fetal bovine serum with 80mM NH₄Cl at pH 6.0

B. Sun has prepared fetal bovine serum using following two methods, however in both cases the resultant pH is around 7.0

Option1

98 ml of 100% Fetal Bovine Serum (pH 7.10) + 2 ml of 80 mM Ammonium Chloride in water (pH 5.71) , pH of resulting final solution is 7.0

Note : Ammonium Chloride in final solution is 1.6 mM

Option 2

98 ml of 100% Fetal Bovine Serum (pH 7.10) + 2 ml of 214 mg/ml Ammonium Chloride in water (pH 5.3) , pH of resulting final solution is 7.0

Note : Ammonium Chloride in final solution is 80 mM

Reagents used are as follows :

Fetal Bovine Serum, Certified,
Origin: United States

Ammonium Chloride:

AR Grade
Assay 99.8%
Mol Wt 53.49

3. In both the options pH of medium specified by FDA (PH 6.0) is not achieved, please provide clarification on composition of medium to be used for the study and whether any one of the above options are suitable for conducting this study.

Thank for your assistance.

Regards,

Bob
Robert Kurkiewicz
US Agent
Sun Pharmaceutical Industries, Ltd.
C/O Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Dr.
Detroit, MI 48202
313-556-4105
Fax 248-926-0231

6. OUTCOME PAGE

ANDA: 203263

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
16499	3/7/2011	Other	Study Amendment	1	1
				Bean Total:	1

NOTE: The review of the data submitted in the current amendment was done earlier and the DBI responses based on the review were given to the firm through email.

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

/s/

SUMAN DANDAMUDI
04/02/2012

SHRINIWAS G NERURKAR
04/03/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
04/03/2012

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	203263		
Drug Product Name	Doxorubicin hydrochloride Liposome Injection		
Strength(s)	2 mg/mL, 10 mL and 25 mL		
Applicant Name	Sun Pharma Global FZE		
Applicant Address	Office # 43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U.A.E		
US Agent Name and the mailing address	Vincent Andolina Sun Pharmaceutical Industries, Inc., 270 Prospect Plains Road Cranbury, NJ 08512		
US agent's Telephone Number	609-495-2808		
US Agent's Fax Number	609-495-2711		
Original Submission Date(s)	June 16, 2011		
Submission Date(s) of Amendment(s) Under Review	N/A		
First Generic (Yes or No)	No		
Reviewer	Suman Dandamudi		
Study Number (s)	PKD_09_030	DOX/003/08	FDD-02/10-11/001
Study Type (s)	Fed	Pilot Fed	In-Vitro
Strength (s)	2 mg/mL	2 mg/mL	2 mg/mL
Clinical Site-1	MNJ Institute of Oncology & Regional Cancer Centre		
Clinical Site-1 Address	Red Hills, Hyderabad- 500 004, India		
Clinical Site-2	Kailash Cancer Hospital & Research Centre		
Clinical Site-2 Address	Goraj, Vadodara- 391760, India		
Clinical Site-3	Dr. G. Vishwanathan Speciality Hospitals		
Clinical Site-3 Address	#27, Babu road, Trichy, Tamilnadu- 620 008, India		
Clinical Site-4	Dr. Kamakshi Memorial Hospital		
Clinical Site-4 Address	No.1, Radial Road, Palikaranai, Chennai- 600 100, India		
Clinical Site-5	NRR Hospital		
Clinical Site-5 Address	Chikkasandra, Bangalore- 560090 (India)		
Analytical Site (fed study)	Sun Pharmaceutical Industries Ltd.,		
Analytical Site Address (fed study)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India		
Analytical Site	Sun Pharmaceutical Industries Ltd.,		
Analytical Site Address	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India		
In Vitro Liposome Size Distribution Testing Site	Sun Pharmaceutical India Ltd.		

In Vitro Testing Site Address	Sun Pharmaceutical India Ltd. Halol-Baroda Highway Halol-389350 Gujarat India		
OSI Status			
REVIEW RESULT	INADEQUATE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	DISSOLUTION	2 MG/ML	INADEQUATE
1	FED STUDY	2 MG/ML	INADEQUATE

1 EXECUTIVE SUMMARY

This is a first generic application.

The submission references NDA 050718, DOXIL ® (Doxorubicin Hydrochloride) Injection, Liposomal, from Ortho Biotech.

DOXIL (Doxorubicin HCl Liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in STEALTH® liposomes for intravenous administration.

DOXIL is provided as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The STEALTH® liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity.

This application contains the results of fed (low-fat breakfast¹) bioequivalence (BE) study comparing the test product, Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL to the corresponding reference product, Ortho Biotech’s Doxil® Injection, Liposomal. The fed study was designed as a single-dose, two-way crossover in ovarian cancer female patients. As per the *a priori* condition mentioned in the protocol there is difference in the number of subjects used for the measurement of free doxorubicin and liposomal doxorubicin. The results are summarized in the tables below:

¹ “Low fat breakfast” as specified in the RLD (Doxil®) labeling.

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Free Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *ng/ml)	22488.86	41	21297.24	41	1.06	92.26	120.86
AUC _∞ (hr *ng/ml)	24505.50	38	22890.91	34	1.07	92.92	123.33
C _{max} (ng/ml)	235.21	41	237.10	41	0.99	85.11	115.63

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Liposomal Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	3265.36	24	2940.69	24	1.11	99.64	123.74
AUC _∞ (hr * µg /ml)	3525.19	24	3414.60	22	1.03	95.71	111.36
C _{max} (µg /ml)	35.17	24	34.75	24	1.01	96.04	106.67

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Total Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	3200.49	24	3009.51	24	1.06	95.81	118.04
AUC _∞ (hr * µg /ml)	3320.84	23	3371.12	22	0.99	90.80	106.87
C _{max} (µg /ml)	33.29	24	33.21	24	1.00	95.36	105.35

However, the fed study is **incomplete** due to deficiencies related to analytical parts of the study.

The firm also submitted the results of in vitro Liposome Size Distribution Study comparing three lots of the test product with 3 lots of reference product. However, the in vitro equivalence study is incomplete pending the firm's submission of in vitro testing data in the Electronic SAS Transport format.

The DBE did not conduct a “dissolution/in vitro drug release only” review on this ANDA. This reviewer is conducting it in this document. There is no USP method for this test product. The external dissolution database for Doxorubicin Hydrochloride Liposome Injection recommends the firm’s to develop a method to characterize in vitro release. The firm conducting comparative drug release testing using its own proposed method [Bottle Rotating Apparatus in 90 mL of USP phosphate buffer pH 6.4 (b) (4) (b) (4) at a speed of 12 rpm at 52°C].

Currently, DBE does not encourage the use of non compendial apparatus/method. Since bottle rotating apparatus is not a compendial apparatus, as per DBE policy the firm’s proposed method is not acceptable. (b) (4)

The firm is recommended to conduct additional in vitro drug release testing (b) (4) for comparison. In addition, it is requested to submit all detailed information concerning the development, optimization and validation of its own test method and the recommended test method.

OSI Inspection:

The fed BE study was conducted at multiple clinical sites. On April 20, 2011, new-site inspection is requested for the clinical sites: MNJ Institute of Oncology & Regional Cancer Center, Hyderabad and Dr. Kamakshi Memorial Hospital for ANDA 201742, and the results of this inspection is still pending [DARRTS for ANDA 201742: SOLANA-SODEINDE, DIANA A 04/27/2011 N/A 04/27/2011 FRM-CONSULT-09(DSI Bioequivalence Audit Request) Original-1 (Not Applicable) Archive.

The other three sites are the new sites and there is no pre-existing OSI inspection history for these three sites: Kailash Cancer Hospital and Research Center, Dr. G. Vishwanathan Speciality Hospitals and NRR Hospital.

No	Name of Clinical Site	Group number/Site ID	Number of Patients	OSI Inspection
1	MNJ Institute of Oncology & Regional Cancer Center, Hyderabad	1/A	31	Pending a new-site inspection
2	Kailash Cancer Hospital and research Center, Goraj, Vadidara	2/B	5	
3	Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu	3/D	11	Pending a new-site inspection
4	Dr. Kamakshi Memorial Hospital Pvt. Ltd., Chennai	4/E	4	
5	NRR Hospital, Bangalore	5/G	9	Inspection to be requested

Based on the number of enrolled patients at each site stated above, the DB I requests that OSI inspections be conducted at least three sites with the highest numbers of enrolled patients. However, two of the three sites are currently pending new-site inspections, the DB I requests only one additional new-site inspection for NRR Hospital, Bangalore India.

The analytical site was inspected for ANDA 090886 on 2/25/2011 and the outcome was NAI [The OSI report is not in the DARRTS till today (01/06/2012) but the information is on this site

[http://fdswv04385/bioproduct/Bioequivalence Project Management/Interface/ASPTTest/DSI/dsiresearch.asp](http://fdswv04385/bioproduct/Bioequivalence%20Project%20Management/Interface/ASPTTest/DSI/dsiresearch.asp).

The analytical site was also inspected for ANDA’s 090745, 090178 and 090362 and the outcome was VAI [DARRTS: BISWAS, GOPA 06/17/2010 N/A 06/17/2010 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 Archive]. The OSI issued a form 483 with 6 deficiencies (1, 2A, 2B, 3A, 3B and 3C). Three (1, 2A and 2B) of these 6 deficiencies were systemic but they were so minor that by the OSI’s conclusion did not compromise the BE study data in the ANDA 090745. Moreover, the firm provided adequate response to these 6 deficiencies and promised to install additional corrective actions on **May 4, 2010**. These 3 systemic deficiencies were i) no incurred samples, ii) no electronic signature on the electronic data record, and iii) physical access to the data was not limited to authorized personnel. These systemic deficiencies may be applicable to this ANDA 203263. However they are also considered minor by the current BE reviewer. The findings might have been corrected at the time of the sample analysis for the current ANDA (The samples in this ANDA (b) (4) were analyzed after **May 4, 2010** (i.e., from 9/14/2011 to 3/6/2011). Thus, the OSI report **should not have** any effect on the integrity of the analytical studies submitted in this ANDA (b) (4).

For in vitro liposome size distribution testing, the site was Sun Pharmaceutical India Ltd. Halol-Baroda Highway, Halol-389350 Gujarat India. This site has not been inspected for such testing. Therefore, the DB I requests a routine OSI inspection for this site.

The application is **Inadequate**.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information^{2, 3}

Test Product	Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL
Reference Product	Doxil® Injection, Liposomal, 20 mg/10 mL and 50 mg/25 mL
RLD Manufacturer	Ortho Biotech
NDA No.	050718
RLD Approval Date	November 17, 1995 (20 mg/10 mL) June 13, 2000 (50 mg/25 mL)
Indication	Doxil® is indicated • For the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy. • For treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy. • In combination with bortezomib is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

² Online-Orange Book (2011). <http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm>

³ Labeling for the RLD Product

3.2 PK/PD Information^{3, 4}

Bioavailability	DOXIL displayed linear pharmacokinetics over the range of 10 to 20 mg/m². Disposition occurred in two phases after DOXIL administration, with a relatively short first phase (≈ 5 hours) and a prolonged second phase (≈ 55 hours) that accounted for the majority of the area under the curve (AUC). The pharmacokinetics of DOXIL at a 50 mg/m² dose is reported to be nonlinear. At this dose, the elimination half-life of DOXIL is expected to be longer and the clearance lower compared to a 20 mg/m² dose. The exposure (AUC) is thus expected to be more than proportional at a 50 mg/m² dose when compared with the lower doses.
Food Effect	Not applicable.
T_{max}	Not available.
Metabolism	Doxorubicinol, the major metabolite of doxorubicin, was detected at very low levels (range of 0.8 to 26.2 ng/mL) in the plasma of patients who received 10 or 20 mg/m ² DOXIL.
Excretion	The plasma clearance of DOXIL was slow, with a mean clearance value of 0.041 L/h/m² at a dose of 20 mg/m². This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24 to 35 L/h/m². Because of its slower clearance, the AUC of DOXIL, primarily representing the circulation of liposome-encapsulated doxorubicin, is approximately two to three orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin HCl as reported in the literature.
Half-life	5 hours (1 st phase) and 55 hours (2 nd phase) for the liposomal doxorubicin (See Bioavailability Section above)
Dosage and Administration	Patients with Ovarian Cancer: DOXIL (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 50 mg/m² (doxorubicin HCl equivalent) at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related adverse reactions are observed, the rate of infusion can be increased to complete administration of the drug over one hour. The patient should be dosed once every 4 weeks, for as long as the patient does not progress, shows no evidence of cardiotoxicity and continues to tolerate treatment. A minimum of 4 courses is recommended. Patients with AIDS-Related Kaposi Sarcoma: DOXIL (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 20 mg/m². An initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over one hour. The dose should be repeated once every three weeks, for as long as patients respond satisfactorily and tolerate treatment.

⁴ <http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=762&sec=monphar>

	Patients with Multiple Myeloma: Bortezomib is administered at a dose of 1.3 mg/m² as intravenous bolus on days 1, 4, 8 and 11, every three weeks. DOXIL 30 mg/m² should be administered as a 1-hr intravenous infusion on day 4 following bortezomib. With the first DOXIL dose, an initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over one hour. Patients may be treated for up to 8 cycles until disease progression or the occurrence of unacceptable toxicity.
Maximum Daily Dose	50 mg/ m² IV every 4 weeks
Drug Specific Issues (if any)	Boxed Warning: WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION 1. The use of DOXIL (doxorubicin HCl liposome injection) may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at a starting dose of 50 mg/m² every 4 weeks. At all cumulative anthracycline doses between 450–500 mg/m² or between 500–550 mg/m², the risk of cardiac toxicity for patients treated with DOXIL was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy. 2. Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. DOXIL should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions. 3. Severe myelosuppression may occur. 4. Dosage should be reduced in patients with impaired hepatic function. 5. Accidental substitution of DOXIL for doxorubicin HCl has resulted in severe side effects. DOXIL should not be substituted for doxorubicin HCl on a mg per mg basis. Doxil is a pregnancy category D drug, can cause fetal harm when administered to a pregnant woman.

3.3 OGD Recommendations for Drug Product

When the test and reference pegylated liposome products

- have the same drug product composition and

- are manufactured by an active liposome loading process with an ammonium sulfate gradient and
- have equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage rates.

Number of studies recommended:	2, fasting and Liposome Size Distribution

1.	Type of study:	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	50 mg/vial
	Dose	50 mg/m ²
	Subjects:	Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy
	Additional Comments:	Patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of Doxil should not be entered into the study. Females should not be pregnant or lactating. Other exclusion criteria include: total cumulative dose of doxorubicin HCl approaches 550 mg/m ² ; patient is < 18 years of age or > 75 years of age; active opportunistic infection with mycobacteria, cytomegalovirus, toxoplasma, P. carinii or other microorganism if under treatment with myelotoxic drugs; clinically significant cardiac, liver or kidney disease

* If the health conditions of patients prevent fasting, the sponsor can provide a non-high-fat diet during the proposed study. Alternatively, the treatment can be initiated 2 hours after a standard (non-high-fat) breakfast

Analytes to measure (in plasma/serum/blood):	free doxorubicin and liposome encapsulated doxorubicin in plasma
Bioequivalence based on:	(90% CI) free doxorubicin and liposome encapsulated doxorubicin
Waiver request of in-vivo testing:	N/A

2.	Type of study:	Liposome Size Distribution
	Design:	In vitro bioequivalence study on at least three lots of both test and reference products
	Parameters to measure:	D10, D50, D90
	Bioequivalence based on (95% CI)	Population bioequivalence based on D50 and SPAN (D90-D10)/D50 or polydispersity index

Source of most recent recommendations:	Based on Guidance for Industry: Individual product Bioequivalence Recommendations; Feb 2010. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf .

Summary of OGD or DBE History	Currently there are no approved generic products of Doxorubicin Hydrochloride Liposome Injection listed in the Orange Book.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fed Pilot	Yes	1
Single-dose fed	Yes	1
Steady-state		
In vitro dissolution	Yes	1
Waiver requests		
BCS Waivers		
Clinical Endpoints		
Failed Studies		
Amendments		

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte 1 Location in Report (Module, Section, Page)	Analyte 1 Location in Report (Module, Section, Page)
Bioanalytical method validation report location	Section 5-3-1-4	Section 5-3-1-4
Study Report Number	Report No.: MV/F-DXR/141	Report No.:PMV/F-DXR/141B
Analyte	Free Doxorubicin	Free Doxorubicin
Internal standard (IS)	(b) (4)	(b) (4)
Method description	High performance liquid chromatography method using Tandem mass spectrometry detection has been used for determination of free doxorubicin in human K3 EDTA plasma using solid phase extraction method (see below for details)	High performance liquid chromatography method using Tandem mass spectrometry detection has been used for determination of free doxorubicin in human K3 EDTA plasma using solid phase extraction method (see below for details)
Limit of quantitation	LLOQ : 5.00 ng/mL ULOQ : 1499.94 ng/mL	LLOQ : 5.03ng/mL, ULOQ : 1483.34 ng/mL
Anticoagulant Used	K3EDTA	K3EDTA
LLOQ Intraday precision (%)	19.5%	6.2%
LLOQ Intraday accuracy (%)	4.8%	-0.6%
LLOQ Interday precision (%)	-	-
LLOQ Interday accuracy (%)	-	-
% recovery (and %CV) at each concentration tested	QC Low : 64.8%, %CV- 7.5 QC Med A: 78.9%, %CV- 2.7 QC Med B: 73.3%, %CV- 4.3 QC High : 75.5%, %CV- 3.8	QC Low A: 104.5%, %CV-5.4 QC Low B: 104.0%, %CV-3.9 QC Med A: 105.4%, %CV-4.0 QC Med B: 110.7%, %CV-1.2 QC High : 105.2%, %CV-6.1
Average recovery of IS (%)	77.2%, %CV- 6.7	106.4%, %CV-5.3

Standard curve concentrations (units/mL)	5.00, 10.00, 20.00, 50.00, 125.00, 249.99, 499.98, 749.97, 999.96, 1499.94 ng/mL	5.03, 10.06, 20.11, 50.28, 125.71, 251.41, 502.83, 754.24, 1005.65, 1483.34 ng/mL
QC concentrations (units/mL)	Low QC : 15.00 ng/mL, Medium QC A : 299.99 ng/mL, Medium QC B : 599.98 ng/mL, High QC : 1199.96 ng/mL	QC Low-A: 15.08 ng/mL, QC Low-B: 45.25 ng/mL, QC Med-A: 301.70 ng/mL, QC Med-B:603.39 ng/mL, QC High: 1206.78 ng/mL
QC Intraday precision range (%)	2.6% to 8.6%	2.6% to 8.6%
QC Intraday accuracy range (%)	-6.1% to 9.4%	-6.1% to 9.4%
QC Interday precision range (%)	6.7% to 9.3%	2.6% to 4.6%
QC Interday accuracy range (%)	-3.0% to 3.7%	-6.7% to 5.3%
Bench-top stability (hrs)	18 hours at room temperature	
	22 hours at room temperature in cartridges in presence of co administered drug	
Stock stability (days)	172 days @ 2-8°C	317 Days @ 2-8°C
Processed stability (hrs)	53 hours @ 10°C ± 2°C	
Freeze-thaw stability (cycles)	03 cycles	
Long-term storage stability (days)	111 days @ -20±5°C (in Human EDTA K ₃ Plasma)	
	170 days @ -2-8°C (in presence of Co-administered drug in HLB Cartridges)	
Dilution integrity (concentration, percent CV) dilution factor, accuracy	3 times of CS10 concentration (4999.81ng/mL) diluted 5 folds.	
	%Difference : 1/5 th : 2.7	
	% Precision : 1/5 th : 3.1	
Selectivity	No interference observed in blank plasma samples	No interference observed in blank plasma samples

For combination products: Did the matrix include all analytes?	All patients who were dosed the study drug had received Dexamethasone and Granisetron Injection before starting infusion. Therefore, effect of the co-administered drugs on the analyte response was evaluated. No significant interference was observed at the retention time of analyte and internal standard	N/A

SOPs submitted	Yes
Was the % recovery consistent across QC concentrations?	Yes (the difference in the recovery of analyte between the QC samples is less than 15%)
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	Yes
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	No study samples were diluted
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	No study samples were diluted
Does the duration of the each of the stability parameters support the sample preparation and assay dates	Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	Yes

Sample preparation:

(b) (4)

Solid Phase Extraction Procedure:

(b) (4)

Reviewer's comments:

- The principle of solid phase extraction technique functions to retain the free doxorubicin on the stationary phase of Hydrophilic Lipophilic Balance (HLB) cartridge. Binding of free doxorubicin to stationary phase is related to adsorption phenomenon. So free doxorubicin can be retained on stationary phase where liposome entrapped doxorubicin cannot be retained.
- The firm performed several partial validation studies for free doxorubicin, under different experimental conditions. However, the reviewer in the current review included only data for the validation studies that were conducted under the experimental condition similar to that of the actual study sample analysis.
- Partial validation (Report No: PMV/F-DXR/141B) was performed, since there was modification in the extraction procedure and chromatographic conditions. For example, (b) (4)

During this partial validation, between and with-in run accuracy and precision and the recovery of analyte and internal standard were evaluated. The mean percent recovery values of free doxorubicin and (b) (4) 105.96% and 106.4%, respectively. Even though the values are slightly greater than 100%, they are consistent among the QC concentrations. The reviewer noticed that with the change in the extraction procedure the extraction efficiency of the analyte improved. The mean percent recovery of free doxorubicin increased from 73.1% (original validation) to 105.96% (partial validation for change in extraction procedure).
- The firm used K₃EDTA as anticoagulant in their fed BE study. So they conducted pre-study and with-in study validation using plasma containing K₃EDTA as the matrix. The calibration standards and quality control samples were prepared with human plasma containing K₃EDTA.
- The firm conducted partial validation (Report No PMV/F-DXR/141) for the confirmation of extraction method **to estimate only free doxorubicin in presence of liposome doxorubicin**. Liposomal doxorubicin solution containing free doxorubicin was used for preparation of working solution of free doxorubicin and spiked in Human EDTA K3 plasma at LQC and HQC levels. All samples were analyzed with calibration standard and 2 set of batch QC's. The mean % difference for LQC is 7.6% and for HQC is 2.9%. Therefore, the data indicate that the extraction procedure is appropriate for free doxorubicin in presence of liposomal doxorubicin.

Confirmation of extraction method for free Doxorubicin

Analyte: FREE DOXORUBICIN

Biological Matrix: Human EDTA K3 Plasma

Analytical Run I.D.: PMV_F-DXR_141_Confirmation_Extraction_Procedure_exp_310708

	Low QC (ng/mL)		High QC (ng/mL)	
	15.18		1199.35	
Range	(b) (4)			
	Measured Conc.	% Difference	Measured Conc.	% Difference
	(b) (4)	10.9	(b) (4)	-4.5
		24.0		3.6
		-0.0		4.1
		2.9		3.5
		-1.9		5.4
		9.8		5.1
N	6		6	
Mean	16.335		1233.702	
SD(+)	1.4520		44.5688	
(%) CV	8.9		3.6	
%Diff.	7.6		2.9	

- As per the clinical study protocol (DOX_21_1476_09), **“For free doxorubicin estimation, since liposome lyses was observed under freezing conditions, sample processing of free doxorubicin shall be done within 12 hours of plasma separation at each time sampling time point”**. For the extraction of free doxorubicin, plasma samples were loaded onto solid phase cartridges and these cartridges (having free doxorubicin retained in they cartridge bed) are stored at 2-8° C until further analysis. At the time of analysis, the analyte was eluted from the cartridges. The fed study sample collection and analysis was carried out into different phases. However, the maximum study sample storage period is 169 days for free Doxorubicin. The firm determined the long term storage stability data of free doxorubicin at -20° C and also in cartridges at 2-8° C. The long term storage data of 170 days at 2-8° C exceed the storage period for the samples of fed (169 days in catridges) BE study.
- The pre-study validation data of doxorubicin are acceptable.

Liposomal Doxorubicin

Information Requested	Analyte 1 Location in Report (Module, Section, Page)	Analyte 1 Location in Report (Module, Section, Page)
Bioanalytical method validation Report location	Section 5-3-1-4	Section 5-3-1-4
Study Report Number	Report No.: MV_L-DXR_137A	Report No.: PMV_L- DXR_137A
Analyte	Liposomal Doxorubicin	Liposomal Doxorubicin
Internal standard (IS)	(b) (4)	(b) (4)
Method description	High performance liquid chromatography method using Tandem mass spectrometry detection has been used for determination of liposomal doxorubicin (encapsulated doxorubicin) in human K3 EDTA plasma using solid phase extraction method (see below for details)	High performance liquid chromatography method using Tandem mass spectrometry detection has been used for determination of liposomal doxorubicin (encapsulated doxorubicin) in human K3 EDTA plasma using solid phase extraction method (see below for details)
Limit of quantitation	LLOQ : 1.00 µg/mL	LLOQ : 1.00 µg/mL
Anticoagulant Used	K3EDTA	K3EDTA
LLOQ Intraday precision (%)	5.4%	6.9%
LLOQ Intraday accuracy (%)	8.7%	111.3%
LLOQ Interday precision (%)	10.3%	-
LLOQ Interday accuracy (%)	0.4%	-
% recovery (and %CV) at each concentration tested	QC Low A: 79.3%, %CV- 5.2 QC Low B: 86.7%, %CV- 4.0 QC Med A: 92.7%, %CV- 3.3 QC Med B: 85.3%, %CV- 1.7 QC High : 80.2%, %CV- 2.6	-
Average recovery of IS (%)	87.8%, %CV- 2.0	-
Standard curve concentrations (units/mL)	1.00, 1.99, 4.16, 13.76, 33.50, 45.81, 56.85, 70.25 µg/mL	1.00, 1.99, 4.16, 13.76, 33.50, 45.81, 56.85, 70.25 µg/mL
QC concentrations (units/mL)	Low QC A: 2.99 µg/mL, Low QC B: 8.96 µg/mL, Medium QC A : 14.67 µg/mL, Medium QC B : 34.40 µg/mL, High QC : 58.21 µg/mL	Low QC A: 2.99 µg/mL, Low QC B: 8.96 µg/mL, Medium QC A : 14.67 µg/mL, Medium QC B : 34.40 µg/mL, High QC : 58.21 µg/mL
QC Intraday precision range (%)	1.8% to 7.7%	2.0 % to 8.6%
QC Intraday accuracy range (%)	-3.1% to 8.7%	97.0% to 106.4%
QC Interday precision range (%)	3.7% to 8.4%	2.9% to 7.4%
QC Interday accuracy range (%)	-1.7% to 1.1%	97.0% to 111.3%

Bench-top stability (hrs)	26 hours at room temperature in plasma	-
	25 hours at room temperature in processed biological matrix.	-
Stock stability (days)	177 days @ 2-8°C	-
Processed stability (hrs)	81 hours @ 10°C ± 2°C	-
Freeze-thaw stability (cycles)	05 cycles at -20±5°C, -35±5°C & -65±10°C	-
Long-term storage stability (days)	191 days at -20±5°C	-
	192 days at -35±5°C & -65±10°C	-
Dilution integrity (concentration, percent CV) dilution factor, accuracy	HQC concentration (58.21µg/mL) diluted 2 folds.	-
	% Difference : 1/2 nd : -3.2	-
	% Precision : 1/2 nd : 2.4	-
Selectivity	No interference observed in blank plasma samples	-
For combination products: Did the matrix include all analytes?	N/A	-

SOPs submitted	Yes
Was the % recovery consistent across QC concentrations?	Yes (the difference in the recovery of analyte between the QC samples is less than 15%)
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	Yes
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	No study samples were diluted
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	No study samples were diluted
Does the duration of the each of the stability parameters support the sample preparation and assay dates	Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	Yes

Sample preparation (1):

(b) (4)



Solid Phase Extraction Procedure for Liposomal Doxorubicin (1): (b) (4)

[Redacted]

Sample preparation (2): (b) (4)

[Redacted]

Solid Phase Extraction Procedure for Entrapped Doxorubicin (2): (b) (4)

[Redacted]

Comments on the Pre-Study Method Validation for Liposomal Doxorubicin:

- The principle of solid phase extraction technique functions to retain the free doxorubicin on the stationary phase of Hydrophilic Lipophilic Balance (HLB) cartridge. Binding of free doxorubicin to stationary phase is related to adsorption phenomenon. So free doxorubicin can be retained on stationary phase where liposome entrapped doxorubicin cannot be retained.
- The firm initially conducted method validation using Liquid Chromatography Method with Tandem mass spectrometry and (b) (4) as the MS detector. However the study sample analyses was performed using Liquid Chromatography Method with Tandem mass spectrometry and (b) (4) as the MS detector. Therefore the firm performed partial validation (Report No PMV_L-DXR_137A) for change in instrument ((b) (4)) during the study sample analysis of Liposomal Doxorubicin (Entrapped).
- It did not appear that the firm conducted cross-validation for the confirmation of extraction method **to estimate only liposomal doxorubicin in the presence of free doxorubicin**. The firm will be asked to provide the cross-validation data.
- The firm used K₃EDTA as anticoagulant in their fed BE study. So they conducted pre-study and with-in study validation using plasma containing K₃EDTA as the

matrix. The calibration standards and quality control samples were prepared with human plasma containing K₃EDTA.

- The fed study samples were stored at -20° C at the clinical and analytical sites. The long term storage data of 191 days at -20° C exceed the storage period for the samples of fed (123 days) BE study.
- The pre-study validation data of liposomal doxorubicin are acceptable.

Information Requested	Analyte 1 Location in Report (Module, Section, Page)	
Bioanalytical method validation Report location	Section 5-3-1-4	
Study Report Number	Report No.: PMV_T-DXR_143	
Analyte	Total Doxorubicin	
Internal standard (IS)	(b) (4)	
Method description	High performance liquid chromatography method using Tandem mass spectrometry detection has been used for determination of total doxorubicin in human EDTA K3 plasma using protein precipitation extraction method	
Limit of quantitation	LLOQ : 0.260 µg/mL ULOQ : 89.006 µg/mL	
Anticoagulant Used	K3EDTA	
LLOQ Intraday precision (%)	5.7%	
LLOQ Intraday accuracy (%)	9.2%	
LLOQ Interday precision (%)	8.7%	
LLOQ Interday accuracy (%)	10.6%	
% recovery (and %CV) at each concentration tested	QC Low A: 79.3%, %CV-2.2 QC Low B: 80.0%, %CV-1.4 QC Med B: 77.8%, %CV-1.2 QC High : 77.9%, %CV-1.4 QC Med A: 78.0%, %CV-0.4	QC Low A: 97.3%, %CV-2.2 QC Low B: 95.9%, %CV-1.4 QC Med B: 97.8%, %CV-0.4 QC High : 98.8%, %CV-1.2 QC Med A: 98.7%, %CV-1.4
Average recovery of IS (%)	91.8%, %CV-2.0	96.6%, %CV-2.0
Standard curve concentrations (units/mL)	0.260, 0.557, 1.022, 3.066, 9.291, 23.227, 46.454, 60.390, 69.681, 89.006 µg/mL	
QC concentrations (units/mL)	QC Low-A : 0.780 µg/mL QC Low-B : 2.341 µg/mL QC Med-A : 18.767 µg/mL QC Med-B : 40.043 µg/mL QC High : 71.167 µg/mL	
QC Intraday precision range (%)	1.3% to 5.7%	

QC Intraday accuracy range (%)	-2.8% to 9.2%
QC Interday precision range (%)	3.7 to 6.1%
QC Interday accuracy range (%)	0.6 to 4.1%
Bench-top stability (hrs)	43 hours at room temperature
Stock stability (days)	104 days @ 2-8°C
Processed stability (hrs)	55 hours @ 10°C ± 2°C
Freeze-thaw stability (cycles)	07 cycles at (-20° ± 5° C, -35° ± 5° C, & -65° ± 10° C)
Long-term storage stability (days)	118 days at (-20° ± 5° C, -35° ± 5° C, & -65° ± 10° C)
Dilution integrity (concentration, percent CV) dilution factor, accuracy	HQC Concentration (71.167µg/mL) diluted 5 folds.
	Mean % Diff. : 1/5 th : 0.1
	% Precision : 1/5 th : 1.2
Selectivity	No interference observed in blank plasma samples
For combination products: Did the matrix include all analytes?	All patients who were dosed the study drug had received Dexamethasone and Granisetron Injection before starting infusion. The firm stated that all the experiments have been evaluated in the presence of dexamethasone and granisetron

SOPs submitted	Yes
Was the % recovery consistent across QC concentrations?	Yes
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	Yes
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	No study samples were diluted
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	No study samples were diluted
Does the duration of the each of the stability parameters support the sample preparation and assay dates	Yes
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	Yes

Comments on the Pre-Study Method Validation for Total Doxorubicin:

- The firm initially conducted method validation using a different extraction procedure. However the firm re-conducted the method validation with the protein extraction procedure similar to that of the study samples.
- The firm used K₃EDTA as anticoagulant in their fed BE study. So they conducted pre-study and with-in study validation using plasma containing K₃EDTA as the matrix. The calibration standards and quality control samples were prepared with human plasma containing K₃EDTA.
- There are two sets of data for the recovery of analyte and the internal standard. The extraction efficiency was calculated in a similar way in both cases. The mean

percent recovery values of total doxorubicin were 78.60 and 97.70. However the recovery of total doxorubicin is consistent across the QC concentration in each experiment conducted.

- The fed study samples were stored at -20° C at the clinical and analytical sites. The long term storage data of 118 days at -20° C exceed the storage period for the samples of fed (103 days) BE study.
- The pre-study validation data of total doxorubicin are acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	Mean Parameters (± SD), Liposome encapsulated Doxorubicin, N=24						Study Report location
					Cmax (µg/mL)	Tmax (hr)	AUCt (µg *hr/mL)	AUCi (µg *hr/mL)	tHalf (hr)	Kel (1/hr)	
Study No: PKD_09_03_0	To monitor the safety of the patients participating in the study and to assess the bioequivalence of Doxorubicin Hydrochloride Liposome Injection, 2 mg/ml (50 mg/m2 dose) of Sun Pharma Limited, India and Doxil® (Doxorubicin Hydrochloride Liposome injection), 2 mg/ml (50 mg/m2 dose) of Ortho Biotech Products in patients with Ovarian Cancer, under fed (normal low fat breakfast) conditions.	A Randomized, multicentre, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence with washout period of at least 28 days under fed (normal low fat breakfast) conditions.	Test (T): Doxorubicin Hydrochloride Liposome Injection 2mg/mL, [Batch No: JK93496A] Mfg Date: Nov 2009	41 Patients with Ovarian Cancer Age: 50.2 (27-74)	35.792 +/- 6.9700	1.533 (1.000 - 9.000)	3401.181 7 +/- 972.5957 0	3663.811 2 +/- 1033.489 29	78.3273 +/- 15.14752	0.00914 +/- 0.00163 0	Section 5.3.1.2
			Reference (R): Doxil® 2 mg/mL Liposome Injection (Doxorubicin Hydrochloride) [Lot No.: 0907642] Expiry Date: Jan 2011		35.247 +/- 5.8877	2.000 (1.000 - 9.000)	3201.510 2 +/- 1179.619 81	3598.015 0 +/- 1164.757 28	79.3151 + /- 19.97835	0.00944 +/- 0.00317 4	

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	Mean Parameters (± SD), Free Doxorubicin, N=41						Study Report location
					Cmax (ng/mL)	Tmax (hr)	AUCt (ng*hr/mL)	AUCi (ng*hr/mL)	tHalf (hr)	Kel (1/hr)	
Study No: PKD_09_03_0	To monitor the safety of the patients participating in the study and to assess the bioequivalence of Doxorubicin Hydrochloride Liposome Injection, 2 mg/ml (50 mg/m2 dose) of Sun Pharma Limited, India and Doxil® (Doxorubicin Hydrochloride Liposome injection), 2 mg/ml (50 mg/m2 dose) of Ortho Biotech Products in patients with Ovarian Cancer, under fed (normal low fat breakfast) conditions.	A Randomized, multicentre, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence with washout period of at least 28 days under fed (normal low fat breakfast) conditions.	Test (T): Doxorubicin Hydrochloride Liposome Injection 2mg/mL, [Batch No: JK93496A] Mfg Date: Nov 2009	41 Patients with Ovarian Cancer Age: 50.2 (27-74)	283.101 +/- 205.9202	4.000 (1.000 – 169.000)	25735.5298 +/- 14554.09686	28047.6784 +/- 15139.08303	91.0730 +/- 36.11544	0.00858 +/- 0.002734	Section 5.3.1.2
			Reference (R): Doxil® 2 mg/mL Liposome Injection (Doxorubicin Hydrochloride) [Lot No.: 0907642] Expiry Date: Jan 2011		261.423 +/- 121.4049	4.000 (0.250 – 169.000)	24549.3522 +/- 12977.08388	52297.0763 +/- 156414.37089	127.6092 +/- 256.06243	0.00918 +/- 0.003630	

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	Mean Parameters (± SD), Total Doxorubicin, N=24						Study Report location
					Cmax (µg /mL)	Tmax (hr)	AUCt (µg*hr/ mL)	AUCi (µg*hr/ mL)	tHalf (hr)	Kel (1/hr)	
Study No: PKD_09_03_0	To monitor the safety of the patients participating in the study and to assess the bioequivalence of Doxorubicin Hydrochloride Liposome Injection, 2 mg/ml (50 mg/m2 dose) of Sun Pharma Limited, India and Doxil® (Doxorubicin Hydrochloride Liposome injection), 2 mg/ml (50 mg/m2 dose) of Ortho Biotech Products in patients with Ovarian Cancer, under fed (normal low fat breakfast) conditions.	A Randomized, multicentre, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence with washout period of at least 28 days under fed (normal low fat breakfast) conditions.	Test (T): Doxorubicin Hydrochloride Liposome Injection 2mg/mL, [Batch No: JK93496A] Mfg Date: Nov 2009	41 Patients with Ovarian Cancer Age: 50.2 (27-74)	33.7543 +/- 5.81021	2.000 (1.083 – 6.000)	3288.9100 +/- 764.37801	3515.0467 +/- 899.75408	77.2907 +/- 19.55669	0.00957 +/- 0.002790	Section 5.3.1.2
			Reference (R): Doxil® 2 mg/mL Liposome Injection (Doxorubicin Hydrochloride) [Lot No.: 0907642] Expiry Date: Jan 2011		33.6060 +/- 4.95509	2.000 (1.083 – 9.000)	3246.1167 +/- 1101.98723	3546.2233 +/- 1119.83156	75.9548 +/- 20.25034	0.00984 +/- 0.003052	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Free Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *ng/ml)	22488.86	41	21297.24	41	1.06	92.26	120.86
AUC _∞ (hr *ng/ml)	24505.50	38	22890.91	34	1.07	92.92	123.33
C _{max} (ng/ml)	235.21	41	237.10	41	0.99	85.11	115.63

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Liposomal Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	3265.36	24	2940.69	24	1.11	99.64	123.74
AUC _∞ (hr * µg /ml)	3525.19	24	3414.60	22	1.03	95.71	111.36
C _{max} (µg /ml)	35.17	24	34.75	24	1.01	96.04	106.67

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Total Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *µg/ml)	3200.49	24	3009.51	24	1.06	95.81	118.04
AUC _∞ (hr * µg /ml)	3320.84	23	3371.12	22	0.99	90.80	106.87
C _{max} (µg /ml)	33.29	24	33.21	24	1.00	95.36	105.35

Are the PK parameters within the acceptance limits for the 90% CI and meeting BE? Yes

Table 3. Reanalysis of Study Samples

Free Doxorubicin

Fed Study, Study No. PKD_09_030 Additional information in Appendix 5.3.1.4								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Unacceptable internal standard response	0	5	0.00	0.34	0	5	0.00	0.34
Sample reanalyzed to obtain confirming value	3	2	0.20	0.14	3	0	0.20	0.00
Inconsistent Profile	9	9	0.61	0.61	3	4	0.20	0.27
Rejected analytical run	38	43	2.58	2.92	32	37	2.18	2.52
Total	50	59	3.40	4.01	38	46	2.58	3.13

Liposomal Doxorubicin

Fed Study, Study No. PKD_09_030 Additional information in Appendix 5.3.1.4								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Unacceptable internal standard response	6	1	0.41	0.07	6	1	0.41	0.07
Incomplete analysis	0	1	0.00	0.07	0	1	0.00	0.07
Sample concentration above Upper Limit of Quantitation	1	0	0.07	0.00	1	0	0.07	0.00
Sample reanalyzed to obtain confirming value	3	4	0.20	0.27	0	1	0.00	0.07
Inconsistent Profile	5	1	0.34	0.07	1	0	0.07	0.00
Rejected analytical run	44	38	2.99	2.58	35	36	2.38	2.45
Total	59	45	4.01	3.06	43	39	2.92	2.65

Total Doxorubicin

Fed Study, Study No. PKD_09_030 Additional information in Appendix 5.3.1.4								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Poor Chromatography	0	1	0.00	0.07	0	1	0.00	0.07
Sample reanalyzed to obtain confirming value	3	5	0.20	0.34	1	1	0.07	0.07
Inconsistent Profile	3	3	0.20	0.20	0	1	0.00	0.07
Rejected analytical run	18	18	1.22	1.22	18	18	1.22	1.22
Total	24	27	1.63	1.84	19	21	1.29	1.43

Table 4. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
PKD/S/019	10/08/2009	Sample reanalysis and Reporting of Final concentrations. (Revision No.: 03)
PKD/S/019	29/09/2010	Sample reanalysis and Reporting of Final concentrations. (Revision No.: 04)

Reanalysis SOPs submitted?	Yes
Do you agree that the reassay criteria: analytical and pharmacokinetic	See comments below
If not, list the criteria that you don't agree and provide additional comment below	
Are the data in the summary table consistent with the data in the full analytical report?	Yes
If not, provide comment below	
Did reviewer reanalyze study results?	Yes
Was the study outcome changed based on reviewer reanalysis?	No
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DBE?	Yes
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Yes

Comments from the Reviewer:

Free Doxorubicin: The firm reassayed the study samples because of the analytical reasons, "Unacceptable internal standard response", "Sample reanalyzed to obtain confirming value", "Inconsistent profile", "Rejected analytical run". The samples reassayed because of Unacceptable internal standard response and rejected analytical run are acceptable. After checking the raw data, the firm reanalyzing the study samples due to "Sample reanalyzed to obtain confirming value",

“Inconsistent profile” is found to be unacceptable because the DBE considers the criteria to be biased and unobjective. Samples reassayed without an objective criterion defined in a reanalysis standard operating procedure (SOP) are considered essentially questionable “PK repeats” and only the original assay values should be used in the final data analysis. The reviewer identified 10 subject samples and plus one extra subject whose re-assayed values were used for statistical analyses. Those subject samples are listed below;

Sample Identification (Subject, Period, Time)	Original Results (ng/mL)	Reassay Results (ng/mL)	Firm Reported Values (ng/mL)	Reviewer Used Values (ng/mL)	Reviewer's Reason for Replacement
SUB_13_P1_337.00_Hrs_B9_3/3	125.55	104.48	104.48	125.55	A
SUB_16_P2_97.00_Hrs_B6_3/3	361.30	257.02	257.02	361.30	A
SUB_17_P1_49.00_Hrs_B5_3/3	895.18	627.89	627.89	895.18	A
SUB_33_P1_169.00_Hrs_B7_2/3	175.48	113.64	113.64	175.48	A
SUB_41_P2_169.00_Hrs_B7_2/3	236.31	324.83	324.83	236.31	A
SUB_61_P2_169.00_Hrs_B7	7158.01	21.87	21.87	22.035	B
SUB_61_P2_169.00_Hrs_B7_D		22.20			
SUB_52_P2_241.00_Hrs_B8	27.90	8.96	8.96	27.9	A
SUB_61_P2_241.00_Hrs_B8	146.84	15.21	15.21	146.84	A
SUB_61_P2_241.00_Hrs_B8_D		15.67			
SUB_60_P2_97.00_Hrs_B6_2/3	1430.01	10.25	10.25	1430.01	A

Explanation of Codes

A: No valid reason for replacement, original result used

B: Original value greater than ULOQ (1464.22 ng/mL), average of two reassayed values was used

The reviewer used the original values in calculating the confidence intervals for those study samples where the firm reassayed for above-mentioned questionable codes. The 90% confidence intervals for LAUC_{0-t}, LAUC_∞ and LC_{max}, are within the acceptable limits of 80-125%. So there is no change in the study outcome.

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Free Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr *ng/ml)	22926.66	41	23244.96	41	0.99	84.66	114.91
AUC _∞ (hr *ng/ml)	25198.38	38	23774.02	35	1.06	91.73	122.46
C _{max} (ng/ml)	239.38	41	248.68	41	0.96	80.48	115.13

Liposomal Doxorubicin: The firm reassayed the study samples because of the analytical reasons, “Unacceptable internal standard response”, “Incomplete analysis”, “Sample reanalyzed to obtain confirming value”, “Sample concentration above the upper limit off quantification”, “Inconsistent profile”, “Rejected analytical run”. The samples reassayed because of above reasons are acceptable except reanalyzing the study samples due to “Sample reanalyzed to obtain confirming value”, “Inconsistent profile”. DBE considers these two criteria to be biased and unobjective. Samples reassayed without an objective criterion defined in a reanalysis standard operating procedure (SOP) are considered essentially questionable “PK repeats” and only the original assay values should be used in the final data analysis. However the firm used original values for the pharmacokinetic and statistical analysis. The firm’s reassay of the fed study samples for analytical reasons are acceptable.

Total Doxorubicin: The firm reassayed the study samples because of the analytical reasons, “Poor Chromatography”, “Sample reanalyzed to obtain confirming value”, “Inconsistent profile”, “Rejected analytical run”. The samples reassayed because of Poor chromatography and rejected analytical run are acceptable. After checking the raw data, the firm reanalyzing the study samples due to “Sample reanalyzed to obtain confirming value”, “Inconsistent profile” is found to be unacceptable because the DBE considers the criteria to be biased and unobjective. Samples reassayed without an objective criterion defined in a reanalysis standard operating procedure (SOP) are considered essentially questionable “PK repeats” and only the original assay values should be used in the final data analysis.

The reviewer used the original values in calculating the confidence intervals for those study samples where the firm reassayed for above codes. The 90% confidence intervals for LAUC0-t, LAUC∞ and LCmax, are within the acceptable limits of 80-125%. So there is no change in the study outcome.

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m2)					
SUMMARY OF STATISTICAL ANALYSIS- Total Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. PKD_09_030					
Parameter (units)	Test	RLD	Ratio	90% C.I.	
AUC0-t (hr * µg/ml)	3200.49	3100.07	1.03	90.90	117.25
AUC∞ (hr * µg /ml)	3320.84	3481.55	0.95	85.20	106.79
Cmax (µg /ml)	33.29	33.29	1.00	95.00	105.28

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No

Is the formulation acceptable?	ACCEPTABLE
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	Current Review (No “dissolution only” review on this ANDA)
Submitted Method (USP, FDA, or Firm)	Firm
Recommended Method (details below)	The external dissolution database for Doxorubicin Hydrochloride Liposome Injection recommends the firm’s to develop a method to characterize in vitro release
Medium	
Volume (mL)	
USP Apparatus type	
Rotation (rpm)	
Specifications	
Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?	No
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	RAPIDLY DISSOLVING
Is method acceptable?	METHOD IS NOT ACCEPTABLE
If not then why?	The firm used non compendial apparatus for conducting dissolution testing

3.9 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested, if applicable	N/A
Waiver regulation cited?	N/A
Strengths considered for 21 CFR 320.24 (b)(6)	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	Pending acceptance of DBE recommended dissolution specification

3.10 Deficiency Comments

1. The firm provided multiple summary tables of calibration curve and QC data for the analytes of free doxorubicin and liposomal doxorubicin. The firm should provide the

justification for submitting multiple summary tables instead of one overall summary of the interday accuracy and precision of all the CC's and QC data during the study sample analyses.

- The firm should submit its in vitro testing data in the **Electronic SAS Transport format** using DBE's template (shown example below). The in vitro data in the correct format will be used by the DBE for PBE statistical analysis and for verification purposes.

PRODUCT	LOT	VIAL	D10	D50	D90	SPAN
TEST	1234	1				
		2				
		3				
		4				
		5				
		6				
		7				
		8				
		9				
		10				

- It did not appear that the firm conducted cross-validation for the confirmation of extraction method **to estimate only liposomal doxorubicin in the presence of free doxorubicin**. The firm will be asked to provide the cross-validation data.

Dissolution Method

- The firm's drug release method is under consideration. However the DBE requests that the firm submit a complete method development and validation report of the proposed drug release method.

- The DBE requests that the firm also conduct the following drug release method (b) (4)

The comparative testing should be conducted on the test and reference product, using one dosage unit (vial) (10 mL of 2 mg/mL) per replicate and six samples taken per unit for six different time points: Six samples of 1 mL of the vial content should be transferred to six separate glass tubes containing the medium of 98% fetal bovine serum with 80 mM NH₄Cl at pH 6.0 to obtain the final volume of 100 mL. The resulting drug concentration should be 20 microgram/mL of liposomal doxorubicin. These glass tubes should be incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome should be determined at the following six time points: 0 hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs. The testing should be replicated for 12 dosage vials per each test and the reference drug product.

(b) (4)

The individual percent doxorubicin release data from each vial at each time point should be submitted, as well as the mean data from 12 vials at each time point for each product (% mean and % CV) over the period of 0 to 4 hours for the test and RLD from 12 dosage units.

3.11 Recommendations

1. The Division of Bioequivalence finds the fed BE study (C10112) conducted by the Sun Pharma Global FZE. on its Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL, lot # JK93496A, comparing it to Ortho Biotech's Doxil[®] Liposomal Injection, 2 mg/mL, lot # 0907642, incomplete due to deficiencies mentioned above.
2. The *in vitro* equivalence study (Liposome Size Distribution) submitted for Doxorubicin Hydrochloride Injection, Liposomal , 2 mg/mL, by Sun Pharma Global FZE, comparing it to Doxil[®] Liposomal Injection, 2 mg/mL, manufactured by Ortho Biotech, is **incomplete** due to deficiency mentioned above.
3. The firm's *in vitro* dissolution testing is incomplete due to the deficiencies mentioned above.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
Bio PM	Please request OSI inspections for the following sites: 1. Clinical Site: NRR Hospital, Bangalore 2. In Vitro Testing Site: Sun Pharmaceutical India Ltd. Halol-Baroda Highway Halol-389350 Gujarat India

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fed Bioequivalence Study

4.1.1.1 Study Design

Table 5 Study Information

Study Number	PKD_09_030
Study Title	A randomized, multi centre, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Doxorubicin Hydrochloride Liposome injection, 2 mg/ml (50 mg/m ² dose) of Sun Pharma Advanced Research Company Limited, India and Doxil® (Doxorubicin Hydrochloride Liposome injection), 2 mg/ml (50 mg/m ² dose) of Ortho Biotech Products, LP Raritan, NJ 08869-0670, in patients with Ovarian Cancer, under fed (normal low fat breakfast) conditions.
Clinical Site (Name & Address)	MNJ Institute of Oncology & Regional Cancer Centre, Red Hills, Hyderabad- 500 004 (India) Ph: +91 (40) 23318414, +91 (40) 23318424
	Kailash Cancer Hospital & Research Centre Goraj, Vadodara- 391760 (India) Ph: 02668- 268038
	Dr. G. Vishwanathan Speciality Hospitals #27, Babu road, Trichy Tamilnadu- 620 008 (India) Ph: 0431- 2705945, 2709250
	Dr. Kamakshi Memorial Hospital No.1, Radial Road, Palikaranai, Chennai- 600 100 (India) Ph: 044- 22469200, 66300300
	NRR Hospital, Chikkasandra Bangalore- 560090 (India) Ph: 080-28374115
Principal Investigator	Dr. M. Ramakrishna
	Dr. Niraj Bhatt
	Dr. K.N. Srinivasan
	Dr. V. Srinivasan
	Dr. Yathish Kumar H.M
Dosing Dates	Refer Table 10A: Dosing Table
Analytical Site (Name & Address)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India Tel: 91-265-2350789, 91-265-6615500
Analysis Dates	From 14th September, 2010 to 6th March, 2011 for Free Doxorubicin, From 30th June, 2010 to 5th March, 2011 for Liposomal Doxorubicin

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	and From 27th June, 2010 to 23rd February, 2011 for Total Doxorubicin.
Analytical Director	Dr. (b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	For Free Doxorubicin : 169 days (In cartridges) For Liposomal Doxorubicin :123 days For Total Doxorubicin :103 days (Note: As study sample collection and analysis was done into different phases/parts, maximum storage period has been mentioned.)

Table 10A: Dosing Table

Groups	Subject Number	Period I		Period II	
		Dosing time (am)	Dosing Date	Dosing time (am)	Dosing Date
1	6	9:30 to 9:31	08/04/10	*	*
	7	*	*	*	*
	8	10:00 to 11:01	15/04/10	10:00 to 11:01	13/05/10
	9	*	*	*	*
	10	9:30 to 10:31	20/04/10	9:30 to 10:31	18/05/10
	11	*	*	*	*
	12	9:30 to 10:31	11/05/10	9:30 to 10:31	08/06/10
	13	9:30 to 10:31	20/05/10	9:30 to 10:31	22/06/10
	14	*	*	*	*
	15	9:45 to 9:47	27/05/10	*	*
	16	9:15 to 10:16	27/05/10	9:15 to 10:16	25/06/10
	17	9:30 to 10:31:20 sec	29/06/10	9:30 to 10:31:20	28/07/10
	18	9:30 to 10:31	14/07/10	9:30 to 10:31	17/08/10
	19	*	*	*	*
	20	9:30 to 10:32	24/08/10	9:30 to 10:32	21/09/10
	21	9:30 to 10:32	31/08/10	*	*
	22	10:30 to 11:34	31/08/10	10:30 to 11:34	28/09/10
	23	9:30 to 10:32	14/09/10	9:30 to 10:32	14/10/10
	24	10:00 to 11:04	21/09/10	*	*
	25	*	*	*	*
	36	10:30 to 11:32	21/09/10	10:30 to 11:32	22/10/10
	37	9:30 to 10:32	28/09/10	9:30 to 10:32	26/10/10
	38	10:00 to 11:01	26/10/10	10:00 to 11:01	23/11/10
	39	10:30 to 11:32	26/10/10	10:30 to 11:32	23/11/10
	40	10:00 to 11:01	02/11/10	10:00 to 11:01	30/11/10
49	10:00 to 10:02	09/11/10	*	*	
50	9:30 to 10:31	23/11/10	*	*	
57	9:30 to 10:31	30/11/10	9:30 to 10:31	28/12/10	
58	10:30 to 11:31	07/12/10	10:30 to 11:31	04/01/11	
61	10:30 to 11:31	14/12/10	10:30 to 11:31	20/01/11	
62	10:45 to 10:46:39 sec	14/12/10	*	*	
2	1	10:16 to 10:17	07/04/10	*	*
	2	10:18 to 11:22	23/06/10	10:33 to 11:40	21/07/10
	3	9:40 to 10:41	14/07/10	9:40 to 10:41	12/08/10
	4	10:04 to 11:08	07/08/10	*	*
	5	9:45 to 9:49	15/10/10	*	*

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3	30	11:00 to 12:01	21/12/10	11:00 to 12:01	29/01/11
	31	11:00 to 11:59	23/08/10	11:00 to 11:59	20/09/10
	32	11:00 to 12:03	31/08/10	11:00 to 12:03	28/09/10
	33	10:30 to 11:29	07/09/10	10:30 to 11:29	05/10/10
	34	10:30 to 11:31	11/10/10	10:30 to 11:31	08/11/10
	35	10:00 to 11:02	23/10/10	10:00 to 11:02	20/11/10
	46	10:00:00 to 10:00: 30 sec	30/10/10	*	*
	47	10:45 to 11:46	03/11/10	10:45 to 11:46	01/12/10
	48	11:15 to 12:16	06/11/10	11:15 to 12:16	04/12/10
	51	10:30 to 11:32	17/11/10	11:30 to 12:32	15/12/10
	52	11:30 to 12:32	25/12/10	11:30 to 12:32	25/01/11
4	26	9:45 to 10:48	23/10/10	9:45 to 10:47	20/11/10
	27	10:00 to 11:00	30/10/10	10:00 to 11:00	30/11/10
	28	10:35 to 11:36	08/11/10	10:35 to 11:36	07/12/10
	29	10:55 to 11:56	15/11/10	10:55 to 11:56	13/12/10
5	41	10:30 to 11:31	03/11/10	10:30 to 11:31	01/12/10
	42	9:30 to 10:32	04/11/10	9:36 to 10:37	03/12/10
	43	9:30 to 10:32	10/11/10	9:30 to 10:31	08/12/10
	44	10:30 to 10:32	24/11/10	*	*
	45	9:15 to 10:16	27/11/10	9:15 to 10:16	25/12/10
	53	9:30 to 10:31	27/12/10	9:30 to 10:30	24/01/11
	54	9:40 to 9:42 10:05 to 11:06	27/12/10	10:05 to 11:05	24/01/11
	59	9:30 to 9:32	30/11/10	*	*
	60	11:00 to 12:01	30/11/10	11:00 to 12:01	28/12/10

*Not Dosed

Table 6. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 ml	Doxil® (Doxorubicin Hydrochloride Liposome injection), 2 mg/ml, 10 ml
Manufacturer	Sun Pharmaceutical Industries Ltd., India.	Ortho Biotech Products, LP Raritan, NJ 08869-0670
Batch/Lot No.	JK93496A	0907642
Manufacture Date	November 2009	
Expiration Date		January 2011
Strength	2 mg/ml, 10 ml	2 mg/ml, 10 ml
Dosage Form	Liposomal Injection/ Intravenous	Liposomal Injection/ Intravenous
Bio-Batch Size	(b) (4) vials	
Production Batch Size	vials	
Potency (Assay)	99.1 %	95.1 %
Content Uniformity (expressed as mean, %CV or per USP)	N/A	
pH	6.3	6.32
Osmolality	357.33 mOsm/Kg	352 mOsm/Kg
Zeta Potential	-10.5 mv	-11.1 mv
Free-drug and entrapment		
Free Drug	2.5%	2.3%
Entrapped Drug	97.5%	98.1%
Dose Administered	2 mg/mL (50 mg/m2 dose)	2 mg/mL (50 mg/m2 dose)
Route of Administration	Intravenous	Intravenous

Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)? N/A

Is the bio-batch size at least the recommended minimum of 100K for oral solid dosage form? N/A

Reviewer's Comments:

Table 7. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 60 Dosed: 54 Completed: 41 Samples Analyzed: 41 Data Analyzed: 41 (Free Doxorubicin), 24 (Liposomal and Total Doxorubicin)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	28 days
Randomization Scheme (Sequence of T and R)	AB: 1, 4, 5, 6, 10, 12, 14, 15, 17, 18, 21, 23, 25, 27, 31, 32, 34, 36, 37, 40, 41, 44, 45, 47, 50, 51, 55, 56, 58, 60, 63, 64 BA: 2, 3, 7, 8, 9, 11, 13, 16, 19, 20, 22, 24, 26, 28, 29, 30, 33, 35, 38, 39, 42, 43, 46, 48, 49, 52, 53, 54, 57, 59, 61, 62,
Blood Sampling Times	Pre-dose, During the intravenous infusion: 0.25, 0.5, 0.75, 1.0 hour after start of infusion and After completion of the intravenous infusion: 0.083 (1.083), 0.250 (1.250), 0.500 (1.500), 1.000 (2.000), 3.000 (4.000), 5.000 (6.000), 8.000 (9.000), 24.000 (25.000), 48.000 (49.000), 96.000 (97.000), 168.000 (169.000), 240.000 (241.000) and 336.000 (337.000) hours post dose
Blood Volume Collected/Sample	10 mL (Pre-dose) 6 mL
Anticoagulant Used	K ₃ EDTA
Blood Sample Processing & Storage (include storage temperature)	The first 12 blood samples were collected from an ante-cubital vein using indwelling cannula and remaining blood samples were collected by direct venipuncture using pre-labeled vacutainers containing K ₃ EDTA as the anticoagulant. After blood collection, tubes were centrifuged at 3000 rpm for 10 minutes at 4° C ± 2° C. Plasma samples were then stored at -20° C ± 5° C until shipment. The separated plasma is divided in three equal aliquots.
IRB Approval	MNJ Institute of oncology & Regional Cancer Center: June 25, 2009 NRR Hospital: October 25, 2010 Kailash Cancer Hospital: March 13, 2010 Dr. Kamakshi Memorial Hospital: October 4, 2010 Dr.G. Vishwanathan Speciality hospitals: July 25, 2010
Informed Consent	Yes
Length of Fasting	The subjects were fasted 10 hours overnight. A normal low fat breakfast was given 30 minutes prior to dosing.
Length of Confinement	At least twelve hours preceding each study day and 48 hours following each dose
Safety Monitoring	Adverse events were collected and reports were tabulated. The vital signs were measured throughout the study.

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No	Name of Clinical Site	Group number/Site ID	Patient Allotment	Number of Patients
1	MNJ Institute of Oncology & Regional Cancer Center, Hyderabad	1/A	6 to 25, 36 to 40, 49, 50, 57, 58, 61, 62	31
2	Kailash Cancer Hospital and research Center, Goraj, Vadidara	2/B	1 to 5	5
3	Dr. G. Vishwanathan Speciality Hospitals, Trichy, Tamilnadu	3/D	30 to 35, 46 to 48, 51, 52	11
4	Dr. KM Hospital Pvt. Ltd., Chennai	4/E	26 to 29	4
5	NRR Hospital, Bangalore	5/G	41 to 45, 53, 54, 59, 60	9

MNJ Institute of Oncology & Regional Cancer Center, Hyderabad

Sr. No	Food Items	Amount	Fat (gm)	Carbohydrate (gm)	Protein (gm)	Energy (Kcal)
1	Idli	200 gm	0.4	57.8	8.4	268.40
2	Sambar	150 gm	1.95	11.25	3.75	77.55
3	Banana	45 gm	0.13	12.24	0.54	52.2
Total Calories						398.15

Kailash Cancer Hospital and Research Centre, Goraj, Vadodara

Sr. No	Food Items	Amount (in gm)	Cooked amount		Fat (gm)	Carbohydrate (gm)	Protein (gm)	Energy (Kcal)
			In gm/mg	In kitchen friendly				
1	Bread	50	50	4 slices (big)	0.35	25.95	3.9	122
2	Jam	70	70	3 tab. spoon	-	53.2	-	171
Total Calories								293

Dr. G. Vishwanathan Speciality Hospitals, Tamilnadu

Sr. No	Food Items	Quantity	Fat (gm)	Carbohydrate (gm)	Protein (gm)	Energy (Kcal)
1	Idly	100 gm	0.34	45.46	5.6	207.7
2	Dhal	100 gm	5.34	11.52	4.46	112
3	Skim milk	200 ml	0.15	6.9	3.75	43.5
4	Sugar	5 gm	0.005	4.75	0.02	19.15
Total Calories						382.35

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Or

Sr. No	Food Items	Quantity	Fat (gm)	Carbohydrate (gm)	Protein (gm)	Energy (Kcal)
1	Chapathi	100 gm	1.02	41.64	7.26	204.6
2	Dhal	100 gm	5.34	11.52	4.46	112
3	Skim milk	200 ml	0.15	6.9	3.75	43.5
4	Sugar	5 gm	0.005	4.75	0.02	19.15
Total Calories						379.25

Dr. KMH Hospital Pvt. Ltd., Chennai

Sr. No	Food Items	Quantity	Fat (gm)	Carbohydrate (gm)	Protein (gm)	Energy (Kcal)
1	Idly	100 gm	0.34	45.46	5.6	207.7
2	Dhal	100 gm	5.34	11.52	4.46	112
3	Skim milk	200 ml	0.15	6.9	3.75	43.5
4	Sugar	5 gm	0.005	4.75	0.02	19.15
Total Calories						382.35

Or

Sr. No	Food Items	Quantity	Fat (gm)	Carbohydrate (gm)	Protein (gm)	Energy (Kcal)
1	Chapathi	100 gm	1.02	41.64	7.26	204.6
2	Dhal	100 gm	5.34	11.52	4.46	112
3	Skim milk	200 ml	0.15	6.9	3.75	43.5
4	Sugar	5 gm	0.005	4.75	0.02	19.15
Total Calories						379.25

NRR Hospital, Bangalore

Sr. No	Food Items	Amount	Fat (gm)	Carbohydrate (gm)	Protein (gm)	Energy (Kcal)
1	Roti	3 Nos	8.34	41.78	9.11	251.8
2	Dhal	100 gm	5.4	12.9	4.9	119.8
Total Calories						371.6

Or

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Sr. No	Food Items	Amount	Fat (gm)	Carbohydrate (gm)	Protein (gm)	Energy (Kcal)
1	Idly	4 Nos	0.8	55.2	9.2	264.8
2	Sambar	200 gm	2.5	15	5.0	98
Total Calories						362.8

Was the study design used for the fed BE study acceptable?

YES

Reviewer's Comments: This is a multi-center study. It was conducted at five different clinical sites. The firm provided the information on number of patients enrolled in each center. The study was conducted under fed conditions using low fat breakfast (as recommended in the RLD labeling). The firm also provided the composition of meal consumed by the patients at each site. All patients who were dosed the study drug had received Dexamethasone Injection, 8 mg, 45 minutes before starting infusion and Granisetron Injection, 2 mg, 30 minutes before.

Prior to the administration of infusion, the location of injection site for all the patients was identified, fixed preferably near to the cubital fossa and the same was recorded. Moreover injection site was cleaned before the administration of study drug.

The dose of Doxorubicin Hydrochloride for individual patient was calculated according to body surface area using following formula.

$$\text{Body Surface Area (m}^2\text{)} = [\text{Height (cm)} \times \text{Weight (kg)} / 3600]^{1/2}$$

The exact quantity of calculated dose of Doxorubicin Hydrochloride was diluted in 250 ml 5 % Dextrose Injection for infusion prior to administration of doses up to 90 mg.

In each of the study periods patients were administered intravenous infusion (administered through infusion pump) of either test or reference product of Doxorubicin Hydrochloride, Liposome injection 2 mg/ml (50 mg/m² dose) by intravenous infusion after dilution over 60-minute period, 30 minutes after administration of normal low fat breakfast, according to randomization schedule. Aseptic technique was observed. Diluted liposomal Doxorubicin HCl was refrigerated at 2°C to 8°C and administered within 24 hours. The site of infusion was same for all patients and the rate of infusion was maintained to complete the administration of the drug in 59-67 minute. Doxorubicin HCl liposome injection was administered at a rate of 1 mg/min for first 10 minutes to minimize the risk of infusion reactions.

The study design is acceptable.

4.1.1.2 Clinical Results

Table 8A. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study No. PKD_09_030			
		Treatment Groups	
		Test Product N = 41	Reference Product N = 41
Age (years)	Mean ± SD	50.2 ± 10.80	50.2 ± 10.80
	Range	27 - 74	27 - 74
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 - 40	8 (19.5%)	8 (19.5%)
	41-64	30 (73.2%)	30 (73.2%)
	65-75	3 (7.3%)	3 (7.3%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	0 (0.0%)	0 (0.0%)
	Female	41 (100.0%)	41 (100.0%)
Race	Asian	41 (100.0%)	41 (100.0%)
	Black	0 (0.0%)	0 (0.0%)
	Caucasian	0 (0.0%)	0 (0.0%)
	Hispanic	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)
BSA	Mean + SD	1.508 ± 0.1346	1.508 ± 0.1346
	Range	1.2 - 1.84	1.2 - 1.84
Other			

Table 8B. Demographics Profile of Individual Subjects Completing the Bioequivalence Study

The study was conducted on female patients only.

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Table 9. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
1	Due to serious adverse event (Dyspnoea and hypertension) in period I	I	NO
4	Due to serious adverse event (anemia) in period I	I	NO
5	Due to serious adverse event (Dyspnoea and hypertension) in period I	I	NO
6	Due to Adverse Event (anaphylactic reaction) in period I	I	NO
7	Due to Adverse Event (high blood pressure) before dosing in period I	I	NO
9	Withdrew herself without any reason, voluntarily from the study before dosing in period I	I	NO
11	Due to Adverse Event (increased pulse rate) before dosing in period I	I	NO
14	Due to Adverse Event (increased blood pressure) before dosing in period I	I	NO
15	Due to serious adverse event (chest pain, pulse abnormal, loss of consciousness) in period I	I	NO
19	Withdrew herself without any reason, voluntarily from the study before dosing in period I	I	NO
21	Withdrew herself without any reason, voluntarily from the study before dosing in period II	II	NO
24	Due to serious adverse event (thrombocytopenia) before dosing in period II	II	NO
25	Due to Adverse Event (sinus tachycardia) before dosing in period I	I	NO
44	Due to serious adverse event (discomfort, bradycardia, hypotension, chest discomfort) in period I	I	NO
46	Due to Adverse Event (anaphylactic reaction) in period I	I	NO
49	Due to serious adverse event (chest pain, dyspnoea) in period I	I	NO
50	Death in period I	I	NO
59	Due to serious adverse event (dyspnoea, bradycardia, dizziness, discomfort) in period I	I	NO
62	Due to serious adverse event (chest pain, dyspnoea, tachycardia and hyperhidrosis) in period I	I	NO

Table 10. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study No.: PKD_09_030	
	Test n (%)	Reference n (%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	2 (5.6)	4 (11.8)
Oropharyngeal pain	0 (0.0)	1 (2.9)
General disorders and administration site conditions		
Pain	1 (2.8)	1 (2.9)
Chest pain	1 (2.8)	2 (5.9)
Hyperhidrosis	1 (2.8)	1 (2.9)
Discomfort	1 (2.8)	1 (2.9)
Chest discomfort	1 (2.8)	0 (0.0)
Fatigue	1 (2.8)	0 (0.0)
Gastrointestinal disorders		
Stomatitis	2 (5.6)	0 (0.0)
Dyspepsia	1 (2.8)	0 (0.0)
Vomiting	3 (8.3)	2 (5.9)
Gastritis	1 (2.8)	0 (0.0)
Diarrhea	0 (0.0)	1 (2.9)
Mucosal inflammation	0 (0.0)	1 (2.9)
Nausea	1 (2.8)	0 (0.0)
Nervous system disorders		
Loss of consciousness	1 (2.8)	0 (0.0)
Dizziness	0 (0.0)	2 (5.9)
Headache	1 (2.8)	0 (0.0)
Neuropathy peripheral	1 (2.8)	0 (0.0)
Skin and subcutaneous tissue disorders		
Skin hyperpigmentation	1 (2.8)	0 (0.0)
Blood and lymphatic system disorders		
Anaemia	5 (13.9)	3 (8.8)
Leukopenia	1 (2.8)	4 (11.8)
Neutropenia	1 (2.8)	2 (5.9)
Thrombocytopenia	1 (2.8)	3 (8.8)
Immune system disorders		
Anaphylactic reaction	1 (2.8)	1 (2.9)
Cardiac Disorders		
Bradycardia	1 (2.8)	1 (2.9)
Tachycardia	0 (0.0)	1 (2.9)
Vascular disorders		
Hypertension	2 (5.6)	0 (0.0)
Hypotension	1 (2.8)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Ovarian cancer	1 (2.8)	0 (0.0)
Investigations		
Pulse abnormal	1 (2.8)	0 (0.0)

Heart rate decreased	0 (0.0)	1 (2.9)
White blood cell count decreased	0 (0.0)	1 (2.9)
Haemoglobin decreased	1 (2.8)	1 (2.9)
Total	36 (100.0)	34 (100.0)

Do any of the adverse events require statistical analysis consideration (e.g. emesis)?

Patients 4, 31 and 48 who received test product and patients 31, 32 who received reference treatment experienced vomiting. The effect was observed at 7, 3.5, 9 days for patients 4, 31, 48 respectively who received test treatment and 2, 1.5 days for patients 31, 32 respectively who received reference treatment.

If yes, does the time exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products) according to the *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*?

Patient 4 who received test product was dropped from the study because of the serious adverse event (oral mucositis, body ache, epigastri burning and anemia). The emesis effect observed is after 2X median of Tmax of doxorubicin hydrochloride for patients 31, 32 and 48. The firm included the above patients for the statistical analysis. The reviewer agrees with the firm and included the above patients for the pharmacokinetic and statistical analysis.

Was the adverse event profile observed during the fed bioequivalence study comparable for the test and reference product? Please comment.

There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug.

Are there any safety concerns based on the adverse event profile?

A total of 54 patients with ovarian cancer received at least one dose of the study medication. Of these, eleven patients (1, 3, 4, 5, 15, 24, 44, 49, 50, 59 and 62) experienced serious adverse events and were dropped from the study. One death (patient 50) occurred during the study. The adverse events that occurred for the other patients than mentioned above were mild to moderate in intensity.

As per the firm, “Patient 50 received test formulation, Liposomal Doxorubicin on Nov 23, 2010 and checked out on (b) (6). At discharge her condition was normal. Her vitals (pulse rate 78/min, BP 100/70) and CBP (Hb: 9.5 g/dL, total WBC count= 5600 cells/cumm, platelet count= 2.95 lacs/cmm) were normal. Patient was called for cycle II on Dec 20, 2010. Through telephone patient attender informed that she was passed away in her sleep on (b) (6) at her residence”. In the Case report Form it was written that the “*Patient 50 was diagnosed with cancer of bilateral ovaries in Feb 2010. She had received six cycles of adjuvant chemotherapy (Carboplatin Injection 450 mg and Paclitaxel Injection 250 mg). Her last CT was on Oct 13, 2010. The disease was progressive after using platinum based chemotherapy*”. This serious adverse event was judged unrelated to Doxorubicin HCl Liposome Injection (SPARC Ltd.), communicated to sponsor and ethics committee on Dec 21, 2010. Since the serious adverse event (death) occurred in patient 50 was after the administration of the test product, DBE is concerned about the safety of the test formulation.

The other patients that experienced serious adverse events were 1, 3, 4, 5, 15, 24, 44, 49, 59 and 62. Patients 1, 3, 4, 5, 15, 44, 50 experienced the serious AEs when the test formulation was administered, and patients 24, 49, 59 and 62 experienced the serious AEs while the reference formulation was administered. The serious adverse events experienced by the patients after the administration of the test formulation were dyspnoea, hypertension, anemia, chest pain, hyperhidrosis, loss of consciousness, pulse abnormal, bradycardia, hypotension, oral mucositis and fatigue. The serious adverse events experienced by the patients after the administration of the reference formulation were chest pain, breathlessness, bradycardia, tachycardia, sweating, giddiness, and thrombocytopenia.

DBE has submitted a clinical consultation to the OGD Clinical Team to ask if the adverse event (death) associated with the test formulation should be of a safety concern [DARRTS for ANDA 203263 at DANDAMUDI, SUMAN 12/20/2011 N/A 12/20/2011 FRM-CONSULT-01(General Consult Request) Original-1 (Unknown) Archive].

The Medical Officer concluded that *“The Division of Clinical Review (DCR) does not find a safety difference in the reported adverse events from the study submitted to this ANDA (203263). The single reported death in the study appears to be related to the progressive ovarian cancer and not to the drug product”* [See DARRTS for ANDA 203263 at GIERHART, BRENDA S 01/03/2012 N/A 01/03/2012 CONSULT REV-CLINICAL-01(General Consult Review) Original-1 (Unknown) Archive].

Table 11. Protocol Deviations, Fed Bioequivalence Study

Study Number: PKD_09_030		
Type	Subject (Test)	Subject (Reference)
Pharmacokinetic and statistical analyses shall not be done and reported for Doxorubicinol.	All	All
Vital signs were not taken at scheduled time for subject number 1 in period I.	Subject Number: 1 (1 Subject)	-
Flow rate deviation occurred for initial 10 minutes for subject number 2 in period I.	-	Subject Number: 2 (1 Subject)
Due to technical problem with infusion pump, dosing was delayed for 4 minutes for subject number 4 in period I.	Subject Number: 4 (1 Subject)	-
Dosing was delayed for 15 minutes for subject number 5. There was a subsequent deviation of +15 minutes in morning breakfast, concomitant medication in period I.	Subject Number: 5 (1 Subject)	-
Week 2 hematology investigation was not performed for subject number 54. Subject was repeatedly called for performing week II hematology test. But subject did not report on scheduled time in period I.	-	Subject Number: 54 (1 Subject)

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Water restriction was not followed for subject number 33 in period I.	-	Subject Number: 33 (1 Subject)
Vital sign was recorded from infusion start time instead of recording after completion of infusion for subject number 48 in period I.	-	Subject Number: 48 (1 Subject)
Breakfast has not been provided for subject number 6, 7, 10, 12, 13 and 23 on scheduled time in period I.	Subject Number: 6, 10, 12 and 23 (4 Subjects)	Subject Number: 7 and 13 (2 Subjects)
Subject number 16, 22, 50, 57, 58 and 61 have not reported to the site for 3 rd week hematology test in period I.	Subject Number: 50 and 58 (2 Subjects)	Subject Number: 16, 22, 57 and 61 (4 Subjects)
Subject number 9 was screened on 23/03/10 and she was checked in on 14/04/10 according to the protocol for the study # PKD_09_030. The screening reports validity is only for 21 days. The patient had been checked in on 22 nd day in period I.	-	Subject Number: 9 (1 Subject)
Due to problem in the infusion pump, dosing was delayed for 6 minutes from the planned time i.e., 36 minutes from the start of breakfast for subject number 42. Subsequently administration of Inj. Dexamethasone and Granisetron was done at 08:45 am and 09:00 am respectively in period II	Subject Number: 42 (1 Subject)	-
Week 4 hematology investigation was not performed for subject number 41, 42 and 60. Subject was repeatedly called for performing week II hematology test. But subject did not report on scheduled time in period II.	Subject Number: 42 (1 Subject)	Subject Number: 41 and 60 (2 Subjects)
The 4 th week hematology investigation and 2-D Echocardiography on 59 th day were not performed, since the patient had not turned up for the respective visits for subject number 28 in period II.	Subject Number: 28 (1 Subject)	-
Water restriction was not followed for subject number 32 and 33 in period II.	Subject Number: 33 (1 Subject)	Subject Number: 32 (1 Subject)
Breakfast has not been provided for subject number 18 on scheduled time. The actual time of providing breakfast is 09:01 am but the scheduled time is 09:00. The breakfast has been provided 1 minute late due to injection Granisetron administration at 9:00 hour in period II.	-	Subject Number: 18 (1 Subject)
2-D Echocardiography was done on 60 th day instead of performing on 59 th day for subject number 33 in period II.	Subject Number: 33 (1 Subject)	-
ECG and 2-D Echocardiography was not performed prior to check in for subject number 17 due to the 'local bandh' in Hyderabad in period II.	-	Subject Number: 17 (1 Subject)

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2-D Echocardiography was not performed on scheduled day for subject number 8 due to subject did not report to the facility in period II.	Subject Number: 8 (1 Subject)	-
2-D Echocardiography was not performed on scheduled day for subject number 16 due to subject did not report to the facility in period II	Subject Number: 16 (1 Subject)	-
2-D Echocardiography was not performed on scheduled day for subject number 18 due to subject did not report to the facility in period II.	-	Subject Number: 18 (1 Subject)
2-D Echocardiography was not performed on scheduled day for subject number 36 due to subject did not report to the facility in period II.	-	Subject Number: 36 (1 Subject)
2-D Echocardiography was not performed on scheduled day for subject number 37 due to subject did not report to the facility in period II.	-	Subject Number: 37 (1 Subject)
2-D Echocardiography was not performed on scheduled day for subject number 57 due to subject did not report to the facility in period II.	Subject Number: 57 (1 Subject)	-
2-D Echocardiography was not performed on scheduled day for subject number 61 due to subject did not report to the facility in period II.	Subject Number: 61 (1 Subject)	-
Only hematology was performed during check out of period II for subject number 8 and 10 in period II.	Subject Number: 8 (1 Subject)	Subject Number: 10 (1 Subject)
Due to technical problem in the infusion pump, dosing was delayed for 15 minutes from the planned time for subject number 2 in period II.	Subject Number: 2 (1 Subject)	-
Subject number 12, 17 and 37 have not reported to the site for 3 rd week hematology test in period II.	-	Subject Number: 12, 17 and 37 (3 Subjects)
The difference in the infusion time between period I and period II for subject number 54 in both periods.	NA	NA
Water restriction was not followed for subject number 34 in both periods.	NA	NA
Water restriction was not followed for subject number 26 and 27 in both periods.	NA	NA
Drug administration time deviation occurred by 1 hour between period I and II for subject number 51 in both periods.	NA	NA

Breakfast has not been provided for subject number 8 on scheduled time in both periods.	NA	NA
Vital signs (Seated blood pressure, pulse, oral temperature and well being) rate has not been performed on scheduled time for subject number 8 in both periods.	NA	NA
Total infusion time in period I was 64 minutes and 67 minutes in period II for subject number 2 in both periods.	NA	NA
Subject number 23, 36, 38, 39 and 40 have not reported to the site for 3 rd week hematology test in both periods.	NA	NA
Meals were served to the patient according to the end time of the infusion but according to the protocol the meals and snacks should be provided based on the start time of the infusion in both periods.	NA	NA
Hb value (8.9 g/dL) is slightly less than the lower acceptable range of 9.0 g/dL as per protocol for subject number 4. Hence it is considered insignificant by the Principal Investigator. Moreover the laboratory report was evaluated by the Principal Investigator prior to dosing of the subject.	All	All

Did dropouts/adverse events/protocol deviations affect the study outcome? No

A total 60 patients were enrolled in the study. Out of which 54 patients received at least. Two patients (9, 19) without any reason voluntarily withdrew from the study before dosing in period I and the study investigator dropped 4 patients (7, 11, 14 and 25) from the study due to the adverse events observed before dosing in period I. Therefore out of 60 patients enrolled, 54 patients received at least one dose of the study medication.

Out of 54 patients dosed, only 41 patients completed the study. Ten patients (1, 4, 5, 15, 24, 44, 49, 50, 59 and 62) experienced serious adverse event and therefore the study investigator dropped them from the study. One patient (21) voluntarily withdrew from the study before the dosing in period II and two patients (6 and 46) were dropped from the study due to the adverse event (anaphylactic reaction) before dosing in period II.

There were some blood sampling deviations during fed bioequivalence study. However, these sampling time deviations occurred in less than 10% of the nominal time points, thus are considered to be insignificant by the reviewer. The sample time deviations did not compromise the outcome of the BE study. The firm used actual sampling times for its PK calculation.

4.1.1.3 Bioanalytical Results

Table 12. Assay Validation – Within the Fed Bioequivalence Study

Free Doxorubicin

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Parameter	Standard Curve Samples									
Concentration (ng/mL)	5.06	9.93	19.85	49.63	124.09	248.17	496.34	744.52	992.69	1464.22
Inter day Precision (%CV)	3.4	6.1	4.9	5.9	4.0	3.2	3.4	3.0	3.1	4.9
Inter day Accuracy (%Actual)	3.2	-2.6	-5.2	-3.2	-2.6	-1.7	2.1	3.8	2.9	3.7
Linearity	0.9956 to 0.9992 (r Value)									
Linearity Range (ng/mL)	5.06 to 1464.22									
Sensitivity/LOQ (ng/mL)	5.06									

Parameter	Quality Control Samples				
Concentration (ng/mL)	15.14	45.42	297.81	595.61	1191.23
Inter day Precision (%CV)	8.0	7.3	7.2	6.9	6.5
Inter day Accuracy (%Actual)	-0.1	0.8	1.7	0.8	0.6

Parameter	Quality Control Samples				
Concentration (ng/mL)	15.14	45.42	297.81	595.61	1191.23
Inter day Precision (%CV)	7.4	8.0	5.6	6.3	9.4
Inter day Accuracy (%Actual)	93.6	94.6	97.5	108.3	109.0

Parameter	Quality Control Samples				
Concentration (ng/mL)	15.03	45.10	300.67	601.33	1202.67
Inter day Precision (%CV)	6.4	5.4	5.9	5.7	7.8
Inter day Accuracy (%Actual)	1.3	0.2	2.7	3.7	2.3

Number of Acceptable Runs	40 acceptable runs and 11 repeated runs which were found acceptable
Number of Rejected Runs (Run ID, volume/page location)	There are two rejected runs (SUB_36_281110, Module 5.3.1.4-Bioanalytical Report Part-2 Pg No: 1183 and REPEAT_02_RE_250910, Pg No: 1385)
If sample and QC diluted during study, specify all dilution factors	No study samples were diluted
Was 100% of raw numerical data submitted?	Yes

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Liposomal Doxorubicin								
Parameter	Standard Curve Samples							
Concentration (µg/mL)	1.00	1.99	4.16	13.76	33.50	45.81	56.85	70.25
Inter day Precision (%CV)	3.0	5.6	5.4	4.8	5.9	3.8	4.5	5.3
Inter day Accuracy (%Actual)	1.1	-2.0	-0.6	1.1	0.5	-0.9	-1.7	2.5
Linearity	0.9943 to 0.9998 (r Value)							
Linearity Range (µg/mL)	1.00 to 70.25 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Parameter	Quality Control Samples				
Concentration (µg/mL)	2.99	8.96	14.67	34.40	58.21
Inter day Precision (%CV)	7.0	5.7	6.0	6.1	6.2
Inter day Accuracy (%Actual)	0.6	2.7	1.5	-0.3	2.6

Liposomal Doxorubicin								
Parameter	Standard Curve Samples							
Concentration (µg/mL)	1.00	1.99	4.16	13.76	33.50	45.81	56.85	70.25
Inter day Precision (%CV)	2.3	5.3	4.7	4.8	4.8	4.0	5.6	4.2
Inter day Accuracy (%Actual)	99.3	101.7	99.3	101.0	99.6	100.6	100.2	98.4
Linearity	0.9943 to 0.9998 (r Value)							
Linearity Range (µg/mL)	1.00 to 70.25 µg/mL							
Sensitivity/LOQ (µg/mL)	1.00 µg/mL							

Parameter	Quality Control Samples				
Concentration (ng/mL)	2.99	8.96	14.67	34.40	58.21
Inter day Precision (%CV)	7.9	7.1	4.6	9.3	12.2
Inter day Accuracy (%Actual)	100.6	103.4	102.2	102.3	103.0

Number of Acceptable Runs	41 acceptable runs and 8 repeated run which were found acceptable
Number of Rejected Runs (Run ID, volume/page location)	There are three rejected runs (SUBJECT_39_120111, Module 5.3.1.4-Bionalytical Report Part-2 Pg No: 1527, SUBJECT_43_01_160111, Pg No: 1533, REPEAT_01_190111, Pg No: 1551)
If sample and QC diluted during study, specify all dilution factors	One study sample was diluted
Was 100% of raw numerical data submitted?	Yes

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Total Doxorubicin										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	0.260	0.557	1.022	3.066	9.291	23.227	46.454	60.390	69.681	89.006
Inter day Precision (%CV)	3.6	6.5	6.7	4.1	4.1	4.7	3.4	3.2	4.2	4.5
Inter day Accuracy (%Actual)	2.6	-3.3	-3.5	-3.7	-0.2	-0.7	2.8	1.7	2.9	1.0
Linearity	0.9950 to 0.9999 (r Value)									
Linearity Range (ng/mL)	5.06 to 1464.22									
Sensitivity/LOQ (ng/mL)	5.06									

Parameter	Quality Control Samples				
Concentration (ng/mL)	0.780	2.341	18.767	40.043	71.167
Inter day Precision (%CV)	9.1	6.8	5.8	4.5	5.4
Inter day Accuracy (%Actual)	-4.8	-4.8	0.2	1.6	0.2

Number of Acceptable Runs	41 acceptable runs and 3 repeated runs which were found acceptable
Number of Rejected Runs (Run ID, volume/page location)	There is one rejected run (SUB_35_090111, Module 5.3.1.4-Bioanalytical Report Part-2 Pg No: 1642)
If sample and QC diluted during study, specify all dilution factors	No study samples were diluted
Was 100% of raw numerical data submitted?	Yes

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes
Do you agree with the firm's accepted and rejected runs?	Yes

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially
Were the chromatograms submitted by the firm acceptable?	Yes

Was the Study Assay Validation acceptable? Incomplete. The firm provided multiple summary tables of calibration curve and QC data for the analytes free doxorubicin and liposomal doxorubicin. The firm should provide the justification for submitting multiple summary tables instead of one overall summary of the interday accuracy and precision of all the CC's and QC data during the study sample analyses.

4.1.1.4 Pharmacokinetic Results

Table 13. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in [Table 17](#) and [Figure 1](#)

Free Doxorubicin

Fed Bioequivalence Study, Study No. PKD_09_030									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
AUC _{0-t} (hr*ng/ml)	25728.97	56.53	9228.79	67828.58	24545.17	52.87	3589.42	63085.43	1.05
AUC _∞ (hr *ng/ml)	27738.93	56.35	10087.14	68524.32	26761.01	52.94	9361.82	65768.87	1.04
C _{max} (ng/ml)	283.101	72.74	89.41	1030.68	261.423	46.44	100.26	592.28	1.08
T _{max} * (hr)	4.000	.	1.00	169.00	4.000	.	0.25	169.00	1.00
Kel (hr ⁻¹)	0.009	26.59	0.00	0.02	0.009	33.01	0.00	0.02	0.99
T _{1/2} (hr)	83.841	29.38	44.94	153.09	85.599	35.68	39.17	184.81	0.98

* T_{max} values are presented as median, range

Liposomal Doxorubicin

Fed Bioequivalence Study, Study No. PKD_09_030									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
AUC _{0-t} (hr*µg/ml)	3400.651	28.59	1847.02	5273.58	3201.545	36.85	1064.01	5473.16	1.06
AUC _∞ (hr * µg/ml)	3667.620	28.27	1984.83	5637.20	3664.916	31.48	1221.15	5902.51	1.00
C _{max} (µg/ml)	35.792	19.47	24.87	52.93	35.247	16.70	23.25	47.38	1.02
T _{max} * (hr)	1.500	.	1.00	9.00	2.000	.	1.00	9.00	0.75
Kel (hr ⁻¹)	0.009	18.59	0.01	0.01	0.010	33.26	0.01	0.02	0.96
T _{1/2} (hr)	78.768	21.73	54.41	133.45	77.937	23.43	33.01	109.69	1.01

* T_{max} values are presented as median, range

Total Doxorubicin

Fed Bioequivalence Study, Study No. PKD_09_030									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC _{0-t} (hr*µg/ml)	3288.426	23.23	1968.13	4812.27	3246.159	33.95	991.67	4855.85	1.01
AUC _∞ (hr * µg/ml)	3489.207	26.32	2001.09	5726.51	3636.437	30.55	1032.60	5533.22	0.96
C _{max} (µg/ml)	33.754	17.21	24.02	46.49	33.606	14.74	20.23	41.94	1.00
T _{max} * (hr)	2.000	.	1.08	6.00	2.000	.	1.08	9.00	1.00
Kel (hr ⁻¹)	0.010	27.88	0.01	0.02	0.010	31.67	0.01	0.02	0.98
T _{1/2} (hr)	74.563	24.39	35.27	130.63	74.541	26.28	36.74	111.84	1.00

* T_{max} values are presented as median, range

Table 14. Geometric Means and 90% Confidence Intervals - Firm Calculated

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Free Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study, Study No. PKD_09_030						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t} (hr *ng/ml)	20430.59	40	19612.10	40	104.17	90.15 - 120.38
AUC _∞ (hr *ng/ml)	22331.79	40	21672.15	40	103.04	89.59 - 118.52
C _{max} (ng/ml)	209.66	41	212.91	41	98.47	84.11 - 115.28

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Liposomal Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study, Study No. PKD_09_030						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t} (hr *µg/ml)	3758.23	23	3512.63	23	106.99	97.10 - 117.89
AUC _∞ (hr * µg /ml)	4039.52	23	3844.87	23	105.06	96.85 - 113.97
C _{max} (µg /ml)	38.10	24	37.53	24	101.53	96.16 - 107.20

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Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Total Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study, Study No. PKD_09_030						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t} (hr * µg/ml)	3486.77	23	3410.36	23	102.24	92.99 - 112.41
AUC _∞ (hr * µg /ml)	3682.99	23	3631.83	23	101.41	92.65- 111.00
C _{max} (µg /ml)	34.45	24	34.55	24	99.72	94.96- 104.73

Table 15. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Free Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study, Study No. PKD_09_030						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t} (hr * ng/ml)	22488.86	41	21297.24	41	1.06	92.26 120.86
AUC _∞ (hr * ng/ml)	24505.50	38	22890.91	34	1.07	92.92 123.33
C _{max} (ng/ml)	235.21	41	237.10	41	0.99	85.11 115.63

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Liposomal Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study, Study No. PKD_09_030						
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-t} (hr * µg/ml)	3265.36	24	2940.69	24	1.11	99.64 123.74
AUC _∞ (hr * µg /ml)	3525.19	24	3414.60	22	1.03	95.71 111.36
C _{max} (µg /ml)	35.17	24	34.75	24	1.01	96.04 106.67

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Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Liposomal Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr * µg/ml)	2952.61	41	2771.09	41	1.07	98.04	115.80
AUC _∞ (hr * µg /ml)	3168.57	40	3130.62	39	1.01	94.41	108.50
C _{max} (µg /ml)	33.32	41	32.47	41	1.03	97.56	107.98

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Total Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr * µg/ml)	3200.49	24	3009.51	24	1.06	95.81	118.04
AUC _∞ (hr * µg /ml)	3320.84	23	3371.12	22	0.99	90.80	106.87
C _{max} (µg /ml)	33.29	24	33.21	24	1.00	95.36	105.35

Doxorubicin Hydrochloride Liposome Injection Dose 2 mg/mL (50 mg/m ²) SUMMARY OF STATISTICAL ANALYSIS- Total Doxorubicin Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study, Study No. PKD_09_030							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC _{0-t} (hr * µg/ml)	2936.31	41	2763.24	41	1.06	96.83	116.61
AUC _∞ (hr * µg /ml)	3046.08	40	3081.72	37	0.99	93.38	104.62
C _{max} (µg /ml)	31.08	41	30.50	41	1.02	96.62	107.47

Table 16. Additional Study Information, Fed Study No. PKD_09_030

Free Doxorubicin

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE
Reason(s) for Selecting Above SAS Program Macro	For the verification of Kel and AUC
Root mean square error, AUC _{0-t}	0.3601
Root mean square error, AUC _∞	0.3352

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Root mean square error, C _{max}	0.4087	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	38 (Reviewer) 40 (Firm)	34 (Reviewer) 40 (Firm)
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	Disagree	Disagree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	1 (sub 17)
C _{max} at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	38	0.93	0.79	0.99
Reference	34	0.92	0.78	0.98

Liposomal Doxorubicin

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE	
Reason(s) for Selecting Above SAS Program Macro	For the verification of Kel and AUC	
Root mean square error, AUC _{0-t}	0.2185	
Root mean square error, AUC _∞	0.1455	
Root mean square error, C _{max}	0.1059	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	24(Reviewer) 23 (Firm)	22 (Reviewer) 23 (Firm)
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	Disagree	Disagree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
C _{max} at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	24	0.93	0.81	0.96
Reference	22	0.92	0.86	0.96

Total Doxorubicin

DBE SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CALCKE	
Reason(s) for Selecting Above SAS Program Macro	For the verification of Kel and AUC	
Root mean square error, AUC _{0-t}	0.2104	
Root mean square error, AUC _∞	0.1526	
Root mean square error, C _{max}	0.1004	
	Test	Reference
If CALCKE program is used, please state how many subjects used by you for determining Kel and AUC _∞	23	22 (Reviewer) 23 (Firm)
If CALCKE program is used, please state if you agree or disagree with firm's determination of Kel and AUC _∞	Agree	Disagree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1 (< 5% C _{max}), sub 39	0
first measurable drug concentration as C _{max}	0	0
C _{max} at the first time point	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	23	0.95	0.84	0.99
Reference	22	0.95	0.87	0.99

Comments on Pharmacokinetic and Statistical Analysis:

The fed BE study was conducted at five different clinical sites i.e the patients in the fed BE study were dosed in five groups (multiple sites). The firm pooled all the data as the treatment*group interaction was not statistically significant. The reviewer run the SAS using the group effect and found that there was no significant TRT*GRP effect (p>0.1) for AUCs and C_{max}. Therefore, the reviewer agrees with the firm and dropped the term TRT*GRP for further analysis.

Free Doxorubicin:

- The firm excluded patient 10 for the calculation of Kel and AUC_i. The reviewer agrees with the firm for excluding patient 10 from Kel and AUC_i analysis after checking their data. The reviewer also excluded patient 10 from Kel and AUC_i analysis. In addition the reviewer also excluded patients 13, 39 and 41 who received test treatment and patients 13, 20, 22, 40, 41, 61 who received reference treatment from the pharmacokinetic and statistical analysis after checking the data.
- The 90% CI's for the least squares geometric means of Ln AUC_{0-t}, Ln AUC_∞ and LnC_{max} calculated by the reviewer agree with the firm's calculations and meet the criteria for BE.

Liposomal Doxorubicin

- In accordance with the clinical study protocol (Protocol No: Dox_21_1476_09), the firm performed the pharmacokinetic and statistical analysis of liposome encapsulated doxorubicin and total doxorubicin on the data of first 24 evaluable patients who completed the study.
- In the clinical study protocol (Protocol No: Dox_21_1476_09), it was stated that *“For total and liposome encapsulated Doxorubicin pharmacokinetic and statistical analysis shall be performed with the first 24 evaluable subjects data and evaluated for BE criteria. Further statistical analysis shall also be performed on 36 subject's data and BE results shall be reported as additional information”*.
- Forty-one patients completed the study. The firm submitted the pharmacokinetic and statistical analysis on 24 patients. The 90% CI's for the least squares geometric means of Ln AUC_{0-t}, Ln AUC_∞ and LnC_{max} was calculated on the data from 24 patients. The firm also performed additional analysis on all the 41 patients that completed the study.
- The firm excluded patient 10 for the calculation of Kel and AUC_i. The reviewer agrees with the firm for excluding patient 10 from Kel and AUC_i analysis after checking their data. The reviewer also excluded patient 10 from Kel and AUC_i analysis. In addition the reviewer also excluded patient 20 who received reference treatment from the pharmacokinetic and statistical analysis after checking the data.
- The 90% CI's for the least squares geometric means of Ln AUC_{0-t}, Ln AUC_∞ and LnC_{max} (from the data of 24 and also 41 patients) calculated by the reviewer agree with the firm's calculations and meet the criteria for BE.

Total Doxorubicin

- The firm excluded patient 10 for the calculation of Kel and AUC_i. The reviewer agrees with the firm for excluding patient 10 from Kel and AUC_i analysis after checking their data. The reviewer also excluded patient 10 from Kel and AUC_i analysis. In addition the reviewer also excluded patient 22 who received test treatment and patient 20 who received reference treatment from the pharmacokinetic and statistical analysis after checking the data.

- The 90% CI's for the least squares geometric means of Ln AUC_{0-t}, Ln AUC_∞ and Ln C_{max} (from the data of 24 and also 41 patients) calculated by the reviewer agree with the firm's calculations and meet the criteria for BE.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

Incomplete due to the deficiencies stated in the Deficiency Section.

Table 17. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Free Doxorubicin

Time (hr)	Test (n=41)		Reference (n=41)		Ratio (T/R)
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0.00	0.00	-	0.00	-	-
0.25	36.66	52.76	49.90	179.04	0.73
0.50	82.58	56.10	69.81	53.46	1.18
0.75	122.69	47.73	116.01	54.70	1.06
1.00	164.82	54.83	155.71	49.58	1.06
1.08	172.62	51.36	167.72	50.18	1.03
1.25	195.71	72.80	177.20	57.31	1.10
1.50	198.03	87.01	166.70	52.56	1.19
2.00	189.03	88.59	168.09	57.09	1.12
4.00	192.30	77.49	181.48	59.85	1.06
6.00	162.39	60.33	147.74	64.99	1.10
9.00	171.05	67.84	143.02	69.31	1.20
25.00	163.02	64.28	168.02	58.91	0.97
49.00	160.91	76.42	153.37	65.09	1.05
97.00	117.26	109.60	100.38	68.38	1.17
169.00	59.02	68.65	59.18	96.85	1.00
241.00	23.76	53.68	29.09	88.72	0.82
337.00	13.42	83.78	15.44	114.24	0.87

Liposomal Doxorubicin

Time (hr)	Test (n=24)		Reference (n=24)		Ratio (T/R)
	Mean (µg/mL)	CV%	Mean (µg/mL)	CV%	
0.00	0.00	-	0.00	-	-
0.25	5.89	25.89	5.80	23.04	1.01
0.50	13.31	22.88	12.84	22.39	1.04
0.75	21.11	23.82	20.42	22.39	1.03
1.00	27.57	25.47	28.88	17.56	0.95
1.08	28.53	28.29	30.48	19.66	0.94
1.25	31.73	19.37	31.58	20.92	1.00
1.50	32.89	16.98	31.83	17.00	1.03
2.00	32.01	18.42	32.64	18.54	0.98

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Time (hr)	Test (n=24)		Reference (n=24)		Ratio (T/R)
	Mean (µg/mL)	CV%	Mean (µg/mL)	CV%	
4.00	32.44	20.60	32.47	17.70	1.00
6.00	30.56	18.36	30.98	17.77	0.99
9.00	30.49	26.21	29.92	17.36	1.02
25.00	25.43	21.08	25.06	20.52	1.01
49.00	19.48	23.78	19.47	26.51	1.00
97.00	13.86	29.19	12.44	46.10	1.11
169.00	7.00	35.92	6.03	69.70	1.16
241.00	3.58	55.03	3.47	66.96	1.03
337.00	1.56	75.76	1.60	87.42	0.97

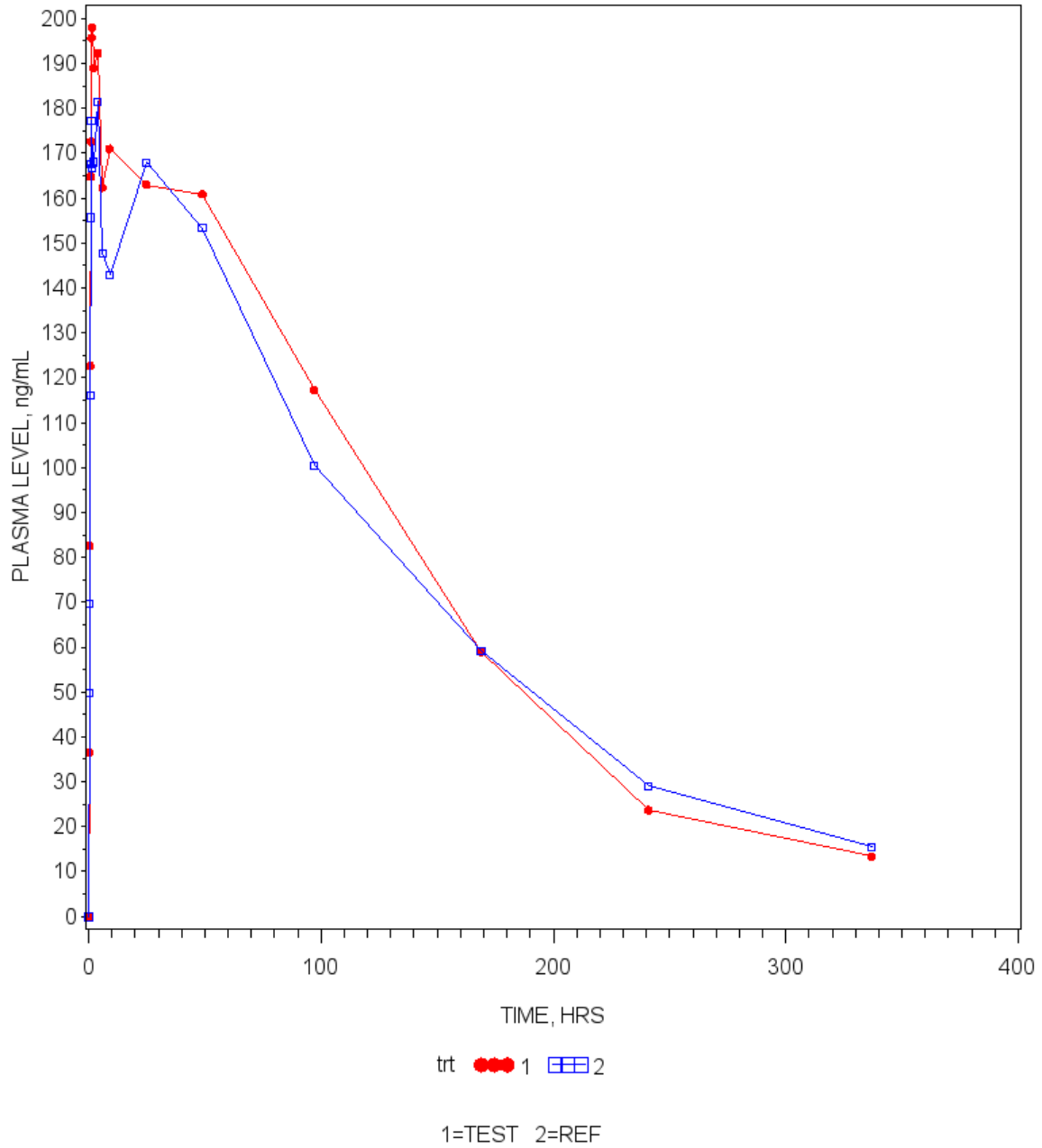
Total Doxorubicin

Time (hr)	Test (n=24)		Reference (n=24)		Ratio (T/R)
	Mean (µg/mL)	CV%	Mean (µg/mL)	CV%	
0.00	0.01	489.90	0.00	.	.
0.25	6.52	72.61	5.70	27.53	1.15
0.50	12.90	21.14	12.85	18.38	1.00
0.75	20.12	21.88	20.51	17.85	0.98
1.00	28.22	20.33	28.18	17.13	1.00
1.08	30.25	17.81	30.66	16.99	0.99
1.25	32.18	16.46	32.08	15.94	1.00
1.50	32.55	17.07	32.14	16.79	1.01
2.00	32.51	15.43	32.32	16.60	1.01
4.00	32.07	19.28	32.06	17.07	1.00
6.00	30.07	17.93	30.24	17.68	0.99
9.00	29.09	26.21	29.56	16.91	0.98
25.00	24.13	16.96	23.99	19.85	1.01
49.00	18.80	19.78	19.36	23.91	0.97
97.00	12.92	24.03	12.51	42.68	1.03
169.00	6.78	35.89	6.57	59.34	1.03
241.00	3.47	48.80	3.44	65.26	1.01
337.00	1.71	79.38	1.69	74.43	1.01

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

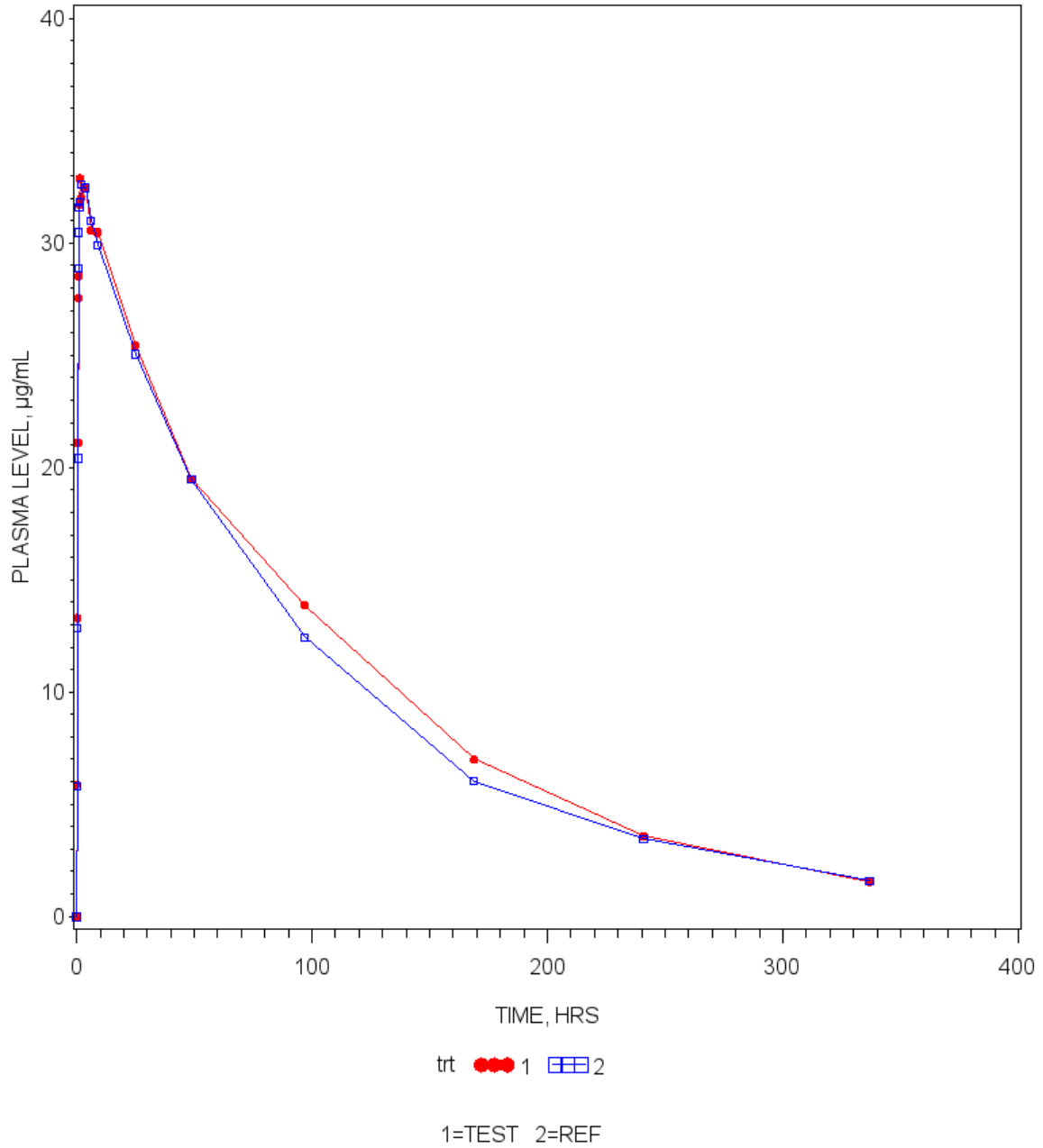
Free Doxorubicin

PLASMA FREE DOXORUBICIN LEVELS
DOXORUBICIN HYDROCHLORIDE INJECTION, ANDA 203263
UNDER FED CONDITIONS
DOSE= 2 MG/ML



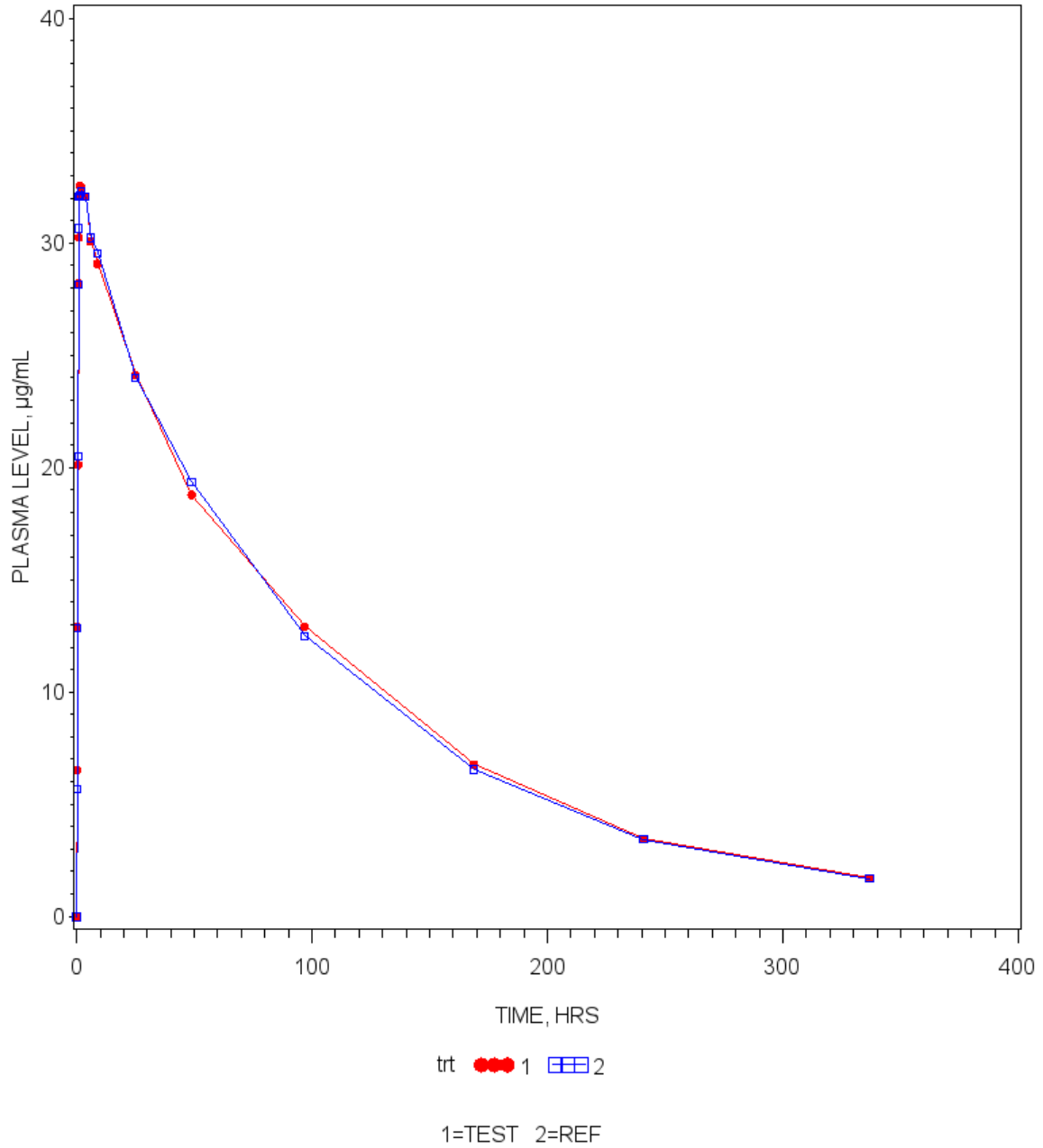
Liposomal Doxorubicin

PLASMA LIPOSOMAL DOXORUBICIN LEVELS
DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION, ANDA 203263
UNDER FED CONDITIONS
DOSE= 2 MG/ML



Total Doxorubicin

PLASMA TOTAL DOXORUBICIN LEVELS
DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION, ANDA 203263
UNDER FED CONDITIONS
DOSE= 2 MG/ML



4.1.2 Single-dose Pilot Fed Bioequivalence Study

Please note that the following summary tables as provided by the firm are listed here as information purpose only. The reviewer did not perform statistical analysis for the firm's pilot study.

1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	Mean Parameters (± SD), Total Doxorubicin, N=10						Study Report location
					Cmax (µg/mL)	Tmax (hr)	AUCt (µg *hr/mL)	AUCi (µg *hr/mL)	tHalf (hr)	Kel (1/hr)	
Study No: DOX/003/08	To assess the bioequivalence of single dose intravenous infusion of Liposomal Doxorubicin HCl 2 mg/mL (50 mg/m ² dose), of Sun pharmaceuticals Industries Ltd., India and Doxil® 50 mg/m ² marketed by Tibotec herapeutics a division of Ortho Biotech, USA, in patients with advanced breast cancer/ovarian cancer under fed conditions	Randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study with washout period of at least 28 days under fed conditions.	Test (T): Doxorubicin Hydrochloride Liposome Injection 2mg/mL, [Batch No: JK71575] Mfg Date:	10 Patients with Ovarian Cancer Age: 49.5 (32-63)	37.0167 +/- 6.0978	4.0 (1.08– 9.000)	3247.657 5 +/- 696.7893 9	3373.135 6 +/- 774.0377 0	65.7999 +/- 18.76406	0.01153 +/- 0.00401 0	Section 5.3.1.2
			Reference (R): Doxil® 2 mg/mL Liposome Injection (Doxorubicin Hydrochloride) [Lot No.: 0702943] Expiry Date:		33.9318 +/- 12.17257	4.0 (1.25– 25.00)	3153.993 1 +/- 654.6939 8	3296.114 6 +/- 733.6813 1	71.5502 + /- 17.23428	0.01029 +/- 0.00295 5	

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Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	Mean Parameters (± SD), Free Doxorubicin, N=10						Study Report location
					Cmax (ng /mL)	Tmax (hr)	AUCt (ng *hr/ mL)	AUCi (ng *hr/ mL)	tHalf (hr)	Kel (1/hr)	
Study No: DOX/003/08	To assess the bioequivalence of single dose intravenous infusion of Liposomal Doxorubicin HCl 2 mg/mL (50 mg/m ² dose), of Sun pharmaceuticals Industries Ltd., India and Doxil® 50 mg/m ² marketed by Tibotec herapeutics a division of Ortho Biotech, USA, in patients with advanced breast cancer/ovarian cancer under fed conditions	Randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study with washout period of at least 28 days under fed conditions.	Test (T): Doxorubicin Hydrochloride Liposome Injection 2mg/mL, [Batch No: JK71575] Mfg Date:	10 Patients with Ovarian Cancer Age: 49.5 (32-63)	893.744 +/- 492.2082	7.5 (1.00– 25.00)	68996.64 21 +/- 23511.66 540	70832.04 44 +/- 23448.32 162	58.4454 +/- 16.64037	0.01267 +/- 0.00326 9	
			Reference (R): Doxil® 2 mg/mL Liposome Injection (Doxorubicin Hydrochloride) [Lot No.: 0702943] Expiry Date:		673.048 +/- 549.7576	7.5 (4.0– 97.00)	56531.14 59 +/- 27681.58 759	57998.03 08 +/- 27237.36 988	60.4658 + /- 18.61936	0.01259 +/- 0.00424 0	

2. Statistical Summary of Comparative Bioavailability Data

Firm's Calculation:

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL 2 mg/mL (50 mg/m ² dose) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fed Bioequivalence Study (DOX/003/08)- Total Doxorubicin								
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.		Intra Subject (%CV)
AUC _{0-t} (hr * µg/ml)	3182.90	10	3086.25	10	103.13	89.46	118.89	17.22
AUC _∞ (hr * µg /ml)	3296.08	10	3215.36	10	102.51	88.86	118.26	17.31
C _{max} (µg/ml)	36.57	10	32.43	10	112.79	96.94	131.21	18.35

Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL 2 mg/mL (50 mg/m ² dose) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals								
Fed Bioequivalence Study (DOX/003/08)- Free Doxorubicin								
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.		Intra Subject (%CV)
AUC _{0-t} (hr * ng/ml)	64762.72	10	49632.56	10	130.48	84.50	201.48	56.02
AUC _∞ (hr * ng /ml)	66731.87	10	51545.98	10	129.46	85.56	195.88	53.05
C _{max} (ng/ml)	777.33	10	503.92	10	154.26	83.64	284.48	84.78

Comments on the statistical results:

The firm conducted a pilot study on 10 ovarian cancer patients to estimate the free and total doxorubicin concentration in human plasma. The 90% CI's for the least squares geometric means of Ln AUC_{0-t}, Ln AUC_∞ and LnC_{max} of free doxorubicin did not meet the BE criteria.

The AUC_{0-t} and AUC_{0-inf} results were within the acceptable limits of 80.00% to 125.00%, but for C_{max} results were not within the acceptable limits of 80.00% to 125.00% for total doxorubicin.

The C_{max}, AUC_t and AUC_i fail to meet the BE criteria most likely due to inadequate study power.

3. Study Information

Study Number	DOX/003/08
Study Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of intravenous infusion of Liposomal Doxorubicin 50 mg/m ² , of Sun pharmaceuticals Industries Ltd., India and Doxil® 50 mg/m ² marketed by Tibotec Therapeutics a division of Ortho Biotech, USA, in patients with advanced breast cancer/ovarian cancer under fed conditions.
Clinical Site (Name & Address)	Meenakshi Mission Hospital & Research Centre Lake area, Melur road, Madurai – 625107 Tamilnadu, India
Principal Investigator	Dr. K.S. Kirushna Kumar M.D
Dosing Dates	Refer Table 3A:Dosing Date
Analytical Site (Name & Address)	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (India) Phone Number: 91-265-2350789, 91-265-6615500
Analysis Dates	From 02nd February, 2008 to 17th June, 2008 for Free Doxorubicin and From 07th February, 2008 to 16th June, 2008 for Total Doxorubicin
Analytical Director	Dr. (b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	From 31st January, 2008 to 17th June, 2008 (139 Days) for Free Doxorubicin and From 31st January, 2008 to 16th June, 2008 (138 Days) for Total Doxorubicin

Patient	Period I	Period II
1-6	January 31, 2008	February 28, 2008 (except patient 5)
7,9-11	March 31, 2008	April 28, 2008 (except patient 9)
8	March 31, 2008	April 30, 2008
12	April 28, 2008	May 30 2008

4. Product information

The firm did not provide the CTD Table # 11 for the pilot study. Since the biolot JK93496A used in the full scale BE study # PKD_09_030 was manufactured on November 2009, it was not used in this pilot study # DOX/003/08. which was conducted during January 2008 to May 2008.

5. Demographics Profile of Subjects Completing the Bioequivalence Study

Pilot Fed Bioequivalence Study No. DOX/003/08		
	Treatment Groups	
	Test Product N = 10	Reference Product N = 41

Age (years)	Mean ± SD	49.5 ± 10.15	49.5 ± 10.15
	Range	32-63	32-63
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 40	3 (30.0%)	3 (30.0%)
	41-64	7 (70.0%)	7 (70.0%)
	65-75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	0 (0.0%)	0 (0.0%)
	Female	10 (100.0%)	10 (100.0%)
Race	Asian	10 (100.0%)	10 (100.0%)
	Black	0 (0.0%)	0 (0.0%)
	Caucasian	0 (0.0%)	0 (0.0%)
	Hispanic	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)
BSA	Mean + SD	1.483 ± 0.1808	1.483 ± 0.1808
	Range	1.23 – 1.77	1.23 – 1.77
Other			

6. Dropout Information

Pilot Fed Bioequivalence Study – DOX/003/08				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
5	Dropped due to adverse event in period I	I	NO	NA
9	Did not appear for period II	I	NO	NA

7. Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Pilot Fed Bioequivalence Study No.: DOX/003/08	
	Test n (%)	Reference n (%)
General disorders and administration site conditions		
Chills	1 (25.0)	1 (25.0)
Gastrointestinal disorders		
Mucositis	0 (0.0)	1 (25.0)
Cardiovascular System		
Palpitation	1 (25.0)	2 (50.0)
Respiratory System		
Chest Discomfort	1 (25.0)	0 (0.0)
Dyspnoea	1 (25.0)	0 (0.0)
Total	4 (100.0)	4 (100.0)

8. Protocol Deviations

Study No. DOX/003/08		
Type	Subject #s (Test)	Subject #s (Ref.)
None		

Comments on Study Design/ Drop Outs/Adverse Events/Protocol Deviations:

- The firm did not submit the clinical report for pilot fed study (DOX/003/08).
- There is no strong evidence suggesting that the test drug caused substantially more serious adverse events compared to the reference drug.

9. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses

Bioequivalence Study No. DOX/003/08 Total Doxorubicin										
Parameter	Standard Curve Samples									
Concentration (µg/mL)	0.250	0.500	1.000	4.000	10.00	30.00	50.00	80.01	100.01	
					1	4	6	0	2	
Inter day Precision (%CV)	3.5	7.2	0.5	2.8	1.3	0.5	3.7	0.6	2.5	
Inter day Accuracy (% actual)	3.8	-3.7	-6.2	-7.5	-3.2	2.8	4.2	4.0	5.7	
Linearity (Range of R values)	0.9969 to 0.9991									
Linearity Range (µg /mL)	0.250 -100.012									
Sensitivity/LOQ (µg /mL)	0.250									
Bioequivalence Study No. DOX/003/08 Total Doxorubicin										
Parameter	Quality Control Samples									
Concentration (µg /mL)	0.750		20.00		40.00		70.00			
Inter day Precision (%CV)	7.1		8.0		12.7		4.2			
Inter day Accuracy (% deviated from actual)	-10.7		1.7		1.9		10.6			

Bioequivalence Study No. DOX/003/08 Free Doxorubicin										
Parameter	Standard Curve Samples									
Concentration (ng/mL)	5.00	10.00	20.00	50.00	125.00	250.00	499.99	749.9	999.9	1499.98
								9	8	
Inter day Precision (%CV)	3.7	6.2	8.7	4.0	4.7	5.2	5.4	4.2	5.2	4.8
Inter day Accuracy (% actual)	2.4	-3.2	-2.8	-3.7	-2.0	2.6	1.1	1.5	0.0	3.1
Linearity (Range of R values)	0.9949 to 0.9997									
Linearity Range (ng /mL)	5.00 -1499.98									
Sensitivity/LOQ (ng /mL)	5.00									

10. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
PKD/S/019	13-02-2008	Sample reanalysis and Reporting of Final concentrations. (Revision No.01)

11. Reanalysis of study samples

Pilot Fed Study, Study No. DOX/003/08 Additional Information is in section 16.5								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual Number		% of total assays		Actual Number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.0	0.0	0.00%	0.00%	0.0	0.0	0.00%	0.00%
Unacceptable internal standard response	0.0	7.0	0.00%	1.94%	0.0	7.0	0.00%	1.94%
Inconsistent profile	0.0	1.0	0.00%	0.28%	0.0	1.0	0.00%	0.28%
Total	0.0	8.0	0.00%	2.22%	0.0	8.0	0.00%	2.22%

Any interfering peaks in chromatograms?	Not provided
Were 20% of chromatograms included?	Not provided
Were chromatograms serially or randomly selected?	Not provided

Comments on Study Assay Validation:

The firm did not provide the validation report.

4.1.3 In Vitro Study: Liposome Size Distribution

4.1.3.1.1 Study Information

Study No.	FDD-02/10-11/001
Study site	Sun Pharmaceutical India Ltd. Halol-Baroda Highway Halol-389350 Gujarat India
Principal Investigator	Dr. Subhas Bhowmick
Study Dates	November 19, 2010
SOP No.	QCI-132, Revision No-01
SOP Effective Date	11/25/2006
SOP Title	Determination of Spray Droplet Size Distribution for Nasal Spray Products Using the (b)(4) Sizer
Testing Method Description	Instrumental Parameter 1. System Conditions Cell check value: (b)(4) Temperature setting: Sensor holder 2. Measure Conditions Sampling Times: 100 3. Display Conditions 3.1 Operation Conditions SPAN operation: Yes Cumulative: 10% to 90% 3.2 Cumulation Cumulative distribution: On Size Class: Passing 3.3 Refractive Index Particle RI: (b)(4) Dispersant RI: (b)(4) Dispersant Viscosity: (b)(4) 3.4. Distribution Graph Form of Distribution: Standard Distribution Base: Scattering Light Intensity (b)(4) Cumulative Particle size: 10%,50% and 90% Procedure for Particle size: Select one vial, pour the sample in vial of (b)(4) such that it covers 80% of cuvette area. Start the measurement using the parameters mentioned and determine 0 I 0, D50, 090 and SPAN.
Testing Equipment Used (e.g., name, model, etc)	(b)(4) Make: (b)(4)
Operating Conditions for Testing Equipment Used	Temperature : 15°C to 35°C Humidity : Less than 85%
Analytical Method Description	Dynamic Light Scattering Select one vial, pour the sample in vial of (b)(4) such that it covers % of cuvette area. Start the measurement using the parameters mentioned and determine DIO, D50, D90 and SPAN.

Study Type	TEST		REFERENCE	
	Lot No.	Manufacture Date	Lot No.	Expiration Date
Bioequivalence study (PK study)	JK93496A	Nov 2009	0907642	Jan 2011
In-Vitro equivalence study	JK93371A	Nov 2009	0910338	Feb 2011
	JK93496A	Nov 2009	0911606	May 2011
	IK93699A	Dec 2009	0907642	Jan 2011

4.1.3.1.2 Validation Summary Table for Droplet Size Distribution by Dynamic Light Scattering

4.1.3.1.2.1 Precision

	D10	D50	D90	Span
Mean	(b) (4)			
%RSD	(b) (4)			
Range	(b) (4)			

4.1.3.1.2.2 Intermediate Precision (By Dates and By Analysts)

Day 1	D10	D50	D90	Span
Mean	(b) (4)			
%RSD	(b) (4)			
Day 2	D10	D50	D90	Span
Mean	(b) (4)			
%RSD	(b) (4)			
%Difference (Day 1 vs. Day 2)	(b) (4)			
Interday %RSD	(b) (4)			

Analyst 1	D10	D50	D90	Span
Mean	(b) (4)			
%RSD	(b) (4)			
Analyst 2	D10	D50	D90	Span
Mean	(b) (4)			
%RSD	(b) (4)			

%Difference (Day 1 vs. Day 2)		(b) (4)
Interday %RSD		

4.1.3.1.3 Results Summary – Liposome Size Distribution by Dynamic Light Scattering Study Information (Firm Calculated)

D ₅₀ Summary								
	Mean Distance		Variability (%CV)				Mean Ratio (T/R)	
			Within Lot (n=10)			Between Lot (n=3)	Total (n=30)	Arithm (n=30)
	Arithm	Geo	Lot 1	Lot 2	Lot 3			
Test								(b) (4)
Ref								

SPAN Summary								
	Mean Distance		Variability (%CV)				Mean Ratio (T/R)	
			Within Lot (n=10)			Between Lot (n=3)	Total (n=30)	Arithm (n=30)
	Arithm	Geo	Lot 1	Lot 2	Lot 3			
Test								(b) (4)
Ref								

Comments:

- Liposome size distribution by dynamic light scattering was performed on 3 lots of 10 vials each for the test and reference products.
- Based on the firm’s calculations, the test product PASSED the PBE statistical criteria for both D50 and span. However, the firm did not submit the SAS Transport files for verification by the reviewer.
- The firm’s liposome size distribution is incomplete. The firm should submit its in vitro testing data in the **Electronic SAS Transport format** using DBE’s template (shown example below). The in vitro data in the correct format will be used by the DBE for PBE statistical analysis and for verification purposes.

4.2 Formulation Data

Ingredient	2 mg/mL (10 mL and 25 mL)	
	Mg/mL	%W/V
Doxorubicin Hydrochloride	2.00	0.200
Hydrogenated Soya Phosphatidyl Choline	9.58	0.958
MPEG-Distearoyl Phosphatidylethanolamine	3.19	0.319
Cholesterol (b) (4) NF	3.19	0.319
Ammonium Sulphate, NF	#	
Histidine USP	(b) (4)	
Sucrose, NF	(b) (4)	
Sodium Hydroxide, NF	(b) (4) (pH adjustment)	
Hydrochloric Acid, NF	(b) (4) (pH adjustment)	
(b) (4)		

Ammonium Sulphate is (b) (4) approximately 2 mg per mL.

Component	Sun Pharmaceuticals Test Formulation ANDA # 203263 (mg/mL)	Ortho Biotech Doxil® Liposome Injection NDA # 050718 (mg/mL)
Doxorubicin Hydrochloride	2.00	2.00
Hydrogenated Soya Phosphatidyl Choline	9.58	9.58
MPEG-Distearoyl Phosphatidylethanolamine	3.19	3.19
Cholesterol (b) (4), NF	3.19	3.19
Ammonium Sulphate, NF	#	2*
Histidine USP	(b) (4)	
Sucrose, NF	(b) (4)	
Sodium Hydroxide, NF	(b) (4) (pH adjustment)	(b) (4) (pH 6.5)
Hydrochloric Acid, NF	(b) (4) (pH adjustment)	(b) (4) (pH 6.5)
(b) (4)		

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	YES
If no, are they all above/within IIG (per day) limits?	
If no, are additional data or Pharm/Tox consult necessary?	NO
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	N/A
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	N/A
Are all strengths of the test formulation acceptable	YES

Reviewer's Comments:

1. The test and the RLD products contain the same active ingredient and inactive ingredients.
2. Based on Guidance for Industry: Individual product Bioequivalence Recommendations for Doxorubicin Hydrochloride Liposome Injection, "Being a parenteral drug product, a generic doxorubicin HCl liposome injection must be qualitatively and quantitatively the same as the RLD, except differences in buffers, preservatives and antioxidants provided that the applicant identifies and characterizes these differences and demonstrates that the differences do not impact the safety/efficacy profile of the drug product".
3. The formulation of the test product is qualitatively (Q1) same but not quantitatively (Q2) as that of the reference listed drug. Based on the calculation below, the amount of the histidine in the test product is within $\pm 5\%$ of the corresponding excipient in the RLD, but not the sucrose concentration (exceeds the allowable 5%).

Histidine = (b) (4)

Sucrose = (b) (4)

4. On Oct 28, 2011, the Regulatory Support Branch consulted the Division of Clinical Review (DCR) regarding “whether or not the concentration in sucrose ((b) (4) in RLD vs. (b) (4) in applicant) will have an effect on any safety aspect.
5. The Division of Clinical Review (DCR) does not find that the difference in sucrose content between the RLD and Test preparations will impact the safety of the administered dose and provided the following justification

“According to the RLD label, "DOXIL doses up to 90 mg must be diluted in 250 mL of 5% Dextrose injection". The 90 mg dose is equivalent to 45 mL at a concentration of 2 mg/mL. Thus, the difference between the (b) (4) (b) (4) sucrose will be further minimized after this 45mL/250 mL dilution: the RLD will have (b) (4) vs. ANDA will have (b) (4). The difference is thus less than (b) (4), which is not of significant safety concern for i.v. injection.

As noted by the chemistry reviewer, “The function of Sucrose is to maintain isotonicity. It is not part of the liposome particle composition. In other words, (b) (4) (b) (4) but not part of the composition in constructing the liposome structure itself.” In addition, it must be noted that the product requires considerable dilution in D5W prior to intravenous administration. Thus, the very small difference in the amount of sucrose present in this formulation versus the 5% allowable difference is unlikely to add further to the safety risk of the product.”

The decision regarding the acceptability of the Sun formulation for filing is deferred to the Division of Bioequivalence 1, the Division of Chemistry and the Regulatory Support Branch. Evaluation of the equivalence of liposomal carriers and doxorubicin BE is deferred to the DBE [DARRTS: GIERHART, BRENDA S 11/23/2011 N/A 11/23/2011 CONSULT REV-CLINICAL-01(General Consult Review) Original-1 (Unknown) Archive].

6. In the amendment dated Nov 3, 2011 the firm stated that “**composition provided in reference listed drug’s package insert states ‘sucrose to maintain tonicity’. Hence during development of generic formulation for Doxil®, at Sun Pharma various lots of Doxil® were evaluated for the quantity of sucrose by HPLC method (RI detector), and based on this determination (b) (4) quantity of sucrose has been decided for Sun’s proposed product**”. Results of sucrose content in Sun’s product and RLD are given below:

Doxil®			Sun’s Proposed product		
Strength	Lot #	Sucrose content(mg/mL)	Strength	Lot #	Sucrose content(mg/mL)
10 mL	0706845	(b) (4)	10 mL	JK93699	(b) (4)
				JK93496	
	0709500		25 mL	JKJ0322	
				JKJ0142	

	0543472	(b) (4)		JK93743	(b) (4)		
	0729032						
25 mL	0710167						
Doxil®			Sun's Proposed product				
Strength	Lot #	Osmolality	Strength	Lot #	Osmolality		
10 mL	0706845	(b) (4)	10 mL	JK93699	(b) (4)		
	0709500			JK93496			
				JK93371			
	0729032			25 mL	JKJ0322		
					JKJ0142		
				0702943			JK93743
0907642							
0543472							
25 mL	0710167						
	0715423						
	0812820						

The above results indicate that the osmolality as well as the sucrose content of the test product is comparable to those of the reference product. In addition, it is noted that the RLD labeling does not specify the sucrose content of Doxil®.

7. As per FDA IIG Database for Approved Drug Products/Unit, the maximum level listed for sucrose is 19.5% for intravenous injection. The amount of sucrose (b) (4) in the current test product is below than the level listed in the IIG database.
8. DBE considers the formulation to be acceptable, even though the formulation of the test product is not quantitatively (Q2) same as that of the reference listed drug (sucrose difference exceeds the allowable 5%) for the following reasons:
 - The function of Sucrose is to maintain isotonicity. It is not part of the liposome composition. In other words, (b) (4), (b) (4), but not part of the composition in constructing the liposome structure itself. The osmolality of the test product is comparable to that of the reference product.
 - The amount of sucrose in the test product is below the level listed in the FDA IIG database.
 - The Division of Clinical Review conclusion that the difference in the sucrose content between the test and RLD formulations will not have any impact on the safety of the administered dose.
 - The firm submitted an in vivo bioequivalence study demonstrating bioequivalence of the test product.

4.3 Dissolution Data

Dissolution Review Path	Current review (No “dissolution only” review on this ANDA)

Table 18. Dissolution Data (TO BE INCLUDED IN ECTD TABLE LIST)

Dissolution Conditions		Apparatus:		Bottle Rotating Apparatus							
		Sinker:		No							
		Speed of Rotation:		12 rpm							
		Medium:		USP phosphate buffer pH 6.4 (b) (4)							
		Volume:		90 mL							
		Temperature:		52°C							
Firm’s Proposed Specifications		0.5 hr: NMT (b) (4)%, 1.5 hr: (b) (4)%, 3 hr: (b) (4)%, 5 hr: (b) (4)%, 7 hr: NLT (b) (4)%									
Dissolution Testing Site (Name, Address)		Sun Pharma Advanced Research Company Limited, Nima Compound, Tandalja, Vadodara-390012, Gujarat, India.									
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units*	Collection Times (hr)					Study Report Location	
					0.5	1.5	3	5	7		
DOX_IV R_US_20 10	12/14/2010 and 12/24/2010	Doxorubicin Hydrochloride Liposome Injection Batch # JK93496 Mfg date: Nov 2009	2 mg/mL Injection	12	Mean	8.00	20.07	46.34	69.67	87.27	Module# 5.3.1.3
					Range	(b) (4)					
					%CV	15.6	14.5	8.8	4.9	3.4	
		Doxil® Liposome Injection Batch # 0910338 Exp. date: Feb 2011	2 mg/mL Injection	12	Mean	9.97	25.54	52.56	76.25	94.67	
					Range	(b) (4)					
					%CV	13.5	13	6.9	4.2	3.20	

* Each lot of Test and Reference were tested on two different dates with 6 tubes of test and 6 tubes of reference on each date

Reviewer's Comments:

There is no "dissolution only" review conducted for this test product.

- There is no USP method for this product. The external dissolution database for Doxorubicin Hydrochloride Liposome Injection recommends the firm's to develop a method to characterize in vitro release.

[Redacted] (b) (4)

The comparative testing should be conducted on the test and reference product, using one dosage unit (vial) (10 mL of 2 mg/mL) per replicate and six samples taken per unit for six different time points: Six samples of 1 mL of the vial content should be transferred to six separate glass tubes containing the medium of 98% fetal bovine serum with 80 mM NH₄Cl at pH 6.0 to obtain the final volume of 100 mL. The resulting drug concentration should be 20 microgram/mL of liposomal doxorubicin. These glass tubes should be incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome should be determined at the following six time points: 0 hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs. The testing should be replicated for 12 dosage vials per each test and the reference drug product.

The individual percent doxorubicin release data from each vial at each time point should be submitted, as well as the mean data from 12 vials at each time point for each product (% mean and % CV) over the period of 0 to 4 hours for the test and RLD from 12 dosage units.

[Redacted] (b) (4)

[Redacted] (b) (4)

- The firm conducting comparative dissolution testing using the following proposed method:

Apparatus: Bottle Rotating Apparatus

Speed of Rotation: 12 rpm

Medium: USP phosphate buffer pH 6.4 [Redacted] (b) (4)

Volume: 90 mL

Temperature: 52°C

[Redacted] (b) (4)

- Currently, DBE does not encourage the use of non compendial apparatus/method. Since bottle rotating apparatus is not a ^{(b) (4)}

[Redacted]

The firm is recommended to conduct additional in vitro drug release testing ^{(b) (4)} for comparison. In addition, it is requested to submit all detailed information concerning the development, optimization and validation of its own test method.

- The firm should submit all detailed information concerning the development, optimization and validation of its own test method and the recommended test method.

4.4 SAS Output

4.4.1 Fed Study Data

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	2	2	1	1	B	0	34.76	112.23	195.28	252.89	291.47	279.75	265.16	232.47	236.90	164.90	153.24	146.88	86.92	159.87
2	2	2	2	1	A	0	28.82	108.05	167.35	239.94	248.83	289.33	269.02	385.77	334.93	369.88	402.76	263.44	415.42	225.86
3	3	2	1	1	B	0	67.99	138.26	185.32	240.98	245.27	229.07	191.77	166.28	147.20	311.28	294.46	139.08	124.79	167.08
4	3	2	2	1	A	0	40.81	83.84	110.54	162.26	160.96	110.77	111.91	119.96	104.96	190.53	182.26	134.41	127.28	114.70
5	8	2	1	1	B	0	40.87	75.60	121.30	161.72	190.23	265.16	304.89	258.79	279.72	249.44	248.12	176.25	89.07	73.13
6	8	2	2	1	A	0	85.21	184.98	290.09	423.72	360.86	645.82	981.63	1030.68	801.61	484.84	459.93	555.27	195.65	169.82
7	10	1	1	1	A	0	21.25	60.46	94.71	111.22	129.51	142.31	133.76	136.55	157.07	210.59	225.63	258.92	143.38	107.96
8	10	1	2	1	B	0	47.88	86.97	112.05	164.03	339.15	414.11	291.20	382.50	374.70	345.95	422.70	387.18	411.63	0.00
9	12	1	1	1	A	0	39.70	100.35	184.42	164.97	203.27	131.07	159.30	169.08	215.76	236.14	338.63	330.92	298.77	147.41
10	12	1	2	1	B	0	76.13	179.82	271.02	322.78	401.80	352.96	328.35	354.30	366.47	482.43	473.06	525.19	312.11	278.45
11	13	2	1	1	B	0	54.15	121.82	225.29	243.94	215.76	136.68	150.10	136.31	156.12	105.05	121.07	98.35	136.25	98.55
12	13	2	2	1	A	0	16.65	40.57	64.53	83.70	101.40	142.82	106.07	97.63	109.28	97.44	113.85	134.37	103.30	93.78
13	16	2	1	1	B	0	77.11	115.72	155.49	236.46	240.60	503.03	435.00	424.88	463.54	403.32	414.27	374.22	195.20	137.93
14	16	2	2	1	A	0	28.20	49.93	72.22	89.51	108.38	121.05	121.83	111.22	116.22	130.86	146.45	166.65	97.04	257.02
15	17	1	1	1	A	0	90.86	189.59	309.68	411.12	397.85	536.07	545.02	574.91	704.85	463.96	480.76	297.04	627.89	105.52
16	17	1	2	1	B	0	592.28	0.00	0.00	123.10	121.73	263.58	281.27	319.59	311.14	190.76	220.13	146.21	164.23	108.07
17	18	1	1	1	A	0	48.60	94.22	132.96	185.43	180.12	192.66	211.13	230.87	260.33	132.68	108.48	124.39	95.34	65.96
18	18	1	2	1	B	0	47.39	98.16	155.21	216.65	242.33	249.99	329.73	337.27	328.19	200.97	181.94	153.05	130.30	72.90
19	20	2	1	1	B	0	59.46	102.76	165.71	242.98	217.73	111.33	102.32	123.52	176.29	147.84	185.21	273.88	138.25	50.84
20	20	2	2	1	A	0	67.75	118.54	181.00	226.91	221.76	152.93	161.70	168.99	170.05	100.76	96.00	72.75	67.46	75.78
21	22	2	1	1	B	0	45.48	64.89	102.85	150.45	187.08	184.13	180.67	230.53	251.97	66.70	67.94	217.70	374.99	183.54
22	22	2	2	1	A	0	56.96	112.66	161.44	234.93	260.18	172.70	167.52	161.30	159.10	181.78	180.62	471.48	236.99	101.27

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
23	23	1	1	1	A	0	54.82	113.99	184.98	285.09	237.22	84.59	84.57	76.12	89.89	179.02	201.18	116.45	238.39	76.16
24	23	1	2	1	B	0	20.32	51.40	73.82	81.82	90.98	93.21	79.73	85.55	88.25	71.09	65.72	173.88	120.24	75.82
25	26	2	1	1	B	0	22.49	63.54	112.93	145.51	209.60	129.54	96.42	83.93	81.81	77.42	68.85	112.45	88.03	44.25
26	26	2	2	1	A	0	25.58	52.62	108.90	109.55	139.57	145.52	155.13	170.60	153.10	116.97	122.54	123.23	91.80	63.52
27	27	1	1	1	A	0	17.10	38.92	65.98	86.19	92.17	84.02	90.56	94.67	107.83	105.51	108.61	125.14	80.77	69.43
28	27	1	2	1	B	0	34.54	72.07	127.12	137.20	157.63	81.90	81.05	98.13	90.03	143.92	112.13	128.76	95.11	130.01
29	28	2	1	1	B	0	29.40	60.32	104.74	149.49	163.44	176.34	158.23	157.95	165.99	139.88	128.48	139.87	106.62	97.18
30	28	2	2	1	A	0	34.27	75.98	127.57	170.78	163.26	158.70	126.06	160.22	112.88	140.41	122.95	95.62	63.96	73.38
31	29	2	1	1	B	0	93.62	64.10	119.10	161.03	162.68	133.20	147.71	142.37	141.20	146.08	136.26	136.49	165.21	109.01
32	29	2	2	1	A	0	22.44	70.07	104.72	113.51	117.36	141.70	117.27	117.70	123.85	115.34	119.01	188.86	94.39	62.97
33	30	2	1	1	B	0	47.52	76.96	135.94	249.26	156.65	179.97	130.14	114.14	122.88	166.77	141.23	113.05	120.22	97.03
34	30	2	2	1	A	0	35.85	74.04	107.74	111.58	133.94	166.83	194.27	170.24	189.54	150.54	123.21	125.62	200.76	91.06
35	31	1	1	1	A	0	72.22	121.89	169.49	233.53	333.26	324.58	315.67	235.18	239.64	307.55	431.63	218.18	231.19	179.53
36	31	1	2	1	B	0	77.62	145.09	260.22	336.90	296.03	229.41	256.08	265.35	323.39	137.03	144.18	291.06	319.89	139.20
37	32	1	1	1	A	0	73.28	266.11	205.05	323.38	309.29	272.43	389.25	314.20	282.59	260.06	269.44	183.88	426.05	95.62
38	32	1	2	1	B	0	27.88	62.42	83.72	135.43	146.75	157.34	164.72	130.63	138.34	173.02	95.21	203.63	296.48	112.41
39	33	2	1	1	B	0	50.60	108.66	209.85	288.07	321.09	391.59	225.38	306.18	359.21	290.09	182.03	244.04	150.63	108.78
40	33	2	2	1	A	0	53.60	88.69	140.03	264.28	206.75	719.71	620.30	263.70	335.76	215.42	332.49	288.81	262.82	250.04
41	34	1	1	1	A	0	27.53	98.38	83.32	109.59	159.95	272.21	165.21	107.04	196.94	146.17	112.04	181.46	52.80	74.06
42	34	1	2	1	B	0	26.10	63.36	93.75	121.13	156.82	184.94	168.42	180.29	193.47	110.18	121.70	333.72	283.98	81.11
43	35	2	1	1	B	0	49.81	88.28	200.20	272.46	228.19	142.29	135.51	168.34	142.58	114.11	95.62	229.48	431.72	334.62
44	35	2	2	1	A	0	48.80	118.18	196.61	287.02	348.86	328.39	349.42	324.60	376.42	244.65	347.84	143.35	231.73	286.17
45	36	1	1	1	A	0	23.75	45.10	62.40	39.24	16.30	134.81	115.99	86.07	93.32	66.48	56.41	94.62	44.04	64.99
46	36	1	2	1	B	0	21.82	45.57	71.79	86.11	98.04	81.31	88.55	96.96	88.47	100.26	97.25	54.65	73.09	44.04
47	37	1	1	1	A	0	25.10	58.03	85.16	106.76	89.98	146.82	178.79	163.37	169.07	118.71	138.52	171.06	278.69	809.66
48	37	1	2	1	B	0	11.65	30.05	45.39	61.45	72.23	70.35	62.75	58.07	66.07	72.49	65.44	86.56	112.27	123.97

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
49	38	2	1	1	B	0	28.00	48.71	84.21	126.56	132.83	140.47	124.64	122.15	99.52	108.49	102.63	109.21	145.17	136.40
50	38	2	2	1	A	0	26.34	70.19	105.72	161.25	143.02	245.78	218.97	253.99	232.98	113.35	123.31	140.04	232.51	64.92
51	39	2	1	1	B	0	13.20	28.39	54.73	72.44	92.01	90.58	101.68	82.47	83.82	133.09	122.14	153.54	199.72	258.89
52	39	2	2	1	A	0	22.58	40.13	63.73	113.09	136.56	227.05	262.71	268.17	185.48	125.30	118.72	93.51	64.46	80.19
53	40	1	1	1	A	0	25.31	54.54	75.36	88.49	114.60	102.27	107.99	99.92	94.55	109.94	105.99	103.14	121.27	51.76
54	40	1	2	1	B	0	20.11	41.74	67.61	75.21	86.36	102.63	103.56	103.48	102.47	76.94	70.84	174.20	124.98	79.99
55	41	1	1	1	A	0	18.20	50.28	80.83	102.44	91.16	82.28	79.30	76.02	70.53	96.50	78.20	96.79	118.51	67.65
56	41	1	2	1	B	0	22.28	46.83	61.82	101.61	72.43	99.64	83.11	80.77	69.31	51.99	61.44	76.41	115.48	84.19
57	42	2	1	1	B	0	43.46	73.16	96.42	149.12	156.51	71.37	69.88	69.63	83.02	72.77	62.18	77.49	76.06	26.74
58	42	2	2	1	A	0	41.88	69.01	98.13	129.06	126.14	172.62	137.50	136.40	159.12	124.08	96.97	105.75	76.57	47.87
59	43	2	1	1	B	0	16.35	49.53	77.73	79.51	171.61	112.75	115.89	118.91	129.04	59.99	43.26	93.10	63.79	55.12
60	43	2	2	1	A	0	29.87	90.28	148.33	229.80	225.05	108.95	133.07	119.93	132.76	155.48	113.87	71.79	64.99	42.99
61	45	1	1	1	A	0	25.77	61.15	79.98	123.16	140.39	131.78	130.62	139.83	153.34	104.77	88.22	88.03	111.79	70.55
62	45	1	2	1	B	0	18.09	37.25	60.60	73.64	62.71	134.54	157.33	143.67	207.39	88.20	117.53	96.59	87.49	94.21
63	47	1	1	1	A	0	38.98	113.12	166.67	265.94	237.09	236.61	217.22	221.36	193.03	210.75	183.26	210.07	269.26	223.12
64	47	1	2	1	B	0	22.93	49.59	69.72	125.16	126.15	120.47	104.67	116.95	95.27	114.68	128.14	171.13	123.68	86.20
65	48	2	1	1	B	0	41.40	95.43	157.87	226.48	237.68	313.00	287.48	295.74	429.79	120.00	147.56	151.95	150.27	94.09
66	48	2	2	1	A	0	17.03	43.04	61.30	64.94	89.41	72.41	67.75	70.37	74.75	77.46	77.98	68.17	63.12	30.70
67	51	1	1	1	A	0	31.14	62.38	98.90	133.42	166.19	153.44	170.63	160.08	226.49	172.04	190.43	165.45	218.34	104.17
68	51	1	2	1	B	0	16.44	50.95	187.25	105.54	117.53	90.64	86.85	103.08	92.31	98.56	91.01	78.02	63.95	62.53
69	52	2	1	1	B	0	6.70	21.35	43.84	91.41	78.64	99.88	146.47	122.27	110.06	112.27	106.10	104.29	66.24	46.48
70	52	2	2	1	A	0	49.21	52.80	124.47	110.38	287.17	212.74	102.10	155.98	80.69	106.37	112.94	69.02	63.94	43.45
71	53	2	1	1	B	0	33.33	62.66	107.89	103.13	123.28	185.73	153.26	163.43	220.05	123.75	116.66	148.98	57.39	51.32
72	53	2	2	1	A	0	33.72	62.08	90.72	127.69	103.39	116.00	105.78	107.38	142.14	87.64	83.37	138.25	106.80	68.10
73	54	2	1	1	B	0	27.14	66.23	102.90	107.18	114.88	129.75	121.83	124.31	154.16	110.65	105.96	124.11	51.43	40.29
74	54	2	2	1	A	0	22.23	50.72	82.04	104.83	96.80	100.04	106.73	91.32	124.04	81.92	65.71	121.32	98.84	56.03

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
75	57	2	1	1	B	0	7.43	20.16	26.35	46.79	53.26	83.72	65.56	86.26	61.62	62.73	53.27	80.49	110.43	30.00
76	57	2	2	1	A	0	18.73	30.86	48.73	85.38	90.98	101.56	100.49	109.91	114.13	84.66	81.11	76.37	102.39	42.80
77	58	1	1	1	A	0	15.48	51.93	107.84	107.00	75.91	117.04	108.12	127.85	120.67	80.11	93.78	92.79	60.87	54.01
78	58	1	2	1	B	0	27.29	76.20	118.66	160.79	172.06	126.75	176.49	95.72	142.76	139.07	139.84	200.27	186.85	76.68
79	60	1	1	1	A	0	20.77	59.11	100.24	128.29	129.18	101.02	91.59	68.75	86.87	66.05	61.96	104.28	61.97	66.13
80	60	1	2	1	B	0	6.14	12.39	21.07	49.82	29.64	186.77	158.81	103.10	120.20	42.42	47.69	54.63	13.23	10.25
81	61	2	1	1	B	0	38.66	53.52	89.57	107.73	95.48	135.17	122.24	105.46	145.94	130.62	111.34	108.83	124.80	54.54
82	61	2	2	1	A	0	26.63	58.93	86.32	108.42	103.33	124.79	107.32	72.20	87.80	95.33	116.01	73.09	55.72	31.54

Obs	c16	c17	c18	KE_FIRST	KE_LAST	trt	c19	i
1	63.93	42.70	27.21	15	18	2	0	20
2	47.97	30.20	22.65	15	18	1	0	20
3	158.47	73.34	21.69	15	18	2	0	20
4	55.19	37.43	18.52	15	18	1	0	20
5	35.30	16.84	6.28	15	18	2	0	20
6	110.83	13.63	14.30	15	18	1	0	20
7	70.80	17.39	9.49	15	18	1	0	20
8	0.00	0.00	0.00	.	.	2	0	20
9	86.30	22.72	24.54	15	18	1	0	20
10	114.48	69.20	18.40	15	18	2	0	20
11	118.25	48.94	104.48	.	.	2	0	20
12	188.48	34.62	35.36	.	.	1	0	20
13	67.85	29.03	9.45	15	18	2	0	20
14	66.62	26.05	12.88	16	18	1	0	20
15	79.02	27.22	0.00	15	17	1	0	20
16	60.02	22.07	22.24	15	18	2	0	20

17	31.41	19.89	7.89	15	18	1	0	20
18	16.15	8.67	0.00	15	17	2	0	20
19	0.00	0.00	35.79	.	.	2	0	20
20	35.67	11.31	0.00	15	17	1	0	20
21	0.00	16.24	5.77	.	.	2	0	20
22	73.59	18.45	8.66	15	18	1	0	20
23	83.91	24.54	21.74	15	18	1	0	20
24	47.97	25.55	25.11	15	18	2	0	20
25	30.06	15.88	14.49	15	18	2	0	20
26	55.22	26.46	16.52	15	18	1	0	20
27	42.28	22.34	11.27	15	18	1	0	20
28	43.52	18.75	7.65	15	18	2	0	20
29	85.01	31.81	9.58	15	18	2	0	20
30	73.90	30.02	8.91	15	18	1	0	20
31	41.02	19.17	12.00	15	18	2	0	20
32	43.49	26.50	11.73	15	18	1	0	20
33	40.53	24.10	9.24	15	18	2	0	20
34	35.62	24.68	14.70	15	18	1	0	20
35	104.10	43.37	17.61	15	18	1	0	20
36	82.66	32.50	18.32	15	18	2	0	20
37	106.77	39.15	39.51	15	18	1	0	20
38	103.56	105.53	43.43	15	18	2	0	20
39	113.64	57.48	28.57	15	18	2	0	20
40	123.25	59.62	42.14	15	18	1	0	20
41	23.05	28.63	20.23	15	18	1	0	20
42	55.20	41.16	12.74	15	18	2	0	20
43	137.88	115.97	26.66	15	18	2	0	20
44	33.82	26.47	18.42	15	18	1	0	20
45	71.42	7.05	0.00	15	17	1	0	20
46	15.85	0.00	0.00	14	16	2	0	20
47	29.85	12.12	6.33	16	18	1	0	20
48	35.05	16.53	8.44	16	18	2	0	20
49	46.35	21.11	8.91	15	18	2	0	20
50	35.05	18.76	12.36	15	18	1	0	20
51	47.27	34.48	17.96	15	18	2	0	20
52	60.72	45.68	31.88	.	.	1	0	20
53	35.60	20.84	11.79	15	18	1	0	20
54	40.41	28.83	27.46	.	.	2	0	20
55	34.30	43.56	35.76	.	.	1	0	20

56	324.83	45.60	13.84	.	.	2	0	20
57	12.59	8.59	0.00	15	17	2	0	20
58	25.36	13.86	0.00	15	17	1	0	20
59	23.68	16.80	11.96	15	18	2	0	20
60	17.60	9.23	5.07	15	18	1	0	20
61	46.11	10.71	6.30	15	18	1	0	20
62	12.52	7.37	0.00	15	17	2	0	20
63	185.00	55.57	16.36	15	18	1	0	20
64	62.79	37.60	13.52	15	18	2	0	20
65	84.43	38.29	15.71	15	18	2	0	20
66	21.39	9.90	5.39	15	18	1	0	20
67	84.12	18.80	10.21	15	18	1	0	20
68	44.83	27.20	13.10	15	18	2	0	20
69	35.03	10.71	0.00	15	17	2	0	20
70	15.55	8.96	0.00	15	17	1	0	20
71	50.94	9.27	10.45	15	18	2	0	20
72	51.44	17.84	11.39	15	18	1	0	20
73	15.49	5.38	0.00	15	17	2	0	20
74	28.30	11.88	0.00	15	17	1	0	20
75	21.54	8.89	5.69	15	18	2	0	20
76	22.20	11.86	11.73	15	18	1	0	20
77	38.31	20.01	8.62	15	18	1	0	20
78	87.13	38.16	11.05	15	18	2	0	20
79	24.29	11.50	0.00	15	17	1	0	20
80	9.91	0.00	0.00	.	.	2	0	20
81	40.19	22.90	15.70	15	18	2	0	20
82	21.87	15.21	0.00	14	16	1	0	20

Liposomal Doxorubicin

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	KE_FIRST	KE_LAST	trt	c19	i
1	2	2	1	1	B	0	4.01	7.79	17.65	30.68	31.10	33.83	37.85	36.38	34.71	38.62	36.34	26.87	18.88	13.82	7.64	3.10	1.75	15	18	2	0	20
2	2	2	2	1	A	0	3.93	12.93	19.61	26.27	30.82	34.78	38.39	35.04	34.45	34.63	33.45	30.77	23.72	17.42	8.98	4.48	1.96	15	18	1	0	20
3	3	2	1	1	B	0	6.96	14.61	23.72	33.12	30.13	30.29	30.48	30.48	27.90	30.67	30.99	26.81	21.22	13.48	9.42	4.86	2.48	15	18	2	0	20
4	3	2	2	1	A	0	6.07	13.16	20.79	31.34	30.10	31.25	26.88	25.29	30.69	18.89	21.16	25.75	19.90	13.63	7.09	3.95	1.87	15	18	1	0	20
5	8	2	1	1	B	0	6.52	12.57	19.98	28.09	31.59	33.38	34.17	34.83	33.52	29.37	27.07	19.95	16.37	8.91	3.52	1.26	0.00	15	17	2	0	20
6	8	2	2	1	A	0	6.24	19.11	19.24	27.08	26.31	26.99	26.80	29.06	29.09	27.50	26.85	19.87	11.24	11.42	4.72	2.14	0.00	15	17	1	0	20
7	10	1	1	1	A	0	3.41	8.18	12.44	17.36	19.47	27.30	28.08	29.16	29.60	25.11	22.30	20.16	15.77	10.29	5.47	2.65	1.21	15	18	1	0	20
8	10	1	2	1	B	0	4.95	11.74	17.38	24.02	27.21	27.97	28.87	28.70	33.89	27.29	25.49	21.84	19.76	0.00	0.00	0.00	0.00	.	.	2	0	20
9	12	1	1	1	A	0	6.32	13.65	29.15	29.98	33.00	21.56	32.60	32.38	32.94	31.50	30.90	26.72	18.29	11.40	5.44	2.43	1.11	15	18	1	0	20
10	12	1	2	1	B	0	7.48	15.14	23.72	27.25	31.79	29.85	30.41	31.09	31.86	30.78	29.09	24.19	17.95	12.23	8.03	4.52	1.95	15	18	2	0	20
11	13	2	1	1	B	0	5.11	11.37	19.53	27.18	20.21	30.07	25.62	30.58	31.48	29.63	33.05	23.56	14.95	9.45	4.76	2.42	1.20	15	18	2	0	20
12	13	2	2	1	A	0	4.17	11.06	14.35	22.36	22.99	28.06	38.42	26.04	24.77	25.89	25.51	21.51	17.12	12.30	6.09	3.49	1.66	15	18	1	0	20
13	16	2	1	1	B	0	6.40	13.04	14.82	22.19	23.43	27.77	28.33	24.99	26.19	25.96	26.35	22.05	14.56	8.67	3.29	1.38	0.00	15	17	2	0	20
14	16	2	2	1	A	0	5.86	11.58	17.04	24.52	26.83	25.27	25.20	25.72	27.15	23.71	25.74	19.87	13.59	7.84	3.79	2.03	0.00	15	17	1	0	20
15	17	1	1	1	A	0	5.95	12.94	21.36	29.77	30.32	29.86	29.83	29.64	29.71	28.91	25.51	20.49	14.76	9.24	3.41	1.69	0.00	15	17	1	0	20
16	17	1	2	1	B	0	2.72	8.13	24.15	30.66	30.50	30.25	26.03	29.74	29.74	26.94	26.49	24.77	18.83	8.54	4.46	1.93	0.00	15	17	2	0	20
17	18	1	1	1	A	0	6.37	12.45	17.46	22.85	22.57	24.43	24.87	23.94	20.78	24.13	21.77	15.48	13.41	6.83	3.10	1.47	0.00	15	17	1	0	20
18	18	1	2	1	B	0	5.65	9.77	15.83	22.05	23.25	21.86	22.58	20.21	18.65	20.48	21.41	14.75	9.59	3.30	0.00	0.00	0.00	13	15	2	0	20
19	20	2	1	1	B	0	5.66	11.25	14.85	22.17	23.32	24.14	22.49	22.95	21.13	18.73	18.58	12.50	8.47	2.12	0.00	0.00	4.03	.	.	2	0	20
20	20	2	2	1	A	0	5.35	9.50	17.86	21.51	16.44	32.58	35.50	32.88	28.75	33.37	31.76	25.48	19.25	11.88	6.03	0.00	0.00	14	16	1	0	20
21	22	2	1	1	B	0	6.98	10.09	15.61	24.70	24.60	25.96	28.37	25.72	24.84	24.07	21.98	17.38	15.75	9.13	0.00	1.67	0.00	15	17	2	0	20
22	22	2	2	1	A	0	6.47	12.88	21.46	25.93	26.31	26.59	31.57	29.56	28.04	30.02	27.66	22.07	16.54	12.53	5.64	2.65	1.20	15	18	1	0	20
23	23	1	1	1	A	0	5.44	12.46	17.87	25.79	27.12	25.95	26.64	26.78	28.34	25.81	18.23	22.67	16.76	12.84	6.32	3.80	2.05	15	18	1	0	20
24	23	1	2	1	B	0	5.51	12.91	19.06	24.95	28.37	25.69	28.73	27.46	32.04	28.04	26.28	26.75	21.34	14.69	8.23	4.34	1.99	15	18	2	0	20
25	26	2	1	1	B	0	6.12	14.88	24.18	32.05	31.12	35.89	35.08	43.44	37.42	34.11	29.16	27.04	18.93	12.56	6.19	3.27	1.46	15	18	2	0	20

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	KE_FIRST	KE_LAST	trt	c19	i
26	26	2	2	1	A	0	4.12	12.28	19.03	27.34	28.69	28.58	32.39	27.30	40.90	40.92	42.89	36.63	28.16	22.89	11.36	6.30	3.04	15	18	1	0	20
27	27	1	1	1	A	0	5.81	13.48	23.67	32.34	31.45	31.37	32.68	34.83	31.28	33.22	31.14	28.59	22.62	14.71	8.58	5.20	2.57	15	18	1	0	20
28	27	1	2	1	B	0	6.16	14.42	25.22	33.70	33.76	36.32	31.45	30.95	34.53	32.64	31.26	28.29	21.86	17.52	10.34	5.07	0.00	15	17	2	0	20
29	31	1	1	1	A	0	10.01	20.92	34.32	46.44	49.05	48.61	46.16	48.27	48.65	39.64	39.15	34.63	24.89	20.30	9.91	5.24	1.88	15	18	1	0	20
30	31	1	2	1	B	0	8.16	19.47	29.17	39.88	47.38	45.73	44.32	39.45	38.42	37.38	33.08	31.48	26.54	18.70	0.00	5.03	1.97	15	18	2	0	20
31	32	1	1	1	A	0	9.27	16.80	32.32	41.94	41.19	36.49	41.46	40.30	40.63	36.57	40.65	33.88	27.13	19.06	9.95	5.03	2.23	15	18	1	0	20
32	32	1	2	1	B	0	7.19	15.31	23.79	33.95	34.75	37.36	36.61	37.37	38.34	38.35	37.42	35.31	28.98	23.04	13.61	6.88	3.45	15	18	2	0	20
33	33	2	1	1	B	0	6.23	16.23	25.08	33.02	37.13	36.91	36.73	37.95	39.19	37.86	36.04	28.85	25.16	18.09	9.83	5.20	2.26	15	18	2	0	20
34	33	2	2	1	A	0	6.86	9.48	23.05	30.71	36.58	35.66	39.71	40.47	41.03	34.72	31.24	30.41	20.74	17.78	8.89	4.96	1.78	15	18	1	0	20
35	34	1	1	1	A	0	4.87	10.94	22.02	29.02	33.15	31.45	36.72	34.82	38.66	34.12	33.00	24.81	19.27	13.26	5.69	2.80	3.02	15	18	1	0	20
36	34	1	2	1	B	0	6.46	16.07	23.86	38.92	36.58	39.22	39.46	42.07	44.00	38.52	32.17	28.57	28.40	14.17	7.22	3.73	1.43	15	18	2	0	20
37	35	2	1	1	B	0	6.45	14.53	21.18	27.64	33.51	35.09	35.21	32.74	35.90	34.02	32.38	25.21	23.02	17.07	4.13	5.43	2.27	15	18	2	0	20
38	35	2	2	1	A	0	5.16	14.36	22.92	35.94	31.36	37.10	34.92	34.49	35.53	29.68	52.93	27.97	23.73	16.60	9.35	5.63	2.70	15	18	1	0	20
39	36	1	1	1	A	0	5.40	18.72	21.72	13.98	6.99	30.64	29.25	27.44	26.11	27.18	27.96	22.27	16.42	9.96	3.61	0.00	0.00	14	16	1	0	20
40	36	1	2	1	B	0	6.62	14.05	20.10	30.21	27.87	33.35	34.78	31.58	36.24	27.31	27.06	23.76	14.19	9.59	3.94	0.00	0.00	14	16	2	0	20
41	37	1	1	1	A	0	5.00	12.51	19.15	21.57	26.04	36.22	32.06	27.44	27.24	25.33	23.71	21.87	16.06	10.88	6.09	2.71	1.08	15	18	1	0	20
42	37	1	2	1	B	0	3.44	9.03	15.93	21.08	23.51	15.08	29.45	31.86	32.90	34.30	35.55	26.69	23.36	10.15	8.46	3.97	1.95	15	18	2	0	20
43	38	2	1	1	B	0	5.79	14.09	22.65	28.39	36.21	36.51	33.79	37.95	32.81	34.13	34.03	28.98	18.63	15.24	7.39	4.31	1.97	15	18	2	0	20
44	38	2	2	1	A	0	5.06	13.06	18.79	27.03	28.85	31.77	30.13	32.82	27.44	31.85	28.31	23.59	21.94	16.09	7.61	3.60	1.46	15	18	1	0	20
45	39	2	1	1	B	0	3.49	9.43	9.23	26.95	29.40	26.85	27.12	40.99	31.28	33.59	37.87	29.31	20.35	19.10	13.00	7.62	4.30	15	18	2	0	20
46	39	2	2	1	A	0	7.55	11.71	18.30	26.59	28.49	35.03	30.20	36.54	34.30	31.04	30.19	23.84	19.26	15.62	11.67	8.15	4.51	15	18	1	0	20
47	40	1	1	1	A	0	6.66	15.19	22.75	24.05	30.65	43.86	38.87	38.08	42.46	39.71	39.66	31.08	27.04	17.97	9.27	5.57	2.00	15	18	1	0	20
48	40	1	2	1	B	0	5.23	12.25	23.43	30.17	34.82	38.45	35.93	33.92	32.22	30.74	28.92	26.57	20.11	18.92	11.28	7.24	3.88	15	18	2	0	20

Total Doxorubicin

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
1	2	2	1	1	B	0.000	4.418	12.698	24.135	32.645	37.577	40.865	41.670	41.944	38.511	40.182	36.101	29.324	20.454
2	2	2	2	1	A	0.000	4.028	12.991	22.472	34.860	37.737	41.782	42.376	41.653	42.422	42.816	40.907	31.720	22.965
3	3	2	1	1	B	0.000	6.462	13.493	22.246	29.387	28.857	29.355	29.510	29.016	29.289	26.563	25.424	23.544	19.570
4	3	2	2	1	A	0.000	5.741	12.856	19.531	27.028	29.165	28.859	29.280	30.421	28.879	28.213	28.547	24.780	19.186
5	8	2	1	1	B	0.000	7.792	16.367	24.020	32.901	37.121	38.563	40.221	38.545	39.940	35.484	34.514	25.960	18.974
6	8	2	2	1	A	0.000	7.049	12.591	20.987	31.735	31.760	35.431	34.830	34.102	34.219	32.620	33.527	24.660	19.029
7	10	1	1	1	A	0.000	3.912	9.438	14.871	20.351	21.575	28.238	26.837	29.541	29.561	25.691	25.899	23.880	16.057
8	10	1	2	1	B	0.000	6.047	13.260	20.344	28.742	32.656	37.684	36.782	35.181	35.750	34.056	33.418	27.248	21.302
9	12	1	1	1	A	0.000	6.421	13.443	20.924	29.507	30.348	30.906	32.019	31.481	32.187	31.269	30.097	25.179	18.130
10	12	1	2	1	B	0.000	7.724	15.691	26.000	33.004	35.042	34.777	33.370	33.769	31.960	31.986	31.356	26.522	20.937
11	13	2	1	1	B	0.000	4.688	10.875	17.552	24.994	28.085	27.408	27.265	28.316	28.325	25.697	24.102	19.420	13.602
12	13	2	2	1	A	0.000	3.964	10.314	15.907	22.018	24.953	27.263	25.688	25.778	24.290	23.290	24.008	19.735	16.388
13	16	2	1	1	B	0.000	6.607	12.490	15.084	20.711	24.223	28.376	31.261	30.874	28.709	27.148	29.762	21.439	14.569
14	16	2	2	1	A	0.000	5.864	11.205	17.453	24.502	26.386	27.514	26.761	27.768	28.439	26.079	27.385	20.416	13.795
15	17	1	1	1	A	0.000	4.560	11.532	18.750	27.971	28.973	27.918	27.621	28.129	28.653	25.656	27.837	20.296	13.643
16	17	1	2	1	B	0.000	1.237	11.644	19.003	28.116	28.368	29.420	28.013	28.819	30.231	27.323	26.829	17.540	16.426
17	18	1	1	1	A	0.000	5.620	11.309	17.337	22.939	22.792	23.618	24.014	24.016	21.914	22.494	22.945	16.678	13.294
18	18	1	2	1	B	0.000	5.017	8.923	15.084	20.159	19.890	20.081	20.116	20.230	18.221	17.845	17.197	12.236	7.620
19	20	2	1	1	B	0.000	6.194	11.279	16.116	22.993	22.509	25.883	22.079	21.240	20.231	18.578	18.141	12.966	8.005
20	20	2	2	1	A	0.000	6.697	11.154	18.980	29.122	30.402	27.906	33.570	33.266	30.267	29.262	29.726	23.196	18.166
21	22	2	1	1	B	0.000	7.130	10.855	16.949	24.159	26.219	26.626	25.992	25.389	24.900	23.915	23.793	20.676	15.727
22	22	2	2	1	A	0.000	27.648	11.676	18.406	25.601	28.783	32.785	32.875	32.989	30.907	31.254	1.149	23.753	17.602
23	23	1	1	1	A	0.000	6.099	11.832	20.033	24.144	26.346	27.942	27.631	26.398	28.729	22.843	24.928	20.140	18.504
24	23	1	2	1	B	0.000	5.513	12.242	19.417	24.255	28.454	27.076	28.010	28.214	33.824	28.085	26.792	27.846	22.884
25	26	2	1	1	B	0.000	5.746	14.450	22.873	31.503	33.668	34.831	33.412	33.755	33.937	31.721	30.310	24.289	20.622

Obs	sub	seq	per	GRP	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14
26	26	2	2	1	A	0.000	4.597	11.986	19.572	28.211	30.180	31.540	30.581	32.346	30.699	31.390	31.477	26.003	14.499
27	27	1	1	1	A	0.000	5.647	11.999	20.581	27.324	30.094	31.146	30.843	32.863	31.216	29.490	30.766	24.960	20.382
28	27	1	2	1	B	0.000	6.083	14.547	22.511	31.362	31.237	30.857	31.049	31.696	34.122	29.202	29.550	24.646	20.911
29	31	1	1	1	A	0.000	8.857	20.923	31.886	40.814	41.578	42.379	42.426	41.983	41.870	37.855	36.152	32.310	24.263
30	31	1	2	1	B	0.000	8.137	18.091	28.210	37.848	37.276	38.121	39.115	38.876	36.965	34.503	33.891	29.809	25.527
31	32	1	1	1	A	0.000	9.164	19.204	30.143	37.285	38.326	38.961	41.750	39.719	39.913	35.108	37.034	28.956	22.608
32	32	1	2	1	B	0.000	6.201	13.794	20.802	28.315	30.892	34.403	34.340	32.737	34.642	33.882	30.779	27.309	24.495
33	33	2	1	1	B	0.000	5.731	14.770	22.029	30.267	33.862	34.053	34.150	34.828	36.070	32.511	31.219	26.449	21.283
34	33	2	2	1	A	0.000	6.530	14.978	23.793	34.756	35.512	36.103	39.030	37.467	39.675	33.513	36.299	26.848	21.993
35	34	1	1	1	A	0.000	4.886	12.577	22.883	34.161	38.476	38.343	39.140	37.763	46.488	37.525	35.664	26.890	25.070
36	34	1	2	1	B	0.000	5.564	14.764	23.027	34.807	36.602	37.074	37.215	37.521	37.338	37.157	34.771	27.632	21.599
37	35	2	1	1	B	0.000	5.791	12.596	21.132	28.266	33.647	32.581	33.771	35.541	33.099	29.535	28.224	24.056	22.125
38	35	2	2	1	A	0.000	5.066	13.675	23.457	34.040	35.243	38.268	36.309	36.374	32.537	30.882	30.483	25.367	20.220
39	36	1	1	1	A	0.000	6.114	16.928	11.573	18.657	23.196	26.082	26.822	26.939	23.462	21.115	23.336	15.947	12.338
40	36	1	2	1	B	0.000	7.138	14.297	23.776	31.635	34.197	35.007	35.110	34.146	35.508	30.093	31.244	23.625	19.034
41	37	1	1	1	A	0.000	4.131	9.593	15.005	19.132	23.109	25.640	28.466	26.917	26.165	25.461	24.841	20.562	16.524
42	37	1	2	1	B	0.000	3.400	8.733	14.359	19.423	20.599	24.978	26.791	28.019	25.837	29.462	30.948	20.586	21.845
43	38	2	1	1	B	0.000	6.244	13.080	22.178	30.757	34.752	35.011	35.807	35.382	33.408	34.330	34.323	26.512	20.050
44	38	2	2	1	A	0.000	5.401	13.013	19.584	28.424	30.390	34.175	31.114	33.073	29.721	30.767	29.494	23.400	20.523
45	39	2	1	1	B	0.000	3.259	9.331	16.859	24.059	27.983	31.918	33.388	35.584	33.091	34.492	34.297	28.899	22.722
46	39	2	2	1	A	0.359	2.683	11.918	19.112	26.431	30.638	33.948	36.789	35.125	33.054	33.732	33.603	26.196	23.606
47	40	1	1	1	A	0.000	5.893	12.541	19.725	28.289	30.039	35.523	34.507	34.231	34.457	33.421	32.175	27.266	22.394
48	40	1	2	1	B	0.000	4.598	10.216	18.503	26.039	32.207	35.072	32.818	36.073	35.542	31.917	32.487	27.226	24.418

Obs	c15	c16	c17	c18	KE_FIRST	KE_LAST	trt	c19	i
1	13.879	7.675	3.176	1.832	15	18	2	0	20
2	17.608	10.066	4.788	2.195	15	18	1	0	20
3	13.725	8.669	4.660	1.992	15	18	2	0	20
4	13.521	7.106	3.936	1.837	15	18	1	0	20
5	10.662	3.935	1.550	0.354	15	18	2	0	20
6	13.606	5.073	2.323	0.711	15	18	1	0	20
7	11.273	5.889	2.542	1.095	15	18	1	0	20
8	0.000	0.000	0.000	0.000	.	.	2	0	20
9	10.385	5.425	2.579	1.068	15	18	1	0	20
10	13.109	8.487	4.821	2.044	15	18	2	0	20
11	8.254	4.182	2.165	1.156	15	18	2	0	20
12	11.872	6.337	3.459	1.621	15	18	1	0	20
13	8.319	3.209	1.517	0.413	15	18	2	0	20
14	8.501	4.403	1.965	0.658	15	18	1	0	20
15	8.591	3.531	1.296	0.485	15	18	1	0	20
16	7.659	3.634	1.332	0.500	15	18	2	0	20
17	7.038	3.107	1.355	0.395	15	18	1	0	20
18	2.505	0.772	0.000	0.000	14	16	2	0	20
19	2.358	0.000	0.000	3.908	.	.	2	0	20
20	10.471	2.952	0.618	0.000	15	17	1	0	20
21	9.932	0.000	1.593	0.621	15	18	2	0	20
22	11.337	6.337	2.813	6.079	.	.	1	0	20
23	11.511	6.332	3.935	1.606	15	18	1	0	20
24	14.829	8.749	4.831	1.756	15	18	2	0	20
25	13.654	6.457	3.345	1.463	15	18	2	0	20
26	14.978	7.952	4.244	1.935	15	18	1	0	20
27	13.618	7.889	4.480	2.085	15	18	1	0	20
28	15.826	9.415	4.799	0.789	15	18	2	0	20
29	17.801	8.992	4.481	1.603	15	18	1	0	20
30	18.393	10.342	5.485	2.220	15	18	2	0	20
31	15.837	9.212	4.615	2.052	15	18	1	0	20
32	18.718	11.183	5.995	3.071	15	18	2	0	20
33	17.563	8.916	4.716	2.054	15	18	2	0	20
34	16.768	8.903	4.690	2.049	15	18	1	0	20
35	12.086	4.970	2.531	1.025	15	18	1	0	20
36	13.064	6.263	2.636	1.107	15	18	2	0	20
37	15.233	8.539	4.876	2.042	15	18	2	0	20
38	15.273	9.058	5.306	2.739	15	18	1	0	20
39	8.604	4.083	1.103	0.445	15	18	1	0	20
40	13.999	4.592	0.990	0.307	15	18	2	0	20

Obs	c15	c16	c17	c18	KE_FIRST	KE_LAST	trt	c19	i
41	11.869	6.338	3.408	1.149	15	18	1	0	20
42	17.305	9.976	4.483	2.583	15	18	2	0	20
43	14.321	7.714	4.676	1.943	15	18	2	0	20
44	14.908	7.603	3.956	1.615	15	18	1	0	20
45	18.390	12.117	7.152	4.248	15	18	2	0	20
46	16.929	12.968	8.394	4.851	15	18	1	0	20
47	15.647	8.201	4.466	1.637	15	18	1	0	20
48	18.490	12.821	7.812	4.222	15	18	2	0	20

Reviewer- Calculated Pharmacokinetic Dataset

Free Doxorubicin

Obs	sub	trt	seq	per	GRP	auct	auci	C _{MAX}	T _{MAX}	THALFR	KEL
1	2	1	2	2	1	47064.67	47211.42	415.42	49.000	4.491	0.15434
2	2	2	2	1	1	28109.05	29697.95	291.47	1.083	40.476	0.01713
3	3	1	2	2	1	24897.70	25107.06	190.53	6.000	7.836	0.08846
4	3	2	2	1	1	40276.53	40538.50	311.28	6.000	8.372	0.08279
5	8	1	2	2	1	47380.58	47552.76	1030.68	2.000	8.346	0.08305
6	8	2	2	1	1	19520.35	19576.24	304.89	1.500	6.168	0.11237
7	10	1	1	1	1	27144.99	27206.25	258.92	25.000	4.474	0.15491
8	10	2	1	2	1	19118.18	.	422.70	9.000	.	.
9	12	1	1	1	1	40189.98	40370.16	338.63	9.000	5.089	0.13620
10	12	2	1	2	1	60693.71	60861.89	525.19	25.000	6.336	0.10941
11	13	1	2	2	1	32001.30	.	188.48	169.000	.	.
12	13	2	2	1	1	32573.10	.	243.94	1.000	.	.
13	16	1	2	2	1	32077.57	32199.83	257.02	97.000	6.579	0.10535
14	16	2	2	1	1	37391.30	37467.98	503.03	1.250	5.624	0.12324
15	17	1	1	1	1	49982.73	50280.55	704.85	4.000	7.584	0.09140
16	17	2	1	2	1	26497.64	27511.45	592.28	0.250	31.597	0.02194
17	18	1	1	1	1	16601.82	17760.02	260.33	4.000	101.749	0.00681
18	18	2	1	2	1	17226.87	17399.58	337.27	2.000	13.808	0.05020
19	20	1	2	2	1	13370.84	13615.06	226.91	1.000	14.967	0.04631
20	20	2	2	1	1	18070.23	.	273.88	25.000	.	.
21	22	1	2	2	1	34244.80	34477.73	471.48	25.000	18.644	0.03718
22	22	2	2	1	1	32319.32	.	374.99	49.000	.	.
23	23	1	1	1	1	27475.65	27869.33	285.09	1.000	12.552	0.05522

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
24	23	2	1	2	1	20356.98	21264.53	173.88	25.000	25.052	0.02767
25	26	1	2	2	1	18719.02	18973.16	170.60	2.000	10.663	0.06500
26	26	2	2	1	1	13546.33	14329.61	209.60	1.083	37.469	0.01850
27	27	1	1	1	1	16775.42	16881.65	125.14	25.000	6.534	0.10608
28	27	2	1	2	1	20751.61	20903.25	157.63	1.083	13.740	0.05045
29	28	1	2	2	1	19021.66	19269.52	170.78	1.000	19.281	0.03595
30	28	2	2	1	1	24008.84	24167.70	176.34	1.250	11.495	0.06030
31	29	1	2	2	1	18843.93	19027.74	188.86	25.000	10.862	0.06382
32	29	2	2	1	1	22677.23	23073.70	165.21	49.000	22.901	0.03027
33	30	1	2	2	1	22882.81	23135.94	200.76	49.000	11.936	0.05807
34	30	2	2	1	1	20156.36	20392.26	249.26	1.000	17.697	0.03917
35	31	1	1	1	1	41441.91	41603.56	431.63	9.000	6.363	0.10894
36	31	2	1	2	1	38298.56	38900.48	336.90	1.000	22.774	0.03044
37	32	1	1	1	1	42224.26	43453.36	426.05	49.000	21.563	0.03215
38	32	2	1	2	1	41851.95	42670.66	296.48	49.000	13.067	0.05305
39	33	1	2	2	1	51366.37	51879.02	719.71	1.250	8.432	0.08220
40	33	2	2	1	1	35114.24	35748.49	391.59	1.250	15.388	0.04505
41	34	1	1	1	1	17175.90	17582.85	272.21	1.250	13.943	0.04971
42	34	2	1	2	1	32038.83	32271.07	333.72	25.000	12.635	0.05486
43	35	1	2	2	1	39378.65	39584.80	376.42	4.000	7.758	0.08935
44	35	2	2	1	1	63085.43	63957.51	431.72	49.000	22.674	0.03057
45	36	1	1	1	1	13882.59	14022.34	134.81	1.250	13.740	0.05045
46	36	2	1	2	1	8521.45	8728.31	100.26	6.000	9.046	0.07662
47	37	1	1	1	1	67828.58	67899.95	809.66	97.000	7.815	0.08870
48	37	2	1	2	1	18615.22	18715.76	123.97	97.000	8.257	0.08395
49	38	1	2	2	1	22225.99	22525.94	253.99	2.000	16.821	0.04121
50	38	2	2	1	1	22884.31	23075.58	145.17	49.000	14.880	0.04658
51	39	1	2	2	1	21101.99	.	268.17	2.000	.	.
52	39	2	2	1	1	34824.40	34949.47	258.89	97.000	4.827	0.14360
53	40	1	1	1	1	16139.24	16308.83	121.27	49.000	9.971	0.06952
54	40	2	1	2	1	20747.54	.	174.20	25.000	.	.
55	41	1	1	1	1	19439.19	.	118.51	49.000	.	.
56	41	2	1	2	1	39683.24	.	324.83	169.000	.	.
57	42	1	2	2	1	11965.82	12459.23	172.62	1.250	24.676	0.02809
58	42	2	2	1	1	8272.53	8565.68	156.51	1.083	23.655	0.02930

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
59	43	1	2	2	1	10732.75	10907.88	229.80	1.000	23.943	0.02895
60	43	2	2	1	1	12261.10	12770.06	171.61	1.083	29.497	0.02350
61	45	1	1	1	1	16277.72	16446.32	153.34	4.000	18.550	0.03737
62	45	2	1	2	1	13968.34	14034.29	207.39	4.000	6.203	0.11175
63	47	1	1	1	1	49270.12	49609.31	269.26	49.000	14.371	0.04823
64	47	2	1	2	1	23352.61	23515.00	171.13	25.000	8.325	0.08326
65	48	1	2	2	1	9372.88	9450.56	89.41	1.083	9.989	0.06939
66	48	2	2	1	1	27388.75	28339.73	429.79	4.000	41.958	0.01652
67	51	1	1	1	1	28624.70	28716.11	226.49	4.000	6.206	0.11169
68	51	2	1	2	1	15327.62	15616.98	187.25	0.750	15.311	0.04527
69	52	1	2	2	1	9620.15	11490.85	287.17	1.083	144.718	0.00479
70	52	2	2	1	1	11947.32	12018.21	146.47	1.500	4.588	0.15107
71	53	1	2	2	1	18019.05	18514.50	142.14	4.000	30.151	0.02299
72	53	2	2	1	1	15314.58	15493.43	220.05	4.000	11.863	0.05843
73	54	1	2	2	1	13132.18	13608.06	124.04	4.000	27.765	0.02496
74	54	2	2	1	1	9961.00	10059.40	154.16	4.000	12.676	0.05468
75	57	1	2	2	1	12395.99	12547.68	114.13	4.000	8.964	0.07733
76	57	2	2	1	1	10919.97	10977.25	110.43	49.000	6.978	0.09933
77	58	1	1	1	1	13769.04	13920.53	127.85	2.000	12.181	0.05690
78	58	2	1	2	1	27619.75	27797.11	200.27	25.000	11.125	0.06230
79	60	1	1	1	1	11598.57	12826.34	129.18	1.083	74.003	0.00937
80	60	2	1	2	1	3589.42	.	186.77	1.250	.	.
81	61	1	2	2	1	9228.79	9484.74	124.79	1.250	11.664	0.05943
82	61	2	2	1	1	17470.00	17702.60	145.94	4.000	10.269	0.06750

Liposomal Doxorubicin

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
1	2	1	2	2	1	4187.52	4206.05	38.39	1.500	6.5534	0.10577
2	2	2	2	1	1	3535.04	3548.47	38.62	6.000	5.3186	0.13032
3	3	1	2	2	1	3358.06	3427.41	31.34	1.000	25.7067	0.02696
4	3	2	2	1	1	3817.77	3854.76	33.12	1.000	10.3384	0.06705
5	8	1	2	2	1	2357.07	2391.70	29.09	4.000	11.2173	0.06179
6	8	2	2	1	1	2301.05	2320.35	34.83	2.000	10.6137	0.06531
7	10	1	1	1	1	2660.67	2672.15	29.60	4.000	6.5788	0.10536
8	10	2	1	2	1	1120.53	.	33.89	4.000	.	.

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
9	12	1	1	1	1	3042.69	3057.34	33.00	1.083	9.1457	0.07579
10	12	2	1	2	1	3408.85	3439.16	31.86	4.000	10.7722	0.06435
11	13	1	2	2	1	3019.25	3038.58	38.42	1.500	8.0706	0.08589
12	13	2	2	1	1	2701.17	2712.38	33.05	9.000	6.4749	0.10705
13	16	1	2	2	1	2124.03	2152.27	27.15	4.000	9.6440	0.07187
14	16	2	2	1	1	2202.36	2220.42	28.33	1.500	9.0681	0.07644
15	17	1	1	1	1	2249.23	2276.62	30.32	1.083	11.2323	0.06171
16	17	2	1	2	1	2525.68	2546.01	30.66	1.000	7.3021	0.09492
17	18	1	1	1	1	1847.02	1874.33	24.87	1.500	12.8779	0.05382
18	18	2	1	2	1	1064.01	1119.91	23.25	1.083	11.7405	0.05904
19	20	1	2	2	1	2650.14	2702.53	35.50	1.500	6.0219	0.11510
20	20	2	2	1	1	1197.86	.	24.14	1.250	.	.
21	22	1	2	2	1	2940.96	2957.34	31.57	1.500	9.4592	0.07328
22	22	2	2	1	1	1904.74	2064.39	28.37	1.500	12.1203	0.05719
23	23	1	1	1	1	3059.69	3106.65	28.34	4.000	15.8783	0.04365
24	23	2	1	2	1	3688.65	3714.36	32.04	4.000	8.9579	0.07738
25	26	1	2	2	1	5273.58	5294.34	42.89	9.000	4.7340	0.14642
26	26	2	2	1	1	3298.91	3320.17	43.44	2.000	10.0936	0.06867
27	27	1	1	1	1	3970.47	4003.31	34.83	2.000	8.8576	0.07825
28	27	2	1	2	1	3857.93	3928.77	36.32	1.250	9.6856	0.07157
29	31	1	1	1	1	4736.84	4774.49	49.05	1.083	13.8798	0.04994
30	31	2	1	2	1	3810.90	3853.64	47.38	1.083	15.0394	0.04609
31	32	1	1	1	1	4702.96	4735.93	41.94	1.000	10.2495	0.06763
32	32	2	1	2	1	5473.16	5512.61	38.35	6.000	7.9258	0.08745
33	33	1	2	2	1	4121.89	4143.19	41.03	4.000	8.2954	0.08356
34	33	2	2	1	1	4427.54	4454.15	39.19	4.000	8.1609	0.08494
35	34	1	1	1	1	3333.77	3363.79	38.66	4.000	6.8907	0.10059
36	34	2	1	2	1	3933.93	3953.49	44.00	4.000	9.4799	0.07312
37	35	1	2	2	1	4417.95	4440.81	52.93	9.000	5.8677	0.11813
38	35	2	2	1	1	3764.80	3792.32	35.90	4.000	8.4055	0.08246
39	36	1	1	1	1	2216.19	2252.60	30.64	1.250	6.9904	0.09916
40	36	2	1	2	1	2179.28	2243.59	36.24	4.000	11.3125	0.06127
41	37	1	1	1	1	2799.26	2816.79	36.22	1.250	11.2514	0.06161
42	37	2	1	2	1	3576.80	3589.41	35.55	9.000	4.4831	0.15461
43	38	1	2	2	1	3627.17	3644.97	32.82	2.000	8.4516	0.08201

Obs	sub	trt	seq	per	GRP	auct	auci	C _{MAX}	T _{MAX}	THALFR	KEL
44	38	2	2	1	1	3715.20	3738.50	37.95	2.000	8.2009	0.08452
45	39	1	2	2	1	4363.37	4419.24	36.54	2.000	8.5874	0.08072
46	39	2	2	1	1	4834.29	4862.93	40.99	2.000	4.6172	0.15012
47	40	1	1	1	1	4555.83	4574.86	43.86	1.250	6.5936	0.10512
48	40	2	1	2	1	4496.64	4552.19	38.45	1.250	9.9238	0.06985

Total Doxorubicin

Obs	sub	trt	seq	per	GRP	auct	auci	C _{MAX}	T _{MAX}	THALFR	KEL
1	2	1	2	2	1	4427.49	4446.02	42.816	6.000	5.8536	0.11841
2	2	2	2	1	1	3680.34	3698.49	41.944	2.000	6.8653	0.10096
3	3	1	2	2	1	3400.18	3424.29	30.421	2.000	9.1003	0.07617
4	3	2	2	1	1	3549.14	3585.71	29.510	1.500	12.7219	0.05448
5	8	1	2	2	1	3140.10	3148.78	35.431	1.250	8.4634	0.08190
6	8	2	2	1	1	2862.44	2867.43	40.221	1.500	9.7804	0.07087
7	10	1	1	1	1	2857.54	2868.24	29.561	4.000	6.7741	0.10232
8	10	2	1	2	1	1359.10	.	37.684	1.250	.	.
9	12	1	1	1	1	2943.03	2956.97	32.187	4.000	9.0429	0.07665
10	12	2	1	2	1	3710.82	3745.53	35.042	1.083	11.7707	0.05889
11	13	1	2	2	1	2918.37	2938.41	27.263	1.250	8.5684	0.08090
12	13	2	2	1	1	2328.91	2344.50	28.325	4.000	9.3465	0.07416
13	16	1	2	2	1	2377.38	2385.56	28.439	4.000	8.6121	0.08049
14	16	2	2	1	1	2309.98	2314.66	31.261	1.500	7.8472	0.08833
15	17	1	1	1	1	2253.13	2259.10	28.973	1.083	8.5311	0.08125
16	17	2	1	2	1	2251.72	2255.92	30.231	4.000	5.8247	0.11900
17	18	1	1	1	1	1968.13	1974.38	24.016	2.000	10.9620	0.06323
18	18	2	1	2	1	991.67	1007.80	20.230	2.000	14.4776	0.04788
19	20	1	2	2	1	2474.88	2482.80	33.570	1.500	8.8780	0.07808
20	20	2	2	1	1	1191.08	.	25.883	1.250	.	.
21	22	1	2	2	1	3006.86	.	32.989	2.000	.	.
22	22	2	2	1	1	2137.92	2148.38	26.626	1.250	11.6722	0.05938
23	23	1	1	1	1	3040.51	3066.95	28.729	4.000	11.4126	0.06074
24	23	2	1	2	1	3851.19	3872.89	33.824	4.000	8.5640	0.08094
25	26	1	2	2	1	3477.51	3497.85	32.346	2.000	7.2838	0.09516
26	26	2	2	1	1	3380.85	3401.12	34.831	1.250	9.6024	0.07218
27	27	1	1	1	1	3599.88	3624.68	32.863	2.000	8.2434	0.08408

Obs	sub	trt	seq	per	GRP	auct	auci	CMAX	TMAX	THALFR	KEL
28	27	2	1	2	1	3813.73	3825.06	34.122	4.000	9.9603	0.06959
29	31	1	1	1	1	4314.96	4345.17	42.426	1.500	13.0669	0.05305
30	31	2	1	2	1	4508.59	4547.83	39.115	1.500	12.2509	0.05658
31	32	1	1	1	1	4111.12	4146.26	41.750	1.500	11.8700	0.05839
32	32	2	1	2	1	4533.38	4570.91	34.642	4.000	8.4718	0.08182
33	33	1	2	2	1	4066.64	4091.77	39.675	4.000	8.5006	0.08154
34	33	2	2	1	1	4018.98	4045.31	36.070	4.000	8.8867	0.07800
35	34	1	1	1	1	3401.18	3411.41	46.488	4.000	6.9171	0.10021
36	34	2	1	2	1	3427.23	3439.98	37.521	2.000	7.9816	0.08684
37	35	1	2	2	1	3900.54	3939.83	38.268	1.250	9.9420	0.06972
38	35	2	2	1	1	3804.85	3833.94	35.541	2.000	9.8766	0.07018
39	36	1	1	1	1	2072.57	2080.08	26.939	2.000	11.6966	0.05926
40	36	2	1	2	1	2953.24	2957.96	35.508	4.000	10.6483	0.06509
41	37	1	1	1	1	2930.90	2942.99	28.466	1.500	7.2964	0.09500
42	37	2	1	2	1	3937.31	3956.83	30.948	9.000	5.2378	0.13233
43	38	1	2	2	1	3553.27	3573.67	34.175	1.250	8.7569	0.07915
44	38	2	2	1	1	3716.26	3738.94	35.807	1.500	8.0918	0.08566
45	39	1	2	2	1	4812.27	4833.69	36.789	1.500	3.0609	0.22645
46	39	2	2	1	1	4733.22	4765.64	35.584	2.000	5.2902	0.13102
47	40	1	1	1	1	3873.79	3892.02	35.523	1.250	7.7230	0.08975
48	40	2	1	2	1	4855.85	4896.43	36.073	2.000	6.6619	0.10405

4.4.2 Fed Study Codes

Free Doxorubicin

```

***** STEP 1: LOCATION OF MACRO FILE (MACROLIB.SAS) . CHANGE LOCATION IF
APPLICABLE *****;
%INCLUDE "M:\SAS\BEPRG\NEW\macrolib.sas";

/*****
ASSIGN WHETHER HAVE GROUP EFFECT:
  TRTGROUP = 1      TRT*GROUP INTERACTION IN GLM MODEL
  TRTGROUP = 2      TRT*GROUP INTERACTION NOT IN GLM MODEL
  TRTGROUP =        NO GROUP EFFECT IN STUDY
NOTE: group variable has to be named GRP in the dataset.
*****/;

*****STEP 2: ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=2;

```

```

*****STEP 3: ENTER ANDA INFORMATION *****;
%let level = FREE DOXORUBICIN;
%let drug= DOXORUBICIN HYDROCHLORIDE INJECTION;
%let dose= 2 MG/ML;
%let anda=203263;
%let studytype=FED;

***** STEP 4: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=C:\Documents and Settings\dandamudi\My
Documents\suman\ANDA\Liposomes\Doxorubicin\SAS\free dox\Group 2;

*****STEP 5: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmxunit = ng/mL;
%let timeunit = hr;

**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC
FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level.ACTUAL.png;

**** DO NOT CHANGE: NAME OF CONC AND PK DATASETS OUTPUT ****;
%LET CONCOUTPUT=&studydir\&anda._&studytype._Datasets_&level..doc;

%LET VARSORT=SUB PER;

%GLOBAL SUB PER SEQ TRT GRP TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME
THALF CLAST KE_FIRST KE_LAST OLDNAME NEWNAME;

*****STEP 6: SELECT TYPE OF ANALYSIS FROM BOTTOM*****;

/****NOTE: THE CURRENT PROGRAM DOES NOT INCLUDE CONTINU OR CONTINU2
OPTIONS*****
*****SELECT TWOWAYCALCKE07MAR2009.SAS IF YOU WANT TO CALCULATE KE AND OTHER
PARAMETERS ***/
/****SELECT TWOWAYCONTINU(2)07MAR2009.SAS IF YOU DO NOT WANT TO RECALCULATE
KE.
FOR TWOWAYCONTINU(2)07MAR2009.SAS, SPONSOR'S KE WILL BE USED FOR CALCULATION
OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED PARAMETERS (CONTINU).
OR WITH STATISTICS ON CALCULATED PARAMETERS (CONTINU2) ***/

%LET FNAME=%QUOTE(V:\DIVISION\BIO\SAS Programs\Macros\CALCKE.SAS);
/**** WRITE DATA FILE NAMES ***/

***** STEP 7: ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
/**** IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3 ***/
/**** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R83C25';
* FILENAME ORGPLASM "&studydir.\&plasmadata";
*%LET FIRSTOBS=1; /* FIRST OBSERVATION */

```

```

*%LET VARPLASM=SUB SEQ PER TRT c1-c22; /* VARIABLE LIST FOR THE PLASMA DATA
FILE */
%LET PLASMLS=900; /* INCREASE LINE SIZE IF NEEDED */
*%READDATA (ORGPLASM, PLASMA, &FIRSTOBS, &VARPLASM, &PLASMLS)
*RUN;

***** NOTE: THE FIRST ROW OF THE EXCEL FILE SHOULD CONTAIN PROPER NAMES OF
THE VARIABLEBES ***;
***** STANDARD NAMES: SUB SEQ PER GRP TRT C1 C2 C3... KE_FIRST KE_LAST
*****;
***** EXCEL FILE DOES NOT NEED TO BE OPEN WHEN RUNNING THIS PROGRAM *****;
* %let excelfile = &studydir fed.xls;

***** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING CONCENTRATION
DATA *****;
* %let sheetname = conc;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
*** STANDARD NAMES: SUB SEQ PER GRP TRT c1-c23 ****;
/*
proc import datafile="&excelfile"
      out=plasma
      dbms=excel replace;
          sheet="&sheetname";
          getnames=yes;
          mixed=yes;
run;
*/

LIBNAME libdata "&studydir";

** STEP 8: ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY FORMATTED..CHAR
OR NUMERIC **;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
DATA PLASMA;
  * SET PLASMA;

  infile ORGPLASM;
  input sub seq per GRP treat $ c1-c18 KE_FIRST KE_LAST;

  if treat = "A" then trt=1;
  else trt=2;

RUN;

data plasma;
  set plasma;

  array conc{*} c1-c19;

  do i=1 to 19;
    if conc{i} < 0 then conc{i} = 0;
  end;
run;

proc print data=plasma;

```

```

run;

%SORTDS(PLASMA, &VARSORT)
RUN;

*****ACTIVATE THIS STEP AND STEP 9A BELOW ONLY IF USING CONTINU.SAS OR
CONTINU2.SAS*****
****PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
****;
**** STEP 9:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY
DATA ****;
/****IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ****/
/**** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPARAM DDE 'EXCEL|pk!R2C1:R83C11';
* FILENAME ORGPARAM "&studydir.\&pkdata";
%LET FIRSTOBS=1; /* FIST OBSERVATION */
%LET VARPARAM=SUB SEQ PER TRT $ TMAX CMAX AUCT AUCI KE THALF; /* VARIABLE
LIST */
%LET PARAMLS=500; /* INCREASE LINE SIZE IF NEEDED */
%READDATA(ORGPARAM, PARAME, &FIRSTOBS, &VARPARAM, &PARAMLS)
RUN;

/*
**** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY DATA
****;
*%let pksheetname = pk;

proc import datafile="&excelfile"
      out=parame
      dbms=excel replace;
          sheet="&pksheetname";
          getnames=yes;
          mixed=yes;

run;
*/

** STEP 10:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY
FORMATTED..CHAR OR NUMERIC **;
DATA PARAME;
  * set parame;

  infile ORGPARAM ls=&paramls;
  input sub seq per GRP treat $ AUCT AUCI CMAX TMAX KE THALF;

  if treat = "A" then trt=1;
  else trt=2;
RUN;

%SORTDS(PARAME, &VARSORT)
RUN;

*****STEP 11: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY *****;
%LET CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,
                  C11, C12, C13, C14, C15, C16, C17, C18);

```

```

/****STEP 12: USE THIS STEP IF COMMON SAMPLING TIMES ARE USED,
          ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE
TIME,
          OR ADD FEW DEVIATED SAMPLING TIME POINTS,
          ALSO MAKE SURE TO DEACTIVATE "SET TIME" AND ACTIVATE
"&TIME" UNDER STEP 15****/
DATA TIME
%LET TIME=%STR(T1=0; T2=0.25; T3=0.5; T4=0.75; T5=1;
T6=1.083; T7=1.25; T8=1.5; T9=2; T10=4; T11=6; T12=9;
T13=25; T14=49; T15=97; T16=169; T17=241; T18=337);

/*USE THIS STEP INSTEAD OF STEP 11 IF ACTUAL SAMPLING TIME DATASET INCLUDED
          IN THE CONCENTRATION DATASET,
          ALSO, MAKE SURE TO ACTIVATE "SET TIME" AND DEACTIVATE
"&TIME" UNDER STEP 15****/;

*DATA TIME;
*SET PLASMA;
*FILE'DESKTOP\TIME';
*PUT SUB TRT SEQ PER GRP T1-T27;
*KEEP SUB TRT SEQ PER GRP T1-T27;

/*PROC PRINT DATA=TIME;RUN;*/

*****STEP 13: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=18;

*****INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE NOT
IN THE DATA SUBMITTED. *****;
** DO NOT CHANGE SINCE KE_FIRST AND KE_LAST VALUES ARE IN CONC DATASET **;
* %LET KE_FIRST=20;
* %LET KE_LAST=27;

*****STEP 14: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION *****;
/****VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL****/
/****LEAVE AS IT IS IF NO CHANGE IS DESIRED****/
/* %LET REMOVSUB=%STR(IF SUB^=10;IF SUB^=15;IF SUB^=34;IF SUB^=37;IF
SUB^=49); */
*%LET REMOVSUB=%STR(IF SUB^=1);

*****IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED *****;
/****CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC ****/
/**** IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM
CLOSED ****/
/* %LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST
IF TREAT='A' THEN TRT=1; ELSE TRT=2 );*/

DATA ORIGIN;
      ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
      ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
SET PLASMA;
*SET TIME;
* SET PARAME;
*SET MERGED;
&TIME;
*KE FIRST=0;
*KE_LAST=0;

```

```

CLAST=C&NO ASSAY;
NEWCMAX=MAX (&CONCENT) ;

/****DO NOT CHANGE: TITLES FOR TABLES****/
%LET TITLE1=MEAN PLASMA &level LEVELS;
%LET TITLE2=MEAN PLASMA &level LEVELS FOR TEST AND REFERENCE PRODUCTS;

/**** DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH ****/
%LET TITLE3=PLASMA &level LEVELS;
%LET TITLE4= &drug, ANDA &anda;
%LET TITLE5=UNDER &STUDYTYPE CONDITIONS;
%LET TITLE6=DOSE= &dose;
%LET FOOTNOT1=1=TEST 2=REF;
%LET FOOTNOT2=Tmax values are presented as median, range.;
%LET FOOTNOT3=;
%LET FOOTNOT4=;
%LET FOOTNOT5=;
%LET LABEL1=PLASMA LEVEL, &cmaxunit;
%LET LABEL2=TIME, HRS;
%LET LABEL3=TEST;
%LET LABEL4=REFERENCE;

%COPYDS(ORIGIN, NEW)
RUN;

proc print data=origin;
run;

*****STEP 15: OPEN IF YOU WANT TO REMOVE, ADD OR EDIT*****;
*%REMUVSUB(NEW, NEW)
RUN;

```

Liposomal Doxorubicin

```

***** STEP 1: LOCATION OF MACRO FILE (MACROLIB.SAS). CHANGE LOCATION IF
APPLICABLE *****;
%INCLUDE "M:\SAS\BEPRG\NEW\macrolib.sas";

/*****
ASSIGN WHETHER HAVE GROUP EFFECT:
    TRTGROUP = 1          TRT*GROUP INTERACTION IN GLM MODEL
    TRTGROUP = 2          TRT*GROUP INTERACTION NOT IN GLM MODEL
    TRTGROUP =           NO GROUP EFFECT IN STUDY
NOTE:  group variable has to be named GRP in the dataset.
*****/;

*****STEP 2: ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=2;

*****STEP 3: ENTER ANDA INFORMATION *****;
%let level = LIPOSOMAL DOXORUBICIN;
%let drug= DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION;
%let dose= 2 MG/ML;
%let anda=203263;
%let studytype=FED;

```

```

***** STEP 4: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=C:\Documents and Settings\dandamudi\My
Documents\suman\ANDA\Liposomes\Doxorubicin\SAS\liposomal dox\Group 2\24
subjects;

*****STEP 5: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = µg hr/mL;
%let cmaxunit = µg/mL;
%let timeunit = hr;

**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC
FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level.ACTUAL.png;

**** DO NOT CHANGE: NAME OF CONC AND PK DATASETS OUTPUT ****;
%LET CONCOUTPUT=&studydir\&anda._&studytype._Datasets_&level..doc;

%LET VARSORT=SUB PER;

%GLOBAL SUB PER SEQ TRT GRP TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME
THALF CLAST KE_FIRST KE_LAST OLDNAME NEWNAME;

*****STEP 6: SELECT TYPE OF ANALYSIS FROM BOTTOM*****;

/****NOTE: THE CURRENT PROGRAM DOES NOT INCLUDE CONTINU OR CONTINU2
OPTIONS*****
*****SELECT TWOWAYCALCKE07MAR2009.SAS IF YOU WANT TO CALCULATE KE AND OTHER
PARAMETERS ***/
/****SELECT TWOWAYCONTINU(2)07MAR2009.SAS IF YOU DO NOT WANT TO RECALCULATE
KE.
FOR TWOWAYCONTINU(2)07MAR2009.SAS, SPONSOR'S KE WILL BE USED FOR CALCULATION
OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED PARAMETERS (CONTINU) .
OR WITH STATISTICS ON CALCULATED PARAMETERS (CONTINU2) ***/

%LET FNAME=%QUOTE(V:\DIVISION\BIO\SAS Programs\Macros\CALCKE.SAS);
/**** WRITE DATA FILE NAMES ***/

***** STEP 7: ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
/**** IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3 ***/
/**** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R49C25';
* FILENAME ORGPLASM "&studydir.\&plasmadata";
*%LET FIRSTOBS=1; /* FIRST OBSERVATION */
*%LET VARPLASM=SUB SEQ PER TRT c1-c22; /* VARIABLE LIST FOR THE PLASMA DATA
FILE */
%LET PLASMLS=900; /* INCREASE LINE SIZE IF NEEDED */
*%READDATA (ORGPLASM, PLASMA, &FIRSTOBS, &VARPLASM, &PLASMLS)
*RUN;

```

```

***** NOTE: THE FIRST ROW OF THE EXCEL FILE SHOULD CONTAIN PROPER NAMES OF
THE VARIABLEs ***;
***** STANDARD NAMES: SUB SEQ PER GRP TRT C1 C2 C3... KE_FIRST KE_LAST
*****;
***** EXCEL FILE DOES NOT NEED TO BE OPEN WHEN RUNNING THIS PROGRAM *****;
* %let excelfile = &studydir\fed.xls;

***** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING CONCENTRATION
DATA *****;
* %let sheetname = conc;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
*** STANDARD NAMES: SUB SEQ PER GRP TRT c1-c23 ****;
/*
proc import datafile="&excelfile"
            out=plasma
            dbms=excel replace;
                sheet="&sheetname";
                getnames=yes;
                mixed=yes;

run;
*/

LIBNAME libdata "&studydir";

** STEP 8: ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY FORMATTED..CHAR
OR NUMERIC **;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
DATA PLASMA;
    * SET PLASMA;

    infile ORGPLASM;
    input sub seq per GRP treat $ c1-c18 KE_FIRST KE_LAST;

    if treat = "A" then trt=1;
    else trt=2;

RUN;

data plasma;
    set plasma;

    array conc{*} c1-c19;

    do i=1 to 19;
        if conc{i} < 0 then conc{i} = 0;
    end;
run;

proc print data=plasma;
run;

%SORTDS(PLASMA, &VARSORT)
RUN;

```

```

*****ACTIVATE THIS STEP AND STEP 9A BELOW ONLY IF USING CONTINU.SAS OR
CONTINU2.SAS*****
****PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
****;

***** STEP 9:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY
DATA *****;
/****IF NO PK PARAMETER DATA, BLOCK READATA AND SORTDS AND GO TO STEP 4 ****/
/**** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPARAM DDE 'EXCEL|pk!R2C1:R49C11';
* FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1; /* FIST OBSERVATION */
*%LET VARPARAM=SUB SEQ PER TRT $ TMAX CMAX AUCT AUCI KE THALF; /* VARIABLE
LIST */
%LET PARAMLS=500; /* INCREASE LINE SIZE IF NEEDED */
*%READATA (ORGPARAM, PARAME, &FIRSTOBS, &VARPARAM, &PARAMLS)
RUN;

/*
***** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY DATA
*****;
*%let pksheetname = pk;

proc import datafile="&excelfile"
            out=parame
            dbms=excel replace;
                sheet="&pksheetname";
                getnames=yes;
                mixed=yes;
run;
*/

** STEP 10:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY
FORMATTED..CHAR OR NUMERIC **;
DATA PARAME;
    * set parame;

    infile ORGPARAM ls=&paramls;
    input sub seq per GRP treat $ AUCT AUCI CMAX TMAX KE THALF;

    if treat = "A" then trt=1;
    else trt=2;
RUN;

%SORTDS (PARAME, &VARSORT)
RUN;

*****STEP 11: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY *****;
%LET CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,
                  C11, C12, C13, C14, C15, C16, C17, C18);

/****STEP 12: USE THIS STEP IF COMMON SAMPLING TIMES ARE USED,
                ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE
TIME,
                OR ADD FEW DEVIATED SAMPLING TIME POINTS,

```

```

                ALSO MAKE SURE TO DEACTIVATE "SET TIME" AND ACTIVATE
"&TIME" UNDER STEP 15***/
DATA TIME
%LET TIME=%STR(T1=0; T2=0.25; T3=0.5; T4=0.75; T5=1;
T6=1.083; T7=1.25; T8=1.5; T9=2; T10=4; T11=6; T12=9;
T13=25; T14=49; T15=97; T16=169; T17=241; T18=337);

/*USE THIS STEP INSTEAD OF STEP 11 IF ACTUAL SAMPLING TIME DATASET INCLUDED
IN THE CONCENTRATION DATASET,
ALSO, MAKE SURE TO ACTIVATE "SET TIME" AND DEACTIVATE
"&TIME" UNDER STEP 15***/;

*DATA TIME;
*SET PLASMA;
*FILE'DESKTOP\TIME';
*PUT SUB TRT SEQ PER GRP T1-T27;
*KEEP SUB TRT SEQ PER GRP T1-T27;

/*PROC PRINT DATA=TIME;RUN;*/

*****STEP 13: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=18;

*****INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE NOT
IN THE DATA SUBMITTED. *****;
** DO NOT CHANGE SINCE KE_FIRST AND KE_LAST VALUES ARE IN CONC DATASET **;
* %LET KE_FIRST=20;
* %LET KE_LAST=27;

*****STEP 14: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION *****;
/****VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL****/
/****LEAVE AS IT IS IF NO CHANGE IS DESIRED****/
/* %LET REMOVSUB=%STR(IF SUB^=10;IF SUB^=15;IF SUB^=34;IF SUB^=37;IF
SUB^=49); */
*%LET REMOVSUB=%STR(IF SUB^=1);

*****IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED *****;
/****CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC ****/
/**** IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM
CLOSED ****/
/* %LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST
IF TREAT='A' THEN TRT=1; ELSE TRT=2 );*/

DATA ORIGIN;
    ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
    ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
SET PLASMA;
*SET TIME;
* SET PARAME;
*SET MERGED;
&TIME;
*KE FIRST=0;
*KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX (&CONCENT);

```

```

/****DO NOT CHANGE: TITLES FOR TABLES****/
%LET TITLE1=MEAN PLASMA &level LEVELS;
%LET TITLE2=MEAN PLASMA &level LEVELS FOR TEST AND REFERENCE PRODUCTS;

/**** DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH ****/
%LET TITLE3=PLASMA &level LEVELS;
%LET TITLE4= &drug, ANDA &anda;
%LET TITLE5=UNDER &STUDYTYPE CONDITIONS;
%LET TITLE6=DOSE= &dose;
%LET FOOTNOT1=1=TEST 2=REF;
%LET FOOTNOT2=Tmax values are presented as median, range.;
%LET FOOTNOT3=;
%LET FOOTNOT4=;
%LET FOOTNOT5=;
%LET LABEL1=PLASMA LEVEL, &cmaxunit;
%LET LABEL2=TIME, HRS;
%LET LABEL3=TEST;
%LET LABEL4=REFERENCE;

%COPYDS(ORIGIN, NEW)
RUN;

proc print data=origin;
run;

*****STEP 15: OPEN IF YOU WANT TO REMOVE, ADD OR EDIT*****;
%REMUVSUB(NEW, NEW)
RUN;

```

Total Doxorubicin

```

***** STEP 1: LOCATION OF MACRO FILE (MACROLIB.SAS). CHANGE LOCATION IF
APPLICABLE *****;
%INCLUDE "M:\SAS\BEPRG\NEW\macrolib.sas";

/*****
ASSIGN WHETHER HAVE GROUP EFFECT:
TRTGROUP = 1 TRT*GROUP INTERACTION IN GLM MODEL
TRTGROUP = 2 TRT*GROUP INTERACTION NOT IN GLM MODEL
TRTGROUP = NO GROUP EFFECT IN STUDY
NOTE: group variable has to be named GRP in the dataset.
*****/;

*****STEP 2: ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=2;

*****STEP 3: ENTER ANDA INFORMATION *****;
%let level = TOTAL DOXORUBICIN;
%let drug= DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION;
%let dose= 2 MG/ML;
%let anda=203263;
%let studytype=FED;

***** STEP 4: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;

```

```

%let studydir=C:\Documents and Settings\dandamudi\My
Documents\suman\ANDA\Liposomes\Doxorubicin\SAS\Total dox\Group 2\24 subjects;

*****STEP 5: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = µg hr/mL;
%let cmaxunit = µg/mL;
%let timeunit = hr;

**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level.ACTUAL.doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC
FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level.ACTUAL.png;

**** DO NOT CHANGE: NAME OF CONC AND PK DATASETS OUTPUT ****;
%LET CONCOUTPUT=&studydir\&anda._&studytype._Datasets_&level..doc;

%LET VARSORT=SUB PER;

%GLOBAL SUB PER SEQ TRT GRP TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME
THALF CLAST KE_FIRST KE_LAST OLDNAME NEWNAME;

*****STEP 6: SELECT TYPE OF ANALYSIS FROM BOTTOM*****;

/****NOTE: THE CURRENT PROGRAM DOES NOT INCLUDE CONTINU OR CONTINU2
OPTIONS*****
*****SELECT TWOWAYCALCKE07MAR2009.SAS IF YOU WANT TO CALCULATE KE AND OTHER
PARAMETERS ***/
/****SELECT TWOWAYCONTINU(2)07MAR2009.SAS IF YOU DO NOT WANT TO RECALCULATE
KE.
FOR TWOWAYCONTINU(2)07MAR2009.SAS, SPONSOR'S KE WILL BE USED FOR CALCULATION
OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED PARAMETERS (CONTINU).
OR WITH STATISTICS ON CALCULATED PARAMETERS (CONTINU2) ***/

%LET FNAME=%QUOTE(V:\DIVISION\BIO\SAS Programs\Macros\CALCKE.SAS);
/**** WRITE DATA FILE NAMES ***/

***** STEP 7: ENTER THE NAME OF THE DATASET FILE (EXCEL FILE) *****;
/**** IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3 ***/
/**** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R49C25';
* FILENAME ORGPLASM "&studydir.\&plasmadata";
  %LET FIRSTOBS=1; /* FIRST OBSERVATION */
  %LET VARPLASM=SUB SEQ PER TRT c1-c22; /* VARIABLE LIST FOR THE PLASMA DATA
FILE */
%LET PLASMLS=900; /* INCREASE LINE SIZE IF NEEDED */
  %READDATA (ORGPLASM, PLASMA, &FIRSTOBS, &VARPLASM, &PLASMLS)
  *RUN;

***** NOTE: THE FIRST ROW OF THE EXCEL FILE SHOULD CONTAIN PROPER NAMES OF
THE VARIABES ***/

```

```

***** STANDARD NAMES:  SUB SEQ PER GRP TRT C1 C2 C3... KE_FIRST KE_LAST
*****;
***** EXCEL FILE DOES NOT NEED TO BE OPEN WHEN RUNNING THIS PROGRAM *****;
* %let excelfile = &studydir\fed.xls;

***** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING CONCENTRATION
DATA *****;
* %let sheetname = conc;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
*** STANDARD NAMES:  SUB SEQ PER GRP TRT c1-c23  ****;
/*
proc import datafile="&excelfile"
            out=plasma
            dbms=excel replace;
                sheet="&sheetname";
            getnames=yes;
            mixed=yes;

run;
*/

LIBNAME libdata "&studydir";

** STEP 8:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY FORMATTED..CHAR
OR NUMERIC **;
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
DATA PLASMA;
    * SET PLASMA;

    infile ORGPLASM;
    input sub seq per GRP treat $ c1-c18 KE_FIRST KE_LAST;

    if treat = "A" then trt=1;
    else trt=2;

RUN;

data plasma;
    set plasma;

    array conc{*} c1-c19;

    do i=1 to 19;
        if conc{i} < 0 then conc{i} = 0;
    end;
run;

proc print data=plasma;
run;

%SORTDS(PLASMA, &VARSORT)
RUN;

*****ACTIVATE THIS STEP AND STEP 9A BELOW ONLY IF USING CONTINU.SAS OR
CONTINU2.SAS*****

```

```

****PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE LIST
*****;

***** STEP 9:  ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY
DATA *****;
/****IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ****/
/**** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPARAM DDE 'EXCEL|pk!R2C1:R49C11';
* FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1; /* FIST OBSERVATION */
*%LET VARPARAM=SUB SEQ PER TRT $ TMAX CMAX AUCTION AUCI KE THALF; /* VARIABLE
LIST */
%LET PARAMLS=500; /* INCREASE LINE SIZE IF NEEDED */
*%READDATA (ORGPARAM, PARAME, &FIRSTOBS, &VARPARAM, &PARAMLS)
RUN;

/*
***** ENTER THE NAME OF THE EXCEL WORKSHEET NAME CONTAINING PK STUDY DATA
*****;
*%let pksheetname = pk;

proc import datafile="&excelfile"
            out=parame
            dbms=excel replace;
            sheet="&pksheetname";
            getnames=yes;
            mixed=yes;

run;
*/

** STEP 10:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY
FORMATTED..CHAR OR NUMERIC **;
DATA PARAME;
  * set parame;

  infile ORGPARAM ls=&paramls;
  input sub seq per GRP treat $ AUCTION AUCI CMAX TMAX KE THALF;

  if treat = "A" then trt=1;
  else trt=2;
RUN;

%SORTDS (PARAME, &VARSORT)
RUN;

*****STEP 11: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY *****;
%LET CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,
                  C11, C12, C13, C14, C15, C16, C17, C18);

/****STEP 12: USE THIS STEP IF COMMON SAMPLING TIMES ARE USED,
            ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE
TIME,
            OR ADD FEW DEVIATED SAMPLING TIME POINTS,
            ALSO MAKE SURE TO DEACTIVATE "SET TIME" AND ACTIVATE
"&TIME" UNDER STEP 15****/
DATA TIME

```

```

%LET TIME=%STR(T1=0; T2=0.25; T3=0.5; T4=0.75; T5=1;
T6=1.083; T7=1.25; T8=1.5; T9=2; T10=4; T11=6; T12=9;
T13=25; T14=49; T15=97; T16=169; T17=241; T18=337);

/*USE THIS STEP INSTEAD OF STEP 11 IF ACTUAL SAMPLING TIME DATASET INCLUDED
    IN THE CONCENTRATION DATASET,
    ALSO, MAKE SURE TO ACTIVATE "SET TIME" AND DEACTIVATE
"&TIME" UNDER STEP 15***/;

*DATA TIME;
*SET PLASMA;
*FILE'DESKTOP\TIME';
*PUT SUB TRT SEQ PER GRP T1-T27;
*KEEP SUB TRT SEQ PER GRP T1-T27;

/*PROC PRINT DATA=TIME;RUN;*/

*****STEP 13: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=18;

*****INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE ARE NOT
IN THE DATA SUBMITTED. *****;
** DO NOT CHANGE SINCE KE_FIRST AND KE_LAST VALUES ARE IN CONC DATASET **;
* %LET KE_FIRST=20;
* %LET KE_LAST=27;

*****STEP 14: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION *****;
/****VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL****/
/****LEAVE AS IT IS IF NO CHANGE IS DESIRED****/
/* %LET REMOVSUB=%STR(IF SUB^=10;IF SUB^=15;IF SUB^=34;IF SUB^=37;IF
SUB^=49); */
*%LET REMOVSUB=%STR(IF SUB^=1);

*****IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED *****;
/****CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC ****/
/**** IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM
CLOSED ****/
/* %LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST
IF TREAT='A' THEN TRT=1; ELSE TRT=2 );*/

DATA ORIGIN;
    ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
    ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
SET PLASMA;
*SET TIME;
* SET PARAME;
*SET MERGED;
&TIME;
*KE FIRST=0;
*KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);

/****DO NOT CHANGE: TITLES FOR TABLES****/
%LET TITLE1=MEAN PLASMA &level LEVELS;
%LET TITLE2=MEAN PLASMA &level LEVELS FOR TEST AND REFERENCE PRODUCTS;

```

```

/*** DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH ***/
%LET TITLE3=PLASMA &level LEVELS;
%LET TITLE4= &drug, ANDA &anda;
%LET TITLE5=UNDER &STUDYTYPE CONDITIONS;
%LET TITLE6=DOSE= &dose;
%LET FOOTNOT1=1=TEST 2=REF;
%LET FOOTNOT2=Tmax values are presented as median, range.;
%LET FOOTNOT3=;
%LET FOOTNOT4=;
%LET FOOTNOT5=;
%LET LABEL1=PLASMA LEVEL, &cmaxunit;
%LET LABEL2=TIME, HRS;
%LET LABEL3=TEST;
%LET LABEL4=REFERENCE;

%COPYDS(ORIGIN, NEW)
RUN;

proc print data=origin;
run;

*****STEP 15: OPEN IF YOU WANT TO REMOVE, ADD OR EDIT*****;
*%REMUVSUB(NEW, NEW)
RUN;

```

4.4.3 Fed Study Output

Free Doxorubicin

Fed STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	41	2 3 8 10 12 13 16 17 18 20 22 23 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 45 47 48 51 52 53 54 57 58 60 61
TRT	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	82
Number of Observations Used	82

Data for Analysis of AUCI LAUCI	
Number of Observations Read	82
Number of Observations Used	72

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	42	19.71264396	0.46934867	3.62	<.0001
Error	39	5.05726944	0.12967358		
Corrected Total	81	24.76991339			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.795830	3.605481	0.360102	9.987632

Source	DF	Type I SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.19050882	0.19050882	1.47	0.2328
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	39	19.25608284	0.49374571	3.81	<.0001
per(GRP)	1	0.20619411	0.20619411	1.59	0.2148
trt	1	0.05985818	0.05985818	0.46	0.5009

Source	DF	Type III SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.19050882	0.19050882	1.47	0.2328
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	39	19.25608284	0.49374571	3.81	<.0001
per(GRP)	1	0.23091222	0.23091222	1.78	0.1898
trt	1	0.05985818	0.05985818	0.46	0.5009

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.19050882	0.19050882	0.39	0.5381
GRP	0	0.00000000	.	.	.

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.05444256	0.08013136	0.68	0.5009

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	40	16.23183729	0.40579593	3.61	0.0002
Error	31	3.48333066	0.11236551		
Corrected Total	71	19.71516795			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.823317	3.326821	0.335210	10.07598

Source	DF	Type I SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.59152512	0.59152512	5.26	0.0287
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	37	15.46855005	0.41806892	3.72	0.0002
per(GRP)	1	0.09687111	0.09687111	0.86	0.3603
trt	1	0.07489101	0.07489101	0.67	0.4205

Source	DF	Type III SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.25499608	0.25499608	2.27	0.1421
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	37	15.58338304	0.42117251	3.75	0.0002
per(GRP)	1	0.12187913	0.12187913	1.08	0.3057
trt	1	0.07489101	0.07489101	0.67	0.4205

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.25499608	0.25499608	0.61	0.4415
GRP	0	0.00000000	.	.	.

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.06815787	0.08348677	0.82	0.4205

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	42	15.27676940	0.36373260	2.18	0.0079
Error	39	6.51411421	0.16702857		
Corrected Total	81	21.79088361			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.701062	7.481823	0.408691	5.462456

Source	DF	Type I SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.02201517	0.02201517	0.13	0.7185
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	39	15.25213836	0.39108047	2.34	0.0046
per(GRP)	1	0.00131945	0.00131945	0.01	0.9296
trt	1	0.00129642	0.00129642	0.01	0.9302

Source	DF	Type III SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.02201517	0.02201517	0.13	0.7185
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	39	15.25213836	0.39108047	2.34	0.0046
per(GRP)	1	0.00100249	0.00100249	0.01	0.9386
trt	1	0.00129642	0.00129642	0.01	0.9302

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.02201517	0.02201517	0.06	0.8137
GRP	0	0.00000000	.	.	.

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	-0.00801217	0.09094360	-0.09	0.9302

Liposomal Doxorubicin

Fed STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	24	2 3 8 10 12 13 16 17 18 20 22 23 26 27 31 32 33 34 35 36 37 38 39 40
TRT	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	48
Number of Observations Used	48

Data for Analysis of AUCI LAUCI	
Number of Observations Read	48
Number of Observations Used	46

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	5.84844896	0.23393796	4.90	0.0002
Error	22	1.05028151	0.04774007		
Corrected Total	47	6.89873047			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.847757	2.718018	0.218495	8.038761

Source	DF	Type I SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.02376018	0.02376018	0.50	0.4879
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	22	5.66849837	0.25765902	5.40	0.0001
per(GRP)	1	0.02457941	0.02457941	0.51	0.4806
trt	1	0.13161100	0.13161100	2.76	0.1110

Source	DF	Type III SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.02376018	0.02376018	0.50	0.4879
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	22	5.66849837	0.25765902	5.40	0.0001
per(GRP)	1	0.02457941	0.02457941	0.51	0.4806
trt	1	0.13161100	0.13161100	2.76	0.1110

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.02376018	0.02376018	0.09	0.7642
GRP	0	0.00000000	.	.	.

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.10472623	0.06307408	1.66	0.1110

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	4.34741499	0.17389660	8.21	<.0001
Error	20	0.42366364	0.02118318		
Corrected Total	45	4.77107863			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.911202	1.783831	0.145544	8.159092

Source	DF	Type I SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.01830042	0.01830042	0.86	0.3637
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	22	4.26939524	0.19406342	9.16	<.0001
per(GRP)	1	0.04854274	0.04854274	2.29	0.1457
trt	1	0.01117659	0.01117659	0.53	0.4760

Source	DF	Type III SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.01698386	0.01698386	0.80	0.3812
seq*GRP	0	0.00000000	.	.	.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sub(seq*GRP)	22	4.27103408	0.19413791	9.16	<.0001
per(GRP)	1	0.04854274	0.04854274	2.29	0.1457
trt	1	0.01117659	0.01117659	0.53	0.4760

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.01698386	0.01698386	0.09	0.7702
GRP	0	0.00000000	.	.	.

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.03187559	0.04388330	0.73	0.4760

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	25	1.27684807	0.05107392	4.56	0.0003
Error	22	0.24661979	0.01120999		
Corrected Total	47	1.52346786			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.838119	2.978860	0.105877	3.554288

Source	DF	Type I SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.00098829	0.00098829	0.09	0.7693
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	22	1.26234192	0.05737918	5.12	0.0002
per(GRP)	1	0.01177680	0.01177680	1.05	0.3165
trt	1	0.00174106	0.00174106	0.16	0.6973

Source	DF	Type III SS	Mean Square	F Value	Pr > F
GRP	0	0.00000000	.	.	.
seq	1	0.00098829	0.00098829	0.09	0.7693
seq*GRP	0	0.00000000	.	.	.
sub(seq*GRP)	22	1.26234192	0.05737918	5.12	0.0002

Source	DF	Type III SS	Mean Square	F Value	Pr > F
per(GRP)	1	0.01177680	0.01177680	1.05	0.3165
trt	1	0.00174106	0.00174106	0.16	0.6973

Tests of Hypotheses Using the Type III MS for sub(seq*GRP) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.00098829	0.00098829	0.02	0.8968
GRP	0	0.00000000	.	.	.

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.01204527	0.03056413	0.39	0.6973

RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS

Free Doxorubicin

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	2	2	1	1	2	28109.05	29697.95	291.47	B	28101.84	33475.67	291.47	0.99974	1.12720	1
2	2	2	2	1	1	47064.67	47211.42	415.42	A	47299.55	52462.18	415.42	1.00499	1.11122	1
3	3	2	1	1	2	40276.53	40538.50	311.28	B	40276.53	42101.72	311.28	1.00000	1.03856	1
4	3	2	2	1	1	24897.70	25107.06	190.53	A	24931.27	27781.40	190.53	1.00135	1.10652	1
5	8	2	1	1	2	19520.35	19576.24	304.89	B	19520.36	20133.92	304.89	1.00000	1.02849	1
6	8	2	2	1	1	47380.58	47552.76	1030.68	A	47380.58	48554.31	1030.68	1.00000	1.02106	1
7	10	1	1	1	1	27144.99	27206.25	258.92	A	.	.	258.92	.	.	1
8	10	1	2	1	2	19118.18	.	422.70	B	.	.	422.70	.	.	1
9	12	1	1	1	1	40189.98	40370.16	338.63	A	40189.98	42825.01	338.63	1.00000	1.06081	1
10	12	1	2	1	2	60693.71	60861.89	525.19	B	60693.71	62367.08	525.19	1.00000	1.02473	1
11	13	2	1	1	2	32573.10	.	243.94	B	32573.10	87775.10	243.94	1.00000	.	1
12	13	2	2	1	1	32001.30	.	188.48	A	32001.30	35758.82	188.48	1.00000	.	1
13	16	2	1	1	2	37391.30	37467.98	503.03	B	37391.30	38196.82	503.03	1.00000	1.01945	1
14	16	2	2	1	1	32077.57	32199.83	257.02	A	32077.57	33412.35	257.02	1.00000	1.03766	1
15	17	1	1	1	1	49982.73	50280.55	704.85	A	49982.73	52129.58	704.85	1.00000	1.03677	1
16	17	1	2	1	2	26497.64	27511.45	592.28	B	26676.48	29670.41	592.28	1.00675	1.07848	1
17	18	1	1	1	1	16601.82	17760.02	260.33	A	16601.83	17509.41	260.33	1.00000	0.98589	1
18	18	1	2	1	2	17226.87	17399.58	337.27	B	17226.87	17850.34	337.27	1.00000	1.02591	1
19	20	2	1	1	2	18070.23	.	273.88	B	18070.23	24872.64	273.88	1.00000	.	1
20	20	2	2	1	1	13370.84	13615.06	226.91	A	13370.84	14227.06	226.91	1.00000	1.04495	1
21	22	2	1	1	2	32319.32	.	374.99	B	32319.33	32707.30	374.99	1.00000	.	1
22	22	2	2	1	1	34244.80	34477.73	471.48	A	34245.18	34945.49	471.48	1.00001	1.01357	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
23	23	1	1	1	1	27475.65	27869.33	285.09	A	27475.65	30583.24	285.09	1.00000	1.09738	1
24	23	1	2	1	2	20356.98	21264.53	173.88	B	20356.98	24292.76	173.88	1.00000	1.14241	1
25	26	2	1	1	2	13546.33	14329.61	209.60	B	13546.33	15940.35	209.60	1.00000	1.11241	1
26	26	2	2	1	1	18719.02	18973.16	170.60	A	18719.02	21415.19	170.60	1.00000	1.12871	1
27	27	1	1	1	1	16775.42	16881.65	125.14	A	16775.42	18242.38	125.14	1.00000	1.08060	1
28	27	1	2	1	2	20751.61	20903.25	157.63	B	20751.61	21494.78	157.63	1.00000	1.02830	1
29	28	2	1	1	2	24008.84	24167.70	176.34	B	24008.84	24747.58	176.34	1.00000	1.02399	1
30	28	2	2	1	1	19021.66	19269.52	170.78	A	19021.66	19729.05	170.78	1.00000	1.02385	1
31	29	2	1	1	2	22677.23	23073.70	165.21	B	22677.23	23931.77	165.21	1.00000	1.03719	1
32	29	2	2	1	1	18843.93	19027.74	188.86	A	18843.93	20340.64	188.86	1.00000	1.06900	1
33	30	2	1	1	2	20156.36	20392.26	249.26	B	20156.36	21123.14	249.26	1.00000	1.03584	1
34	30	2	2	1	1	22882.81	23135.94	200.76	A	22882.81	25669.44	200.76	1.00000	1.10950	1
35	31	1	1	1	1	41441.91	41603.56	431.63	A	41441.91	43220.25	431.63	1.00000	1.03886	1
36	31	1	2	1	2	38298.56	38900.48	336.90	B	38298.57	40214.10	336.90	1.00000	1.03377	1
37	32	1	1	1	1	42224.26	43453.36	426.05	A	42224.26	47540.30	426.05	1.00000	1.09405	1
38	32	1	2	1	2	41851.95	42670.66	296.48	B	41851.95	50015.01	296.48	1.00000	1.17212	1
39	33	2	1	1	2	35114.24	35748.49	391.59	B	35114.24	38612.15	391.59	1.00000	1.08011	1
40	33	2	2	1	1	51366.37	51879.02	719.71	A	51366.37	57678.58	719.71	1.00000	1.11179	1
41	34	1	1	1	1	17175.90	17582.85	272.21	A	17175.90	20229.11	272.21	1.00000	1.15050	1
42	34	1	2	1	2	32038.83	32271.07	333.72	B	32038.83	33320.10	333.72	1.00000	1.03251	1
43	35	2	1	1	2	63085.43	63957.51	431.72	B	63085.44	65935.67	431.72	1.00000	1.03093	1
44	35	2	2	1	1	39378.65	39584.80	376.42	A	39378.65	44459.46	376.42	1.00000	1.12314	1
45	36	1	1	1	1	13882.59	14022.34	134.81	A	13882.59	14795.47	134.81	1.00000	1.05514	1
46	36	1	2	1	2	8521.45	8728.31	100.26	B	8521.45	9754.66	100.26	1.00000	1.11759	1
47	37	1	1	1	1	67828.58	67899.95	809.66	A	67828.58	68524.32	809.66	1.00000	1.00920	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
48	37	1	2	1	2	18615.22	18715.76	123.97	B	18615.22	19620.54	123.97	1.00000	1.04834	1
49	38	2	1	1	2	22884.31	23075.58	145.17	B	22884.31	23796.21	145.17	1.00000	1.03123	1
50	38	2	2	1	1	22225.99	22525.94	253.99	A	22226.00	23994.93	253.99	1.00000	1.06521	1
51	39	2	1	1	2	34824.40	34949.47	258.89	B	34824.40	37912.34	258.89	1.00000	1.08478	1
52	39	2	2	1	1	21101.99	.	268.17	A	21101.99	29381.68	268.17	1.00000	.	1
53	40	1	1	1	1	16139.24	16308.83	121.27	A	16139.24	18017.32	121.27	1.00000	1.10476	1
54	40	1	2	1	2	20747.54	.	174.20	B	20747.54	25217.54	174.20	1.00000	.	1
55	41	1	1	1	1	19439.19	.	118.51	A	19439.19	29092.82	118.51	1.00000	.	1
56	41	1	2	1	2	39683.24	.	324.83	B	39683.24	40433.78	324.83	1.00000	.	1
57	42	2	1	1	2	8272.53	8565.68	156.51	B	8272.53	9164.00	156.51	1.00000	1.06985	1
58	42	2	2	1	1	11965.82	12459.23	172.62	A	11965.82	13576.04	172.62	1.00000	1.08964	1
59	43	2	1	1	2	12261.10	12770.06	171.61	B	12261.10	15223.40	171.61	1.00000	1.19212	1
60	43	2	2	1	1	10732.75	10907.88	229.80	A	10732.75	11294.45	229.80	1.00000	1.03544	1
61	45	1	1	1	1	16277.72	16446.32	153.34	A	16277.72	16873.10	153.34	1.00000	1.02595	1
62	45	1	2	1	2	13968.34	14034.29	207.39	B	13968.34	14546.89	207.39	1.00000	1.03652	1
63	47	1	1	1	1	49270.12	49609.31	269.26	A	49270.12	50410.54	269.26	1.00000	1.01615	1
64	47	1	2	1	2	23352.61	23515.00	171.13	B	23352.62	24818.60	171.13	1.00000	1.05544	1
65	48	2	1	1	2	27388.75	28339.73	429.79	B	27388.75	28964.44	429.79	1.00000	1.02204	1
66	48	2	2	1	1	9372.88	9450.56	89.41	A	9372.88	10023.28	89.41	1.00000	1.06060	1
67	51	1	1	1	1	28624.70	28716.11	226.49	A	28624.70	29567.96	226.49	1.00000	1.02966	1
68	51	1	2	1	2	15327.62	15616.98	187.25	B	15327.62	17112.71	187.25	1.00000	1.09578	1
69	52	2	1	1	2	11947.32	12018.21	146.47	B	11947.32	13109.79	146.47	1.00000	1.09083	1
70	52	2	2	1	1	9620.15	11490.85	287.17	A	9620.15	10458.78	287.17	1.00000	0.91018	1
71	53	2	1	1	2	15314.58	15493.43	220.05	B	15314.58	16511.46	220.05	1.00000	1.06571	1
72	53	2	2	1	1	18019.05	18514.50	142.14	A	18019.05	19415.47	142.14	1.00000	1.04866	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
73	54	2	1	1	2	9961.00	10059.40	154.16	B	9961.01	10345.78	154.16	1.00000	1.02847	1
74	54	2	2	1	1	13132.18	13608.06	124.04	A	13132.18	14240.86	124.04	1.00000	1.04650	1
75	57	2	1	1	2	10919.97	10977.25	110.43	B	10919.97	11693.26	110.43	1.00000	1.06523	1
76	57	2	2	1	1	12395.99	12547.68	114.13	A	12395.99	14005.98	114.13	1.00000	1.11622	1
77	58	1	1	1	1	13769.04	13920.53	127.85	A	13769.04	14740.53	127.85	1.00000	1.05891	1
78	58	1	2	1	2	27619.75	27797.11	200.27	B	27619.75	28516.31	200.27	1.00000	1.02587	1
79	60	1	1	1	1	11598.57	12826.34	129.18	A	11598.57	12545.25	129.18	1.00000	0.97808	1
80	60	1	2	1	2	3589.42	.	186.77	B	3589.42	4295.30	186.77	1.00000	.	1
81	61	2	1	1	2	17470.00	17702.60	145.94	B	17470.00	20380.47	145.94	1.00000	1.15127	1
82	61	2	2	1	1	9228.79	9484.74	124.79	A	9228.79	12231.99	124.79	1.00000	1.28965	1

Liposomal Doxorubicin

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	2	2	1	1	2	3535.04	3548.47	38.62	B	3534.20	3731.97	38.62	0.99976	1.05171	1
2	2	2	2	1	1	4187.52	4206.05	38.39	A	4196.87	4410.38	38.39	1.00223	1.04858	1
3	3	2	1	1	2	3817.77	3854.76	33.12	B	3817.77	4147.66	33.12	1.00000	1.07598	1
4	3	2	2	1	1	3358.06	3427.41	31.34	A	3361.55	3599.27	31.34	1.00104	1.05014	1
5	8	2	1	1	2	2301.05	2320.35	34.83	B	2301.05	2395.59	34.83	1.00000	1.03243	1
6	8	2	2	1	1	2357.07	2391.70	29.09	A	2357.07	2541.10	29.09	1.00000	1.06246	1
7	10	1	1	1	1	2660.67	2672.15	29.60	A	.	.	29.60	.	.	1
8	10	1	2	1	2	1120.53	.	33.89	B	.	.	33.89	.	.	1
9	12	1	1	1	1	3042.69	3057.34	33.00	A	3042.69	3149.50	33.00	1.00000	1.03014	1
10	12	1	2	1	2	3408.85	3439.16	31.86	B	3408.85	3639.82	31.86	1.00000	1.05835	1
11	13	2	1	1	2	2701.17	2712.38	33.05	B	2701.17	2836.80	33.05	1.00000	1.04587	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
12	13	2	2	1	1	3019.25	3038.58	38.42	A	3019.25	3233.80	38.42	1.00000	1.06425	1
13	16	2	1	1	2	2202.36	2220.42	28.33	B	2202.37	2311.76	28.33	1.00000	1.04114	1
14	16	2	2	1	1	2124.03	2152.27	27.15	A	2124.03	2340.37	27.15	1.00000	1.08739	1
15	17	1	1	1	1	2249.23	2276.62	30.32	A	2249.23	2392.58	30.32	1.00000	1.05094	1
16	17	1	2	1	2	2525.68	2546.01	30.66	B	2525.68	2693.24	30.66	1.00000	1.05783	1
17	18	1	1	1	1	1847.02	1874.33	24.87	A	1847.02	1984.83	24.87	1.00000	1.05895	1
18	18	1	2	1	2	1064.01	1119.91	23.25	B	1064.01	1220.72	23.25	1.00000	1.09001	1
19	20	2	1	1	2	1197.86	.	24.14	B	1197.86	1907.95	24.14	1.00000	.	1
20	20	2	2	1	1	2650.14	2702.53	35.50	A	2650.14	3274.83	35.50	1.00000	1.21176	1
21	22	2	1	1	2	1904.74	2064.39	28.37	B	1904.74	2047.32	28.37	1.00000	0.99173	1
22	22	2	2	1	1	2940.96	2957.34	31.57	A	2940.86	3064.90	31.57	0.99997	1.03637	1
23	23	1	1	1	1	3059.69	3106.65	28.34	A	3059.69	3366.26	28.34	1.00000	1.08357	1
24	23	1	2	1	2	3688.65	3714.36	32.04	B	3688.65	3928.11	32.04	1.00000	1.05754	1
25	26	2	1	1	2	3298.91	3320.17	43.44	B	3298.91	3468.93	43.44	1.00000	1.04480	1
26	26	2	2	1	1	5273.58	5294.34	42.89	A	5273.58	5661.69	42.89	1.00000	1.06938	1
27	27	1	1	1	1	3970.47	4003.31	34.83	A	3970.47	4325.36	34.83	1.00000	1.08044	1
28	27	1	2	1	2	3857.93	3928.77	36.32	B	3857.93	4521.10	36.32	1.00000	1.15077	1
29	31	1	1	1	1	4736.84	4774.49	49.05	A	4736.84	4927.90	49.05	1.00000	1.03213	1
30	31	1	2	1	2	3810.90	3853.64	47.38	B	3810.90	4021.45	47.38	1.00000	1.04354	1
31	32	1	1	1	1	4702.96	4735.93	41.94	A	4702.96	4956.25	41.94	1.00000	1.04652	1
32	32	1	2	1	2	5473.16	5512.61	38.35	B	5473.17	5902.52	38.35	1.00000	1.07073	1
33	33	2	1	1	2	4427.54	4454.15	39.19	B	4427.54	4687.79	39.19	1.00000	1.05245	1
34	33	2	2	1	1	4121.89	4143.19	41.03	A	4121.89	4309.52	41.03	1.00000	1.04015	1
35	34	1	1	1	1	3333.77	3363.79	38.66	A	3333.77	3692.86	38.66	1.00000	1.09783	1
36	34	1	2	1	2	3933.93	3953.49	44.00	B	3933.93	4083.90	44.00	1.00000	1.03299	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
37	35	2	1	1	2	3764.80	3792.32	35.90	B	3764.80	4034.72	35.90	1.00000	1.06392	1
38	35	2	2	1	1	4417.95	4440.81	52.93	A	4417.95	4777.28	52.93	1.00000	1.07577	1
39	36	1	1	1	1	2216.19	2252.60	30.64	A	2216.19	2503.72	30.64	1.00000	1.11148	1
40	36	1	2	1	2	2179.28	2243.59	36.24	B	2179.28	2508.90	36.24	1.00000	1.11826	1
41	37	1	1	1	1	2799.26	2816.79	36.22	A	2799.26	2913.01	36.22	1.00000	1.03416	1
42	37	1	2	1	2	3576.80	3589.41	35.55	B	3576.80	3801.88	35.55	1.00000	1.05919	1
43	38	2	1	1	2	3715.20	3738.50	37.95	B	3715.20	3965.04	37.95	1.00000	1.06059	1
44	38	2	2	1	1	3627.17	3644.97	32.82	A	3627.17	3772.95	32.82	1.00000	1.03511	1
45	39	2	1	1	2	4834.29	4862.93	40.99	B	4834.29	5514.75	40.99	1.00000	1.13404	1
46	39	2	2	1	1	4363.37	4419.24	36.54	A	4363.37	5156.49	36.54	1.00000	1.16683	1
47	40	1	1	1	1	4555.83	4574.86	43.86	A	4555.83	4781.85	43.86	1.00000	1.04525	1
48	40	1	2	1	2	4496.64	4552.19	38.45	B	4496.64	5106.69	38.45	1.00000	1.12181	1

Total Doxorubicin

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	2	2	1	1	2	3680.34	3698.49	41.944	B	3679.33	3871.06	41.944	0.99972	1.04666	1
2	2	2	2	1	1	4427.49	4446.02	42.816	A	4435.66	4683.54	42.816	1.00184	1.05342	1
3	3	2	1	1	2	3549.14	3585.71	29.510	B	3549.15	3776.57	29.510	1.00000	1.05323	1
4	3	2	2	1	1	3400.18	3424.29	30.421	A	3403.64	3633.65	30.421	1.00102	1.06114	1
5	8	2	1	1	2	2862.44	2867.43	40.221	B	2862.44	2888.10	40.221	1.00000	1.00721	1
6	8	2	2	1	1	3140.10	3148.78	35.431	A	3140.10	3202.10	35.431	1.00000	1.01693	1
7	10	1	1	1	1	2857.54	2868.24	29.561	A	.	.	29.561	.	.	1
8	10	1	2	1	2	1359.10	.	37.684	B	.	.	37.684	.	.	1
9	12	1	1	1	1	2943.03	2956.97	32.187	A	2943.03	3054.89	32.187	1.00000	1.03311	1
10	12	1	2	1	2	3710.82	3745.53	35.042	B	3710.82	3951.32	35.042	1.00000	1.05494	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
11	13	2	1	1	2	2328.91	2344.50	28.325	B	2328.91	2462.94	28.325	1.00000	1.05052	1
12	13	2	2	1	1	2918.37	2938.41	27.263	A	2918.37	3118.41	27.263	1.00000	1.06126	1
13	16	2	1	1	2	2309.98	2314.66	31.261	B	2309.98	2343.22	31.261	1.00000	1.01234	1
14	16	2	2	1	1	2377.38	2385.56	28.439	A	2377.38	2435.52	28.439	1.00000	1.02094	1
15	17	1	1	1	1	2253.13	2259.10	28.973	A	2253.13	2292.39	28.973	1.00000	1.01474	1
16	17	1	2	1	2	2251.72	2255.92	30.231	B	2251.72	2292.93	30.231	1.00000	1.01641	1
17	18	1	1	1	1	1968.13	1974.38	24.016	A	1968.13	2001.12	24.016	1.00000	1.01354	1
18	18	1	2	1	2	991.67	1007.80	20.230	B	991.68	1030.69	20.230	1.00000	1.02272	1
19	20	2	1	1	2	1191.08	.	25.883	B	1191.08	1879.70	25.883	1.00000	.	1
20	20	2	2	1	1	2474.88	2482.80	33.570	A	2474.88	2506.33	33.570	1.00000	1.00948	1
21	22	2	1	1	2	2137.92	2148.38	26.626	B	2137.92	2193.04	26.626	1.00000	1.02079	1
22	22	2	2	1	1	3006.86	.	32.989	A	3006.85	4140.65	32.989	1.00000	.	1
23	23	1	1	1	1	3040.51	3066.95	28.729	A	3040.51	3236.72	28.729	1.00000	1.05535	1
24	23	1	2	1	2	3851.19	3872.89	33.824	B	3851.19	4053.87	33.824	1.00000	1.04673	1
25	26	2	1	1	2	3380.85	3401.12	34.831	B	3380.85	3546.62	34.831	1.00000	1.04278	1
26	26	2	2	1	1	3477.51	3497.85	32.346	A	3477.51	3704.28	32.346	1.00000	1.05902	1
27	27	1	1	1	1	3599.88	3624.68	32.863	A	3599.88	3863.03	32.863	1.00000	1.06576	1
28	27	1	2	1	2	3813.73	3825.06	34.122	B	3813.73	3893.32	34.122	1.00000	1.01784	1
29	31	1	1	1	1	4314.96	4345.17	42.426	A	4314.96	4474.92	42.426	1.00000	1.02986	1
30	31	1	2	1	2	4508.59	4547.83	39.115	B	4508.59	4750.60	39.115	1.00000	1.04459	1
31	32	1	1	1	1	4111.12	4146.26	41.750	A	4111.12	4354.99	41.750	1.00000	1.05034	1
32	32	1	2	1	2	4533.38	4570.91	34.642	B	4533.38	4936.46	34.642	1.00000	1.07997	1
33	33	2	1	1	2	4018.98	4045.31	36.070	B	4018.98	4254.15	36.070	1.00000	1.05162	1
34	33	2	2	1	1	4066.64	4091.77	39.675	A	4066.64	4300.34	39.675	1.00000	1.05097	1
35	34	1	1	1	1	3401.18	3411.41	46.488	A	3401.18	3510.24	46.488	1.00000	1.02897	1

Obs	sub	seq	per	GRP	trt	FDAAREA	FDAAUCI	FDACMAX	treat	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
36	34	1	2	1	2	3427.23	3439.98	37.521	B	3427.23	3530.85	37.521	1.00000	1.02642	1
37	35	2	1	1	2	3804.85	3833.94	35.541	B	3804.85	4053.03	35.541	1.00000	1.05715	1
38	35	2	2	1	1	3900.54	3939.83	38.268	A	3900.54	4282.23	38.268	1.00000	1.08691	1
39	36	1	1	1	1	2072.57	2080.08	26.939	A	2072.57	2109.65	26.939	1.00000	1.01421	1
40	36	1	2	1	2	2953.24	2957.96	35.508	B	2953.24	2974.98	35.508	1.00000	1.00575	1
41	37	1	1	1	1	2930.90	2942.99	28.466	A	2930.90	3057.39	28.466	1.00000	1.03887	1
42	37	1	2	1	2	3937.31	3956.83	30.948	B	3937.31	4267.88	30.948	1.00000	1.07861	1
43	38	2	1	1	2	3716.26	3738.94	35.807	B	3716.26	3954.10	35.807	1.00000	1.05755	1
44	38	2	2	1	1	3553.27	3573.67	34.175	A	3553.27	3727.95	34.175	1.00000	1.04317	1
45	39	2	1	1	2	4733.22	4765.64	35.584	B	4733.22	5431.37	35.584	1.00000	1.13969	1
46	39	2	2	1	1	4812.27	4833.69	36.789	A	4812.27	5642.16	36.789	1.00000	1.16726	1
47	40	1	1	1	1	3873.79	3892.02	35.523	A	3873.79	4058.01	35.523	1.00000	1.04265	1
48	40	1	2	1	2	4855.85	4896.43	36.073	B	4855.85	5495.46	36.073	1.00000	1.12234	1

Note: All the tables produced by the reviewer in the verification of study was done using the SAS code “calcke”

BIOEQUIVALENCE DEFICIENCIES

ANDA: 203263
APPLICANT: Sun Pharma Global FZE
DRUG PRODUCT: Doxorubicin Hydrochloride Injection,
Liposomal, 2 mg/mL (10 mL and 25 mL)

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The deficiencies below have been identified.

Bioanalytical Report:

1. You have provided multiple summary tables of calibration curve (CC) and quality control (QC) data for the analytes of free doxorubicin and liposome encapsulated doxorubicin. Please provide justification for submitting multiple summary tables, instead of one overall summary of the interday accuracy and precision of all the CC's and QC data from the study sample analyses.

In Vitro Liposome Size Distribution Testing

2. Please submit in vitro liposome size distribution testing data in **electronic SAS Transport files** using the following table format for verification analysis by the DBE.

PRODUCT	LOT	VIAL	D10	D50	D90	SPAN
TEST	1234	1				
		2				
		3				
		4				
		5				
		6				
		7				
		8				
		9				
		10				

3. It did not appear that you conducted cross-validation study for confirmation of the extraction method to estimate only liposomal doxorubicin in the presence of free doxorubicin. Please provide the cross-validation data.

Dissolution Testing

4. You have submitted *in vitro* drug release testing data using your proposed testing method with bottle rotating apparatus. However, currently the DBE does not encourage the use of non-compendial apparatus in *in vitro* drug release testing. Since the bottle rotating apparatus is not considered a compendial apparatus, your proposed method is considered incomplete at this time. Please submit all detailed information concerning the development, optimization and validation of your proposed test method for a full evaluation.

5. In addition, please conduct the following *in vitro* drug release testing. Please note that this recommended method does not employ any dissolution apparatus.

The comparative testing should be conducted on the test and reference product, using one dosage unit (vial) (10 mL of 2 mg/mL) per replicate and six samples taken per unit for six different time points: Six samples of 1 mL of the vial content should be transferred to six separate glass tubes containing the medium of 98% fetal bovine serum with 80 mM NH₄Cl at pH 6.0, to obtain the final sample volume of 100 mL. The resulting drug concentration should be 20 microgram/mL of liposomal doxorubicin. These glass tubes should be incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome should be determined at the following six time points: 0 hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs. The testing should be replicated for 12 dosage vials per each test and the reference drug product.

The individual percent doxorubicin release data from each vial at each time point should be submitted, as well as the mean data from 12 vials at each time point for each product (% mean and % CV) over the period of 0 to 4 hours for the test and RLD from 12 dosage units.

Please submit a complete validation data and report for the above-recommended test method.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

COMPLETED ASSIGNMENT FOR 203263 ID: 15742

Reviewer: Dandamudi, Suman **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
15742	6/16/2011	Bioequivalence Study	Fed Study	1	1	Edit	Delete
15742	6/16/2011	Bioequivalence Study	Pivotal Study (Blanching)	1	1	Edit	Delete
15742	6/16/2011	Bioequivalence Study	In-Vitro Study (Nasal, Binding)	1	1	Edit	Delete
				Bean Total	3		

A one point credit has been transferred from Dandamudi Suman to Chung Hee Sun because Hee Sun conducted the necessary research to complete this document. The completion of this document was essential because there is shortage of Doxorubicin. Since Suman is to be away from office for an extended period, Hee Sun performed the research.

5 COMPLETED ASSIGNMENT FOR 203263 ID: 16133

Reviewer: Chung, Hee Sun **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Technical Research

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
16133	6/16/2011	Other	Dissolution Review	1	1	Edit	Delete
				Bean Total:	1		

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

/s/

SHRINIWAS G NERURKAR
02/16/2012

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/16/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203263

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

10 APR 2012

ANDA: 203263

Drug Product Name

Proprietary: N/A

Non-proprietary: Doxorubicin Hydrochloride Liposomal Injection

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
4/9/2012	4/9/2012	N/A	4/9/2012

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
6/16/2011	1	12/29/2011

Applicant/Sponsor

Name: Sun Pharmaceutical Industries Limited

Address: Acme Plaza, Andheri-Kurla Road, Andheri (East), Mumbai-400059, India

US Agent

Name: Sun Pharmaceutical Industries, Inc.

Address: 1150 Elijah McCoy Drive, Detroit, MI 48202

Representative: Robert Kurkiewicz

Telephone: 313 556 4105

Name of Reviewer: Jesse Wells, Ph.D.

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

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Amendment
 - 2. SUBMISSION PROVIDES FOR:** Response to microbiology deficiencies
 - 3. MANUFACTURING SITE:** Sun Pharmaceutical Industries, Ltd. Halol-Baroda Highway, Halol-389350, Gujarat, India
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile liposomal solution; IM or Subcutaneous injection; 2 mg/ mL; 10 mL fill in 10 mL vials and 25 mL fill in 25 mL vials; single dose
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
(b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** Indicated for treatment of ovarian cancer or Kaposi's sarcoma
- B. SUPPORTING/RELATED DOCUMENTS:** none
- C. REMARKS:** The amendment was filed electronically. Expedited review has been granted.

filename: 203263a1.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – The submission is recommended for approval on the basis of sterility assurance.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - (b) (4)
 (b) (4) The drug product is filled using (b) (4)
 (b) (4)
- B. **Brief Description of Microbiology Deficiencies** – None identified
- C. **Assessment of Risk Due to Microbiology Deficiencies** – None; sufficient sterility assurance information is provided.

III. Administrative

- A. **Reviewer's Signature** _____
- B. **Endorsement Block**
 Microbiologist/ Jesse Wells, Ph.D.
 Microbiology Team Leader/CDR Paul Dexter, M.S.
- C. **CC Block**
 cc: Field Copy

Applicant's Response: The applicant acknowledges.

Acceptable

APPEARS THIS WAY ON
ORIGINAL

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

/s/

JESSE WELLS
04/24/2012

ELIZABETH T MCNEAL
04/24/2012
Checked file and submission link. Both correct.

PAUL L DEXTER
05/04/2012

Product Quality Microbiology Review

29 DEC 2011

ANDA: 203263

Drug Product Name

Proprietary: N/A

Non-proprietary: Doxorubicin Hydrochloride Liposomal Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
6/16/2011	6/16/2011	N/A	12/20/2011

Submission History (for amendments only)

None

Applicant/Sponsor

Name: Sun Pharmaceutical Industries Limited

Address: Acme Plaza, Andheri-Kurla Road, Andheri (East), Mumbai-400059, India

US Agent

Name: Sun Pharmaceutical Industries, Inc.

Address: 1150 Elijah McCoy Drive, Detroit, MI 48202

Representative: Robert Kurkiewicz

Telephone: 313 556 4105

Name of Reviewer: Jesse Wells, Ph.D.

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original ANDA
 2. **SUBMISSION PROVIDES FOR:** Initial marketing of a sterile drug product.
 3. **MANUFACTURING SITE:** Sun Pharmaceutical Industries, Ltd. Halol-Baroda Highway, Halol-389350, Gujarat, India
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile liposomal solution; IM or Subcutaneous injection; 2 mg/ mL; 10 mL fill in 10 mL vials and 25 mL fill in 25 mL vials; single dose
 5. **METHOD(S) OF STERILIZATION:** (b) (4)
(b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Indicated for treatment of ovarian cancer or Kaposi's sarcoma
- B. **SUPPORTING/RELATED DOCUMENTS:**
DMF (b) (4) and associated microbiology review (b) (4) mic18.doc by Y. Smith, dated 9/1/2011 ANDA 202203, and associated microbiology reviews 202203.doc and 202203a1.doc by J. Wells, dated 2/10/2011 and 10/27/2011 respectively.
- C. **REMARKS:** The ANDA was filed electronically. Expedited review has been granted. Some of the same (b) (4) validation data provided in the subject ANDA was also provided for ANDA 202203.

filename: 203263.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies can be found in the “Product Quality Microbiology Review” and “List of Deficiencies and Comments” sections.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - (b) (4)
 (b) (4) The drug product is filled (b) (4)
 (b) (4).
- B. Brief Description of Microbiology Deficiencies – Incomplete/Inadequate** (b) (4)
 (b) (4)
- C. Assessment of Risk Due to Microbiology Deficiencies** – The safety risk due to the microbiology deficiencies is considered “high.”

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
 Microbiologist/ Jesse Wells, Ph.D.
 Microbiology Team Leader/CDR Paul Dexter, M.S.
- C. CC Block**
 cc: Field Copy

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 203263 APPLICANT: Sun Pharmaceutical Industries, Inc.

DRUG PRODUCT: Doxorubicin Hydrochloride Liposomal Injection

A. Microbiology Deficiencies:

1.

2.

3.

4.



(b) (4)

5.

6.

(b) (4)

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

(b) (4)

Please clearly identify your amendment to this facsimile as “RESPONSE TO MICROBIOLOGY DEFICIENCIES”. The “RESPONSE TO MICROBIOLOGY DEFICIENCIES” should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

CDR Paul Dexter, M.S.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

JESSE WELLS
02/02/2012

ELIZABETH T MCNEAL
02/02/2012
Checked file and submission link.

PAUL L DEXTER
02/08/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203263

OTHER REVIEWS

MEMORANDUM

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

DATE: November 20, 2012

TO: Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence-I
Office of Generic Drugs

FROM: Young Moon Choi, Ph.D.
Pharmacologist, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D. Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering ANDA 203-263,
Doxorubicin Hydrochloride Liposome Injection,
2 mg/mL, 10 mL, Sponsored by Sun Pharma
Global FZE, U.A.E.

At the request of the Division of Bioequivalence I (DBI), the Division of Bioequivalence and GLP Compliance (DBGC) conducted an audit of the following bioequivalence study:

Study Number: PKD_09_030

Study Title: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of doxorubicin hydrochloride liposome injection, 2 mg/ml (50 mg/m² dose) of Sun Pharma Advanced Research Company Limited, India, and Doxil[®] (Doxorubicin hydrochloride liposome injection), 2 mg/ml (50 mg/m² dose) of Ortho Biotech Products, LP Raritan, NJ 08869-0670, in patients with ovarian cancer, under fed (normal low fat breakfast) conditions

The inspection of the clinical site was conducted by Mr. Scott B. Laufenberg (OIP - India FDA Office) at **NRR Hospital, Bangalore, India (NRR)**. The request for inspection of the clinical site G. Vishwanathan Specialty Hospital, in Tiruchirappalli, India, was canceled by OGD in an e-mail on November 14, 2012. OSI provided an EIR Review memorandum for inspection of the *in vitro* bioequivalence study at Sun Pharma in Halol, India, on August 17, 2012.

Following the inspection (August 27 - September 4, 2012), Form FDA 483 was issued (**Attachment 1**). The firm's response was received on October 1, 2012 (**Attachment 2**).

The Form FDA-483 observation, NRR response to Form FDA-483, and our evaluation follow:

1) Failure to maintain possession and/or control of investigational product test and reference retention samples. Specifically, Test and Reference retention samples maintained per regulatory requirements were shipped to a third party archival site on 18 Aug 2011; per the sponsor's request. The study sponsor made the arrangements with the third party archival facility, entered into a contract with the archival facility and requested the PI send the retention samples to that facility for storage. Due to the fact the sponsor was the only entity that signed this contract, the sponsor may have had access to the samples. There was no assurance provided that only the PI could access and retrieve the retention samples.

In their response to Form FDA-483, NRR stated that the product was transferred from the clinical site to a third party (b)(4), directly and returned to the clinical site for the FDA inspection. Following NRR's request, the third party contact (b)(4) provided a letter confirming that the sponsor has not accessed the reserve samples at (b)(4).

The sponsor shipped test and reference products to this clinical site on three occasions. NRR retained a total of eight test units and three reference units. However, NRR did not retain the reserves from each shipment, as required by the Final Rule, item 3d¹. The dates of shipment from drug accountability and dispensing records show that the three units of reference and test products must have been retained from the first shipment on 10/28/2010. However, we cannot ascertain where the additional five units of test reserve were originated.

¹ Retention of Bioavailability and Bioequivalence Testing Samples. Federal Register 58(80):25918-25928.

NRR selection of reserve samples for retention did not meet the requirements of the Final Rule. However, this reviewer notes that each of the three shipments of test and reference products came from the same respective lots (See Attachment 3).

2) Failure to assure that an Ethics Committee complying with applicable regulatory requirements and following their own written procedures was responsible for the initial and continuing review and approval of a clinical study.

Specifically,

A) Letter dated 03 Nov 2010 from the PI, provides the IEC with protocol amendment/version D05 (dated 30 Oct 2010) and informed consent document Version D05, dated 14 Oct 2010 in English and Kannada languages. There was no correspondence from the IEC that the documents had been reviewed and approved; however the study was conducted per amendment D05 and consent Version D05 was used to consent/re-consent subjects.

B) Letter dated 15 Dec 2010 from the PI, provides the IEC with informed consent document Version D06, dated 10 Dec 2010 in English and Kannada languages. There was no correspondence from the IEC that the documents had been reviewed and approved; however consent version D05 was used to consent/re-consent subjects.

In response to this observation in Form FDA-483, NRR asked the ethics committee for review and approval of the protocol amendment/informed consent version D05 and D06. The chairperson of the IEC evaluated the documents and sent correspondence indicating that the changes (increasing subject recruitment from 24 to 36, and subject injury compensation) are minor with respect to the safety of patients, because the procedures and safety criteria approved in the earlier protocol were not affected.

This reviewer is of the opinion that post-hoc review and approval by the IEC are not ideal; however, the correspondence clarifies the IEC chairperson's position that the protocol changes had no significant impact on subject safety.

3) Failure to obtain informed consent in accordance with 21 CFR Part 50 from each subject prior to conducting study related activities.

Specifically, the original, signed study specific Informed Consent Form for Subjects #44 and #59 was a poor quality scanned copy of original document. This scanned copy of the form is very difficult to read, possibly illegible.

In their response to Form FDA-483, NRR acknowledged that the

copy of the informed consent form (ICF), written in the vernacular language, for subjects #44 and #59 was difficult to read, but that it was legible by a person familiar with the vernacular language.

Subjects #44 and #59 were discontinued from the study because of severe adverse events in period 1. This reviewer is of the opinion that the adverse events in these patients were due to the investigational drug products, and unrelated to the legibility of the ICF.

4) There was no statement in the informed consent for screening document that described the extent, if any, to which confidentiality of records identifying the subjects would be maintained; and that noted the possibility that regulatory agencies might inspect the records.

In response, the firm proposes to modify future ICFs to include confidentiality of records. In the opinion of this reviewer, the corrective action is adequate.

5) Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the clinical investigation.

Specifically,

A) Subject #42 was scheduled for dosing on 03 Nov 2010 but was not dosed, due to tachycardia which was documented in the CRF. However, there was no AE Reporting Form completed for this event as required by the protocol which required daily documentation of AEs. Due to the fact the PI/site did not complete an Adverse Event Reporting form, the event was not identified as an AE and not carried forward to the sponsor.

In response to Form FDA-483, NRR said they reported tachycardia to the sponsor as a pre-dose adverse event in Subject #42, after FDA's inspection.

The ORA investigator confirmed that all other AEs documented in NRR records were described accurately in the study report.

B) Laboratory Reports for at least 4 subjects (including #41, #42, #43, #44) contained signatures/dates for the review of the report which was prior to the date the lab report was generated. For example, Subject #42 Period 11, Check-In Lab Report was generated on 02/12/2010; however the PI signed/dated the review on 01/12/10. There was no explanation in the study records concerning the date

discrepancies.

In response to Form FDA-483, NRR explained that the investigator evaluated clinical lab results through phone prior to the generation of lab report. However, due to the oversight, the NRR acknowledged that they could not record this event. In addition, NRR explained that they recorded the phone conversation for the other five subjects. As corrective action, the NRR shall sign the current date of receipt of lab report and cross reference the phone discussion form or add an explanatory remark.

This reviewer is of the opinion that this observation will have no impact on study outcome.

C) A total of three aliquots were generated from each PK sampling time point. Two aliquots were stored on site, the third was apparently immediately provided to members of the sponsor's Bioanalytical department who were on-site for special handling of the aliquots. There was no documentation of the tracking or transfer of this third aliquot.

In response to Form FDA-483, NRR explained that during the study, the third aliquot was physically handed to an analyst from the sponsor's bioanalytical department who was on-site for special handling of the aliquots, and the analysts recorded the time and date of sample receipt in their own records, although the firm did not document tracking or transfer of the third aliquot at the clinical site in the study records. As a preventive action, the firm amended 'training manual 01' to require recording of such events.

This reviewer is of the opinion that this observation has no impact on study outcome, as the events could be verified from other documents, including the analytical data.

Conclusion:

DBGC recommends that clinical data from study PKD_09_030 are acceptable for review. In addition, please consider the pre-dose adverse event of tachycardia for subject #42.

Final Classification:

VAI - NRR Hospital, Bangalore, India

FEI 3009654552

Note: The initial classification of the field investigator was OAI. However, OSI reviewer, upon review, downgraded to

Page 6 - BIMO Assignment, ANDA 203-263, Doxorubicin
Hydrochloride Liposome Injection, 2 mg/mL, 10 mL

VAI because each of the three shipments of test and reference products came from the same respective lots, and the impact of the observations on the study outcome is not significant, and the data is acceptable for review.

Attachment 1. Form FDA 483
Attachment 2. Response to FDA 483
Attachment 3. Study Drug Receipt Form

cc: OSI/Moreno
OSI/DBGC/Taylor/Haidar/Skelly/Dejernet/Choi/Mada/Chen/CF
OPS/OGD/DBI/Ramson/Conner OGROP/OIP/Laufenberg/Gavini
CDER DSI PM TRACK
Draft: YMC 11/19/2012
Edit: SRM 11/20/2012; MFS 11/21/2012; SHH 11/27 & 11/29/2012
DSI: BE 6315; O:\Bioequiv\EIRCover\203263 amend.sun.dox.doc
FACTS: 1387772

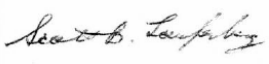
Attachment 1. Form FDA 483

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER Dr. Sam Haidar, Center For Drug Evaluation and Research 10903 New Hampshire Avenue, Bldg 51, Room 5330 Silver Spring MD 20993 Phone: 1-(301)-496-3393 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 27 Aug - 04 Sept 2012	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Dr. Yathish Kumar H.M., M.B.B.S., M.S., DNB, Mch DNB, Principal Investigator		FEI NUMBER 3009654552	
FIRM NAME Dr. Yathish Kumar at N.R.R. Hospital	STREET ADDRESS No. 3 & 3A, Hesarghatta Main Road, Chikkasandra		
CITY, STATE AND ZIP CODE Bangalore 560 090 Karnataka, India	TYPE OF ESTABLISHMENT INSPECTED Clinical Investigator		
THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.			
DURING AN INSPECTION OF YOUR FIRM (I) ☒ (ME) OBSERVED:			
Pertaining to the conduct of clinical study: PKD-09-030 "A randomized, multi-center, open-label, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study of Doxorubicin Hydrochloride Liposome Injection, 2mg/mL (50 mg/m2 dose)..." 1) Failure to maintain possession and/or control of investigational product test and reference retention samples. Specifically, Test and reference retention samples maintained per regulatory requirements were shipped to a third party archival site on 18 Aug 2011; per the sponsor's request. The study sponsor made the arrangements with the third party archival facility, entered into a contract with the archival facility and requested the PI send the retention samples to that facility for storage. Due to the fact the sponsor was the only entity that signed this contract, the sponsor may have had access to the samples. There was no assurance provided that only the PI could access and retrieve the retention samples. 2) Failure to assure that an Ethics Committee complying with applicable regulatory requirements and following their own written procedures was responsible for the initial and continuing review and approval of a clinical study. Specifically, A) Letter dated 03 Nov 2010 from the PI, provides the IEC with protocol amendment/version D05 (dated 30 Oct 2010) and informed consent document Version D05, dated 14 Oct 2010 in English and Kannada languages. There was no correspondence from the IEC that the documents had been reviewed and approved; however the study was conducted per amendment D05 and consent Version D05 was used to consent/re-consent subjects. B) Letter dated 15 Dec 2010 from the PI, provides the IEC with informed consent document Version D06, dated 10 Dec 2010 in English and Kannada languages. There was no correspondence from the IEC that the documents			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Scott B. Laufenberg, Assistant Country Director, FDA Office - India	DATE ISSUED 09/04/2012

FORM FDA 483 (9/08) PREVIOUS EDITION OBSOLETE

INSPECTIONAL OBSERVATIONS

Page 1 of 3

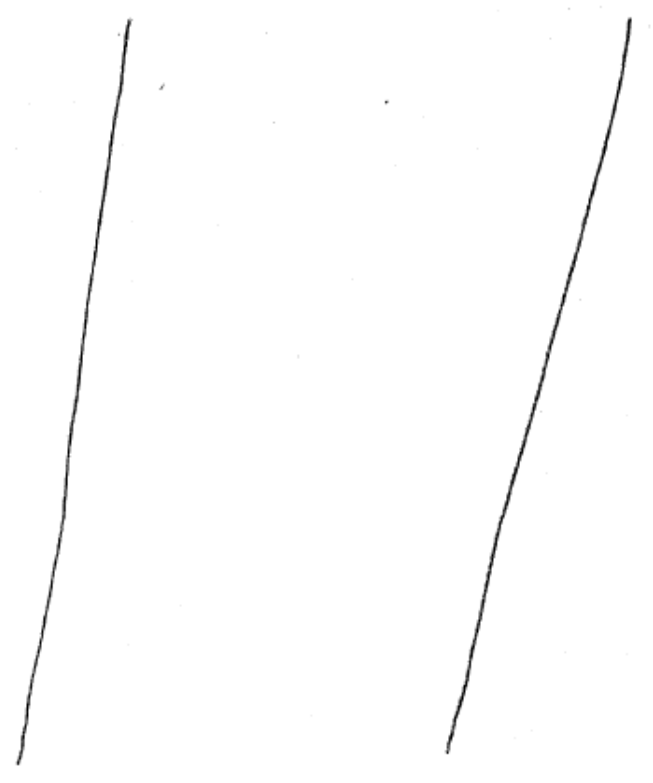
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER Dr. Sam Haidar, Center For Drug Evaluation and Research 10903 New Hampshire Avenue, Bldg 51, Room 5330 Silver Spring MD 20993 Phone: 1-(301)-496-3393 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 27 Aug - 04 Sept 2012	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Dr. Yathish Kumar H.M., M.B.B.S., M.S., DNB, Mch DNB, Principal Investigator		FEI NUMBER 3009654552	
FIRM NAME Dr. Yathish Kumar at N.R.R. Hospital	STREET ADDRESS No. 3 & 3A, Hesarghatta Main Road, Chikkasandra		
CITY, STATE AND ZIP CODE Bangalore 560 090 Karnataka, India	TYPE OF ESTABLISHMENT INSPECTED Clinical Investigator		
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SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Scott B. Laufenberg, Assistant Country Director, FDA Office - India	DATE ISSUED 09/04/2012

FORM FDA 483 (9/08)

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INSPECTIONAL OBSERVATIONS

Page 2 of 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER Dr. Sam Haidar, Center For Drug Evaluation and Research 10903 New Hampshire Avenue, Bldg 51, Room 5330 Silver Spring MD 20993 Phone: 1-(301)-496-3393 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 27 Aug - 04 Sept 2012	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Dr. Yathish Kumar H.M., M.B.B.S., M.S., DNB, Mch DNB, Principal Investigator		FEI NUMBER 3009654552	
FIRM NAME Dr. Yathish Kumar at N.R.R. Hospital	STREET ADDRESS No. 3 & 3A, Hesarghatta Main Road, Chikkasandra		
CITY, STATE AND ZIP CODE Bangalore 560 090 Karnataka, India	TYPE OF ESTABLISHMENT INSPECTED Clinical Investigator		
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SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Scott B. Laufenberg, Assistant Country Director, FDA Office - India	DATE ISSUED 09/04/2012

FORM FDA 483 (9/09)

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INSPECTIONAL OBSERVATIONS

Page 3 of 3

Following this page, 11 Pages Withheld in Full as (b)(4)

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

/s/

YOUNG M CHOI
11/29/2012

SAM H HAIDAR
11/29/2012

WILLIAM H TAYLOR
11/29/2012

MEMORANDUM

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

DATE: August 21, 2012

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

From: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority Pre-Approval Data Validation
Inspection** Bioresearch Monitoring, Human Drugs, CP
7348.001

RE: ANDA 203-263

DRUG: Doxorubicin Hydrochloride Liposome
Injection, 2mg/mL, 10 mL and 25 mL

SPONSOR: Sun Pharma Global FZE
Sharjah, U.A.E.

U.S. AGENT: Sun Pharmaceutical Industries, Inc.
Cranbury, NJ

This addendum memo requests that you arrange inspection of the clinical portion of the following *in vivo* bioequivalence study at a second clinical site in addition to the site included in the memo dated February 28, 2012. The inspection should be completed before **December 30, 2012**.

This application is filed under the 'Drug Shortage Expedited Review Category.' Under this expedited category, FDA expects to complete reviews on an accelerated schedule.

Please contact DBGLPC upon receipt of this assignment to arrange scheduling of the clinical inspection. Following identification of the investigator, background material will be forwarded directly.

Please DO NOT identify the application type or number, the studies to be inspected, the drug name, or the names of the study investigators prior to the start of inspection. The

information will be provided to the site at the inspection opening meetings.

Please also note that this inspection will be conducted under the Bioresearch Monitoring Compliance Program CP 7348.001 and not conducted under CP 7348.811 for Good Clinical Practices (GCP).

At the completion of inspection, please send a scanned copy of the completed sections A & B to Sam Haidar and the DBGLPC Point of Contact (POC) listed at the end of this memo.

Study Protocol # PKD-09-030: "A randomized, multi-center, open label, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study of Doxorubicin Hydrochloride Liposome Injection, 2mg/mL (50 mg/m² dose) of Sun Pharma Advanced Research Company Limited, India and Doxil® (Doxorubicin Hydrochloride Liposome Injection), 2 mg/mL (50 mg/m² dose) of Ortho Biotech Products, LP, Raritan, NJ, in patients with Ovarian cancer under fed (normal low fat breakfast) conditions"

This was a multicenter study conducted at 5 sites in India in female subjects with ovarian cancer. Audit of the following clinical site is requested:

Clinical Site: G. Vishwanathan Specialty Hospital
Department of Oncology
27 Babu Road, Trichy-620008
Tamil Nadu, India.

Investigator

and

Contact Person: Dr. K.N. Srinivasan
Tel +91-4312705945
 (b) (6) cell Phone)

OBJECTIVE: The objectives of this study were to demonstrate comparable safety of the subjects participating in the study and to assess the bioequivalence between Doxorubicin Hydrochloride Liposome injection (Test), and Doxil® (Doxorubicin Hydrochloride Liposome injection)(Reference), in patients with Ovarian Cancer, under fed conditions.

SECTION A

RESERVE SAMPLES: Because this is a bioequivalence study, the study director (i.e., each principal investigator) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies:

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>). Please refer to CDER's Guidance for Industry, Handling and Retention of BA and BE Testing Samples (May 2004), that clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>). Please follow the instructions below:

- Verify if reserve samples were retained as per regulations.**
- Verify reserve samples were retained from all shipments. (Study drugs shipped by the sponsor were received by the clinical site on August 12, 2010 and November 10, 2010 in two shipments.)**
- If the reserve samples were stored at an alternate site, please verify and collect an affidavit to confirm that the alternative site is independent from the sponsor, packager or the manufacturer. In an event reserve samples are not retained or not adequate; please notify the DBGLPC POC immediately.**
- Please get a written assurance from the clinical investigator or the responsible person at the clinical investigator's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit.
- Samples of the test and reference products should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Benjamin (Nick) Westenberger

(Phone: 314-539-3869)
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101

SECTION B

Data Audit Checklist:

- Any evidence of under-reporting of AEs identified?:_____
 - Any evidence of inaccuracy in data capture?:_____
 - Presence of 100% of signed and dated informed consent forms obtained according to regulations:_____
 - Reports for 100% of subjects audited
 - Total number of subjects screened at the site:_____
 - Total number of subjects enrolled at the site:_____
 - Total number of subjects completing the study:_____
 - Confirm that the clinical assessments were conducted in a consistent manner and in accordance with protocol-defined requirements:_____
 - Number of subject records reviewed during the inspection:_____
 - Include a brief statement summarizing your findings (**IRB approvals, protocol deviations if any, adverse events, concomitant medications, inclusion/exclusion criteria, inadequate records, randomization schedule was strictly followed for dosing of subjects, etc.**)
 - Comments if any:
-
-

Additional instructions to ORA Investigator:

In addition to the compliance program elements, additional study specific instructions and questions may be provided by DBGLPC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further follow-up instructions before the inspection regarding any data anomalies or questions noted during review of study report. ORA investigator should contact DBGLPC POC for inspection related questions or clarifications.

Page 5 - BIMO Assignment, ANDA 203-263 Doxorubicin Hydrochloride Liposome Injection, 2mg/mL, 10 mL and 25 mL

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, the violations appear to warrant an OAI classification, please notify the DBGLPC POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written responses as soon as you receive to Sam Haidar and DBGLPC point of contact (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).

DBGLPC Point of Contact: Arindam Dasgupta, Ph.D.
(301) 796-3326
arindam.dasgupta@fda.hhs.gov

CC:
CDER OSI PM TRACK
OSI/DBGC/Taylor/Haidar/Biswas/Dasgupta/Dejernett/CF
ORA/ORO/DFFI/IOB/Turner, Cheryl A/Arline, Yvett D/Montemurro,
Ann M
OPS/OGD/DBI/Conner/Ramson
Draft: AD 8/21/2012
Edit: GB 8/21/2012
OSI File #6315; O:\BE\assigns\bio203263add.doc
FACTS: 1387772
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB

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

/s/

ARINDAM DASGUPTA
08/30/2012

WILLIAM H TAYLOR
08/31/2012

MEMORANDUM

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

DATE: August 17, 2012

TO: Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence-I (DBI)
Office of Generic Drugs

FROM: Xikui Chen, Ph.D.
Pharmacologist, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., RPh
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering ANDA 203-263, Doxorubicin
Hydrochloride Liposome Injection, 2mg/mL, 10 mL,
Sponsored by Sun Pharma Global FZE, Sharjah, U.A.E.

At the request of the Division of Bioequivalence I (DBI), the Division of Bioequivalence and GLP Compliance (DBGC) conducted an audit of the following in vitro bioequivalence study:

Study Number: FDD-02/10-11/001

Study Title: "In Vitro bioequivalence study of Doxorubicin HCl Liposome Injection, 2 mg/mL, 10 mL of Sun Pharma Advanced Research Company Limited and Doxil® (Doxorubicin Hydrochloride Liposome Injection, 20 mg in 10 mL (2mg/mL) of Ortho Biotech Products, L.P."

Analytical Site: Sun Pharmaceutical India Ltd.
Halol, Gujarat, INDIA

The inspection of the in vitro bioequivalence study and manufacturing of doxorubicin liposome injection was conducted at Sun Pharmaceutical India Ltd., Halol, Gujarat, INDIA by ORA inspectors Mr. Scott B. Laufenberg and Dr. Mural B. Gavini, both of OIP-INDIA. Bioequivalence reserve samples were collected from Sun Pharmaceutical India Ltd. and forwarded to the Office of Pharmaceutical Science, Office of Testing and Research, Division of Pharmaceutical Analysis (DPA) in St. Louis. Following the inspection (June 11-13, 2012), Form FDA 483 was issued. At the time of this review, OSI has not received the firm's response to the Form FDA 483 observations (Attachment 1). Inspections are pending at two clinical sites for in vivo bioequivalence study PKD 09 030. OSI expedites this review because of the Drug Shortage urgency. Our evaluation of the Form FDA 483 observations pertinent to the in vitro bioequivalence study follows:

1. The frequency of calibration of (b) (4) Laser Diffraction instrument was inadequate. The instrument was used for (b) (4)

• The (b) (4) - Performance Qualification Procedure stated "***The following nominal size standards will be needed for this test: (b) (4) nm***". However, during the Performance Qualification (conducted on 18 Aug. 2004) for instrument (b) (4), testing was only performed for the (b) (4) nm size. This is the instrument used for analysis on the in vitro BEQ study of Doxorubicin HCl Liposome Injection, 2 mg/ml, 10 ml (FDD-02/10-11/001).

• Additionally, during the calibration/verification conducted on this instrument on 27 Aug 2010; just prior to the aforementioned study, only the (b) (4) nm size standard was used. The study was designed to analyze at (b) (4) nm particle size.

Performance verification or performance check is necessary to demonstrate the accuracy and precision of measurements by the (b) (4) Dynamic Light Scattering (DLS) Particle Size Analyzer (b) (4) because the equipment was not adjusted according to calibrators. Instead, staff relied on the wavelength of incident and scattered light adjusted by the

refractive index of the suspending medium, and the viscosity of the suspending medium for the instrument's calibration.

Individual values for the refractive index and viscosity for the suspending medium of calibrators and test samples are appropriate, especially if they are not identical, because these values are used in the calculations of particle sizes from the scattered light signals. Demonstration of accuracy and precision for measuring a range of known particle sizes of standards would require knowledge of their absolute sizes, typically from microscopic measurements. Because incorrect refractive index and viscosity values may have been used (see below), and they enter the calculation as nonlinear operators, a range of particle size calibrators approximately the same size as study sample particles (b) (4) should have been used to demonstrate accuracy of the size measurement. Calibrators also were not used in calculation of particle sizes for unknown (test) samples.

The performance qualification (PQ) for particle size analyzer (b) (4) in the Halol manufacturing facility was conducted by the instrument vendor on August 18, 2004, using only a nominal standard (b) (4) particle. Nominal standards (b) (4) nm were not used in the PQ, although nominal standards (b) (4) nm were listed on the (b) (4) (b) (4) form. The same instrument in the Halol facility was used for particle size measurements in the in vitro BEQ study and in manufacturing controls of the finished product.

The same model of (b) (4) was installed in the nearby Vadodara R&D facility. However, at that facility, the PQ for installation and annual performance checks were conducted using three nominal (b) (4) standards with diameters (b) (4) (b) (4) nm. Method validation of the particle size analysis was conducted using the (b) (4) instrument in Vadodara R&D facility on October 5 and 6, 2010.

According to standard operating procedure (SOP) QCI-132/01, entitled "Operation and Performance Check of Particle Size Analyzer," effective 25 November 2006, performance check frequency is recommended once per year. (b) (4)

(b) (4)
An annual performance check for the (b) (4) in the Halol facility was performed using only the (b) (4) nm size standard on August 27, 2010, prior to the in vitro BE study. Results of

mean particle size diameters (nm) for standard (b) (4) nm using (b) (4) in the Halol facility are listed as follows:

Run No.	1	2	3	4	5	Mean
(b) (4)						

The results for standard (b) (4) nm met the acceptance criteria of within 20% of the average mean diameter of (b) (4) nm and relative standard deviation (RSD) of the data within 20%, specified in SOP QCI-132/01.

In vitro Study FDD-02/10-11/001 for Doxorubicin Hydrochloride Liposome Injection was conducted on November 19, 2010. Another annual performance check for the (b) (4) in the Halol facility was conducted using three standards: (b) (4) (b) (4) nm on September 20, 2011. Results of mean particle size diameters (nm) for the three standards using the (b) (4) in Halol facility are listed as follows:

Run No.		(b) (4)
1		
2		
3		
4		
5		
Mean		

(b) (6) performed the method validation for particle size analyses using the (b) (4) in Vadodara R&D facility. The validation included particle size analyses within (b) (4) analysts (b) (6), and within and between days (October 5 and 6). (b) (6) was the main analyst in the in vitro study, and (b) (6) performed the role of quality control on the in vitro study, using the same model of (b) (4) in the Halol manufacturing facility. The same reference product Doxil lot# 907642 was used in both the validation and the in vitro study. Results of mean particle size diameters (nm) for Doxil lot# 907642 performed by (b) (6) using (b) (4) are listed as follows:

Vial No.	10/5/2010 in Vadodara	10/6/2010 in Vadodara	11/19/2010 in Halol
1			(b) (4)
2			
3			

(b) (4)

The reference product Doxil lot# 907642 was used as a secondary standard for performance verification of (b) (4) in the Halol facility. Performance results of the standards and the Doxil lot were within acceptance criteria of 20% difference from nominal standard values, and the performance verifications on (b) (4) in the Halol facility are within these criteria.

Additional Observations from EIR review:

We note that Sun Pharmaceutical used the (b) (4) manufacturer's recommended parameters of (b) (4) for particle refractive index, (b) (4) for dispersant refractive index (b) (4) and (b) (4) for dispersant viscosity (b) (4) in the method validation and in the in vitro study. For particle size measurements, samples from each vial of test or reference product were poured into a cuvette and the particle size was determined using the defined parameters. Due to the (b) (4) (b) (4) we suspect that the refractive index should have been (b) (4) and the viscosity should have been (b) (4) for the suspending medium. The parameter of (b) (4) for refractive index of liposome particles was not verified.

The D10, D50, D90, and span values in particle size distributions reported in the in vitro study were calculated from scattered light signals by the (b) (4) DLS software. (b) (4)

(b) (4)

The particle size data for D10, D50, D90, and span in the in vitro BE study need to be evaluated when the refractive index and viscosity of suspending medium and the refractive index of liposome particles can be confirmed.

Preliminary ORA Classification was OAI. After OSI evaluation of the Form FDA 483 observations and the EIR, the final classification for the firm was VAI because performance checks on (b) (4) in the Halol facility were conducted for standard (b) (4) on August 27, 2010, prior to the in vitro BE study; for Doxil lot# 907642 (a secondary standard) on November 19, 2010, during the in vitro BE study; and for three standards: (b) (4) nm on September 20, 2011, after the in vitro BE study, and the performance results met the acceptance criteria.

Conclusion:

Following evaluation of the inspectional observations for the in vitro study FDD-02/10-11/001, the DBGC reviewer recommends:

1. The analytical data for the particle size distributions for Doxorubicin Hydrochloride Liposome Injection are acceptable if the refractive indexes of liposome particles and the suspending media, and viscosity of the suspending media for liposome particles are confirmed. **Sun Pharma has not been requested to confirm these values.**
2. If the instrument settings did not use correct refractive index and viscosity values for the suspending media, and correct refractive index of the liposome particles, the particle size distribution data are not usable.

Final Classification:

VAI - Sun Pharmaceutical India Ltd., Halol-Baroda Highway
Halol-389350, Gujarat, India.
FEI 3002809586

cc:

OSI/Moreno

OSI/DBGC/Taylor/Haidar/Skelly/Dejernett/Chen/CF

OPS/OGD/DBI/Ramson/Conner

OGROP/OIP/Laufenberg/Gavini

CDER DSI PM TRACK

Draft: XC 7/26/2012,

Edit: MFS 7/27/2012; SHH 8/14/2012, WHT 8/17/2012

DSI: BE 6315; O:\Bioequiv\EIRCover\203263.sun.dox.doc

FACTS: 1387772

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Dr. Sam Haidar, Center For Drug Evaluation and Research 10903 New Hampshire Avenue, Bldg 51, Room 5330 Silver Spring MD 20993 Phone: 1-(301)-496-3393 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION June 11-13, 2012
	FEI NUMBER 3003789481

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Sampad Bhattacharya, Vice President of Operations

FIRM NAME Sun Pharmaceuticals Industries Ltd.	STREET ADDRESS Halol - Baroda Highway
CITY, STATE AND ZIP CODE Halol 389 350 (Gujarat), India	TYPE OF ESTABLISHMENT INSPECTED In-vitro BEQ Testing CRO and Drug Manufacturing (GMP)

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

During the conduct of Study No. FDD-02/10-11/001 In vitro bioequivalence study of Doxorubicin HCl Liposome Injection, 2 mg/ml, 10 ml and overall assessment of product stability and manufacturing practices:

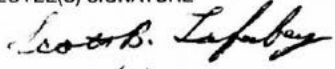
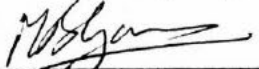
1. The frequency of calibration of (b)(4) Laser Diffraction instrument was inadequate. The instrument was used for (b)(4)

- The (b)(4) - Performance Qualification Procedure stated "****The following nominal size standards will be needed for this test: (b)(4) nm****". However, during the Performance Qualification (conducted on 18 Aug. 2004) for instrument (b)(4), testing was only performed for the (b)(4) nm size. This is the instrument used for analysis on the in-vitro BEQ study of Doxorubicin HCl Liposome Injection, 2 mg/ml, 10 ml (FDD-02/10-11/001).

- Additionally, during the calibration/verification conducted on this instrument on 27 Aug 2010; just prior to the aforementioned study, only the (b)(4) nm size standard was used. The study was designed to analyze at (b)(4) nm particle size.

2. Firm's review of the (b)(4) temperature and relative humidity data printouts was inadequate. Additionally, the adequacy of the procedure QCI-087/04 was not justified as it did not require:

- Data review to include identification, investigation and mitigation of trends such as systemic drifts and abnormal change in the T and RH data variance.
- Identification, documentation and correlation of planned chamber interruptions with the observed data excursions.
- Establishment of procedure to be followed in the event of contingencies such as chamber or components failures.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE  	EMPLOYEE(S) NAME AND TITLE (Print or Type) Scott B. Laufenberg - Consumer Safety Officer Murali B. Gavini - Consumer Safety Officer	DATE ISSUED 13 June 2012

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER* Dr. Sam Haidar, Center For Drug Evaluation and Research 10903 New Hampshire Avenue, Bldg 51, Room 5330 Silver Spring MD 20993 Phone: 1-(301)-496-3393 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION June 11-13, 2012
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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Sampad Bhattacharya, Vice President of Operations

FIRM NAME Sun Pharmaceuticals Industries Ltd.	STREET ADDRESS Halol - Baroda Highway
CITY, STATE AND ZIP CODE Halol 389 350 (Gujarat), India	TYPE OF ESTABLISHMENT INSPECTED In-vitro BEQ Testing CRO and Drug Manufacturing (GMP)

- Impact assessment (section 5.12.4) for excursion of the T and RH limits for more than 72 hours.
- Consideration of limits on the magnitude and frequency of excursions that could occur in a 24-hour period based on the understanding of the normal functioning of the chamber.

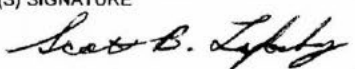
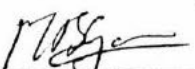
MANUFACTURING AND MATERIAL CONTROL SYSTEMS

3. The adequacy of a single Liposome particle size measurement performed at all the (b) (4) in-process tests at various stages of the process and finished product particle size measurement testing were not justified. The method validation study revealed that the precision of the finished product particle size measurement was (b) (4)%. Additionally, the in-process test reports were not verified by a second person or supervisor and signed.

4. Particle size data after (b) (4) for (b) (4) commercial batches manufactured during 2011 showed several excursions with values as low as (b) (4) nm after (b) (4). The relative standard deviation of the data was (b) (4). No reason was provided for not compiling and charting the data and for not recognizing and investigating the excursions. Based on the variability in the commercial batch data the adequacy of control of (b) (4) process was not justified.

5. The attribute data and the charts for Doxorubicin HCl Liposome Injection revealed that the total impurities varied from about (b) (4)%. The data were not compiled charted and variability recognized. Review of the development data during the inspection revealed that temperature of (b) (4) (b) (4) was not justified. For example, any other and total impurities have reduced to minimum at (b) (4) while (b) (4) showed a minimum at (b) (4). The temperature range of (b) (4) was not investigated to recognize the optimum process temperature.

6. Critical process information was not adequately recorded in the batch records. For example, executed batch record for Doxorubicin HCl revealed that (b) (4) (b) (4). Hence the actual temperature during most of the time of (b) (4) of this critical process step was unknown.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE  	EMPLOYEE(S) NAME AND TITLE (Print or Type) Scott B. Laufenberg - Consumer Safety Officer Murali B. Gavini - Consumer Safety Officer	DATE ISSUED 13 June 2012

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Dr. Sam Haiḍar, Center For Drug Evaluation and Research 10903 New Hampshire Avenue, Bldg 51, Room 5330 Silver Spring MD 20993 Phone: 1-(301)-496-3393 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION June 11-13, 2012
	FEI NUMBER 3003789481

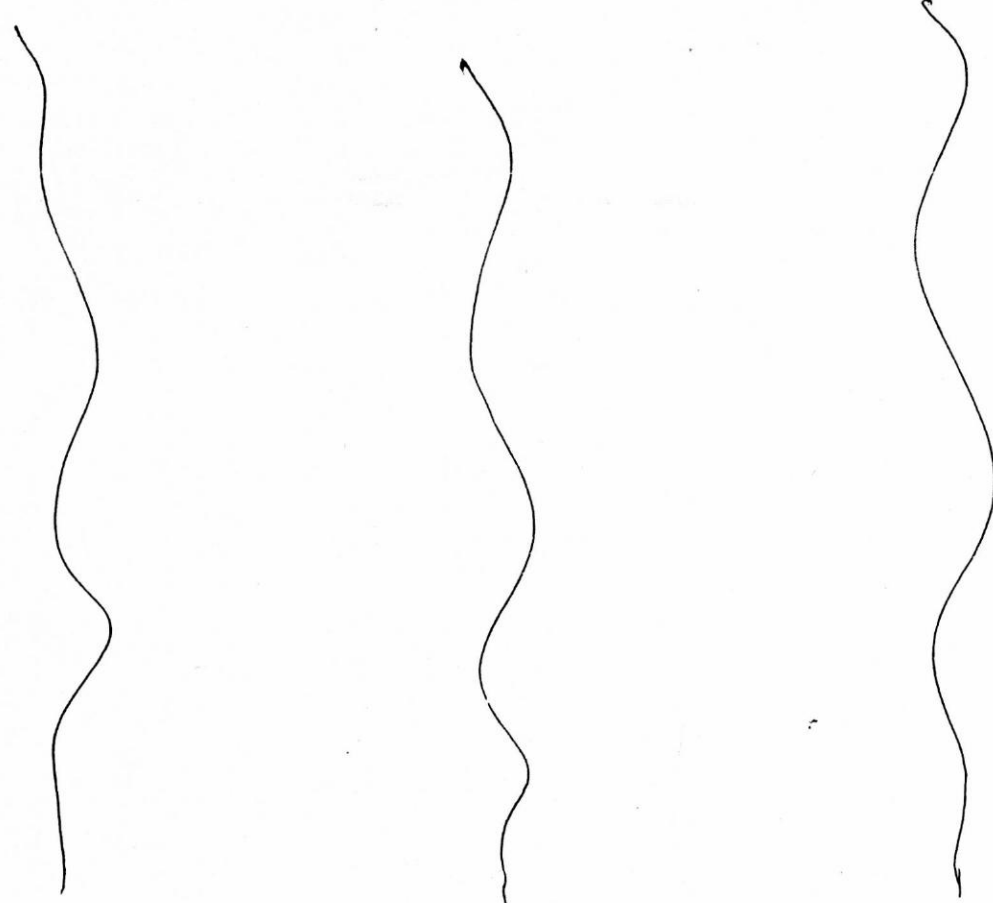
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Sampad Bhattacharya, Vice President of Operations

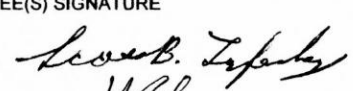
FIRM NAME Sun Pharmaceuticals Industries Ltd.	STREET ADDRESS Halol - Baroda Highway

CITY, STATE AND ZIP CODE Halol 389 350 (Gujarat), India	TYPE OF ESTABLISHMENT INSPECTED In-vitro BEQ Testing CRO and Drug Manufacturing (GMP)

QUALITY SYSTEM

7. Annual product review for Doxorubicin HCl Liposome Injection product was not prepared for 2011 although it has been manufactured at this site for domestic markets for the last ten years. The site has been a USFDA inspected and approved site since 2004.



SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE  	EMPLOYEE(S) NAME AND TITLE (Print or Type) Scott B. Laufenberg - Consumer Safety Officer Murali B. Gavini - Consumer Safety Officer	DATE ISSUED 13 June 2012

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

/s/

XIKUI CHEN
08/17/2012

SAM H HAIDAR
08/17/2012

WILLIAM H TAYLOR
08/17/2012

MEMORANDUM

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

DATE: February 28, 2012

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

From: Sam H. Haidar, R.Ph., Ph.D. _____
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority Pre-Approval Data Validation
Inspection** Bioresearch Monitoring, Human Drugs, CP
7348.001

RE: ANDA 203-263

DRUG: Doxorubicin Hydrochloride Liposome
Injection, 2mg/mL, 10 mL and 25 mL

SPONSOR: Sun Pharma Global FZE
Sharjah, U.A.E.

U.S. AGENT: Sun Pharmaceutical Industries, Inc.
Cranbury, NJ

This memo requests that you arrange inspection of the clinical portion of the following *in vivo* bioequivalence study and the analytical portion of the following *in vitro* bioequivalence study. **This application is filed under the 'Drug Shortage Expedited Review Category.'** Under this expedited category, FDA expects to complete reviews on an accelerated schedule. Please contact DBGK upon receipt of this assignment to arrange scheduling of the analytical inspection. The sites and sponsor should not be informed in advance of the application, drug name, the studies to be inspected, study investigators, or the focus of the inspections. The information will be provided to the sites at the inspection opening meetings. The inspections should be completed before July 30, 2012.

Study Number: PKD-09-030

Study Title: "A randomized, multi-center, open-label, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study

of Doxorubicin Hydrochloride Liposome Injection, 2mg/mL (50 mg/m² dose) of Sun Pharma Advanced Research Company Limited, India and Doxil® (Doxorubicin Hydrochloride Liposome Injection), 2 mg/mL (50 mg/m² dose) of Ortho Biotech Products, LP, Raritan, NJ, in patients with Ovarian cancer under fed (normal low fat breakfast) conditions"

Clinical Site:

NRR Hospital
No. 3&3A, Hesarghatta Main Road
Chikkasandra,
Near Chikkabanavara Railway Station,
Bangalore - 560090, Karnataka, INDIA
TEL: +91-80-28374115
FAX: Not available

Investigator

and

Contact Person:

Yathish Kumar H.M, M.B.B.S., M.S.
Email:dryathish@hotmail.com
TEL: +91-80-28374115

(b) (6) (Cell phone)

Please have the records of all study subjects audited. The subject records in the ANDA submission should be compared to the original documents at the site. **The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined.** The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings.

Please check the batch numbers of the test and reference products used in this study with the descriptions in documents submitted to FDA. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63. The

site conducting the above bioequivalence study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please refer to CDER's guidance document "Handling & Retention of BA and BE Testing Samples" that clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>). Samples of the test and reference products should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101

Also, obtain a written assurance from the clinical investigator (CI) or the responsible person at each CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample. Examine the surveillance drug samples collected and ship them to DPA under current program directives. Please see the IOM and/or contact your district or DFFI for assistance with the Sample Collection Report.

Analytical Site Inspection for In Vitro Bioequivalence Study:

Study Number: FDD-02/10-11/001
Study Title: "In Vitro bioequivalence study of Doxorubicin HCl Liposome Injection, 2 mg/mL, 10 mL of Sun Pharma Advanced Research Company Limited and Doxil® (Doxorubicin Hydrochloride Liposome Injection, 20 mg in 10 mL (2mg/mL) of Ortho Biotech Products, L.P."

Analytical site: Sun Pharmaceutical India Ltd.
QC Department
Halol-Baroda Highway,
Halol-389350, Gujarat, INDIA

Contact Person: Subhas Bhowmick
TEL: +91-265-2350789; +91-265-6615500
FAX: +91-265-2354897

Methodology: Dynamic Light Scattering using (b)(4) analyzer

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The analytical data provided in the ANDA submission should be compared with the original documents at the site. The analytical method and the actual assay should be examined. **The SOP(s) for the method and other relevant procedures must also be scrutinized.** In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Please check the batch numbers of the test and reference products used in this *in vitro* bioequivalence study with the descriptions in documents submitted to FDA. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63. The site conducting the above bioequivalence study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please refer to CDER's guidance document "Handling & Retention of BA and BE Testing Samples" that clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>). Samples of the test and reference products should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101

Also, obtain a written assurance from the responsible person at the analytical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the responsible person's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit. Include the written statement in

Page 5 - BIMO Assignment, ANDA 203-263 Doxorubicin Hydrochloride Liposome Injection, 2mg/mL, 10 mL and 25 mL

Sample Collection Report (CR) as a DOC sample. Examine the surveillance drug samples collected and ship them to DPA under current program directives. Please see the IOM and/or contact your district or DFFI for assistance with the Sample Collection Report.

Following the identification of the investigator, background materials will be forwarded directly.

Headquarters Contact Person: Arindam Dasgupta, Ph.D.
(301) 796-3326
arindam.dasgupta@fda.hhs.gov

CC:

CDER OSI PM TRACK

OSI/DBGC/Taylor/Haidar/Skelly/Patel/Dasgupta/Dejernett/CF

HFC-130/ORA HQ DFFI IOB BIMO

OPS/OGD/DB I/Conner/Ramson

Draft: JBP 2/27/2012

Edit: MFS 2/27/2012

OSI File #6315; O:\BE\assigns\bio203289.doc

FACTS: 1387772

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

/s/

JYOTI B PATEL
02/28/2012

SAM H HAIDAR
02/28/2012

**Medical Safety Consultation
Doxorubicin Hydrochloride Liposome Injection,
2 mg/mL, 10 mL and 25 mL**

Re: ANDA 203263 Sun Pharma Global FZE:
Regulatory Support Branch question on safety of
formulation sucrose content

RLD: Doxil® (doxorubicin HCl liposome injection) for
intravenous infusion 2 mg/mL, 10 mL and 25 mL;
NDA 050718, approved 11/17/1995, Ortho Biotech

To: Suman Dandamudi, Reviewer
Division of Bioequivalence 1, Team 8
Office of Generic Drugs

Hoainhon Nguyen, Acting Deputy Director
Division of Bioequivalence 1,
Office of Generic Drugs

Dale Conner, Director
Division of Bioequivalence 1,
Office of Generic Drugs

Reviewer: John R Peters, M.D.
Acting Director, Division of Clinical Review (DCR),
Office of Generic Drugs

Drug Class: Anthracycline Topoisomerase Inhibitor

Chemical Name: (8S,10S)-10-[(3-amino-2,3,6-trideoxy α -L-lyxo-
hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-
trihydroxy-1-methoxy-5,12-naphthacenedione
hydrochloride)

Date Received: December 20, 2011
Review Completion Date: December 21, 2011

Reason for Consultation:

Doxorubicin Hydrochloride Liposomal Injection is a medically necessary drug that is in serious short supply and the reference listed drug (RLD) Doxil® (NDA 050718) is not currently in production due to manufacturing issues. The available supply of Doxil is currently very limited. As noted in the Background Summary (below) the Sun product is under consideration by the Drug Shortage Program (DSP) for importation and review of this ANDA is being expedited. In the course of their review the Division of

Bioequivalence 1 (DBE1) noted that “A preliminary bioequivalence review has not identified any obvious bioequivalence-related issues. However, based on the clinical report of the study, some serious adverse reactions including one death were reported. To be sure that these serious adverse reactions are not directly related to the test formulation and that they are not considered as a major safety concern that could affect the importation decision, we request your expedited clinical evaluation of these AEs.” This review will evaluate the question of safety relative to the identified serious adverse reactions and death encountered in the study.

Recommendations:

The Division of Clinical Review (DCR) does not find a safety difference in the reported adverse events from the study submitted to this ANDA (203263). The single reported death in the study appears to be related to the progressive ovarian cancer and not to the drug product

Background Summary:

Sun Pharmaceuticals, Ltd. submitted ANDA 203263 for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL on 6/16/2011. This is the **first generic** application for Doxorubicin Hydrochloride Liposome Injection. In the filing review of 10/6/2011 the Division of Bioequivalence (DBE) determined that “with respect to bioequivalence demonstration, the application is acceptable for filing. However, the ANDA should also be reviewed by the Division of Chemistry for the completeness and acceptability with respect to demonstration of pharmaceutical equivalence of the test product.”

There is no Chemistry Filing Review currently listed in DARRTS. In an email of 10/28/2011 the Chemistry Reviewer (Xiaobin Zhao) noted:

“1. The function of Sucrose is to maintain isotonicity. It is not part of the liposome particle composition. In other words, (b) (4), but not part of the composition in constructing the liposome structure itself.

2. According to the RLD label, "DOXIL doses up to 90 mg must be diluted in 250 mL of 5% Dextrose injection". The 90 mg dose is equivalent to 45 mL at a concentration of 2 mg/mL. Thus, the difference between the (b) (4) (b) (4) sucrose will be further minimized after this 45mL/250 mL dilution: the RLD will have (b) (4) vs. ANDA will have (b) (4). The difference is thus less than (b) (4)%, which is not of significant safety concern for iv. Injection.

Based on the above considerations, I think the difference of sucrose concentration itself is not a REAL concern to refuse the ANDA for filing. However, during the review process, we do need to monitor if the sucrose

difference will (b) (4)
(b) (4) cc

On 10/28/2011 the Division of Clinical Review (DCR) was consulted by the Regulatory Support Branch regarding “whether or not the concentration in sucrose (b) (4) in RLD vs. (b) (4) in applicant) will have an effect on any safety aspect.”

On 11/23/2011 the DCR determined that prior to intravenous administration the patient’s dose must be prepared by diluting the appropriate dosage with 5% Dextrose Injection, USP (D5W). In the average adult male 1.5-2.5 vials would be diluted with 375 ml or 625 ml of D5W. It is very unlikely that the (b) (4) of sucrose in the Sun formulation will have any impact on the safety of the drug following standard dilution in dose preparation.

On 12/9/2011 an internal meeting was held to discuss the acceptability of Sun’s application for filing based on the findings of the Chemistry Reviewer and on the regulatory aspects of the application. On 12/12/2011 ANDA 203263 was accepted for filing and granted an expedited review with the following statement:

“ANDA is being accepted since it isn’t entirely clear what the quantitative amount of sucrose is in the RLD. The approved FDA label for this product does not include a concentration level for Sucrose. This is odd since Sucrose is a tonicity agent with the amount present required to be in the RLD label. Labels for this drug which are marketed outside of the United States indicated that approximately 94 mg/mL of Sucrose is present (b) (4) (b) (4) However, Sun submitted information to the ANDA which indicates that there is significant variability in the amount of Sucrose present in Doxil. After two internal OGD meetings held on 12/2 (K. Webber, Lawrence Yu, Dale Connor, Hoai Caramenico, Harvey Greenberg, Tim Jetton and myself) and 12/9/2011 (Lawrence Yu, Dale Connor, Hoai Caramenico, Radhika Rajagopalan, Xiaobin Zhao, Tim Jetton and myself) it was decided that this ANDA could be filed. Sun has provided sufficient evidence from a filing perspective to indicate that their product meets the requirements for filing at 21 CFR 314.94(a)(9)(iii). Furthermore, this ANDA will automatically be granted expedited review due to a pending shortage of this drug product. –Martin H. Shimer 12/12/2011.”

An additional internal meeting was held on 12/19/2011 to discuss the importation of Sun’s Doxorubicin Liposomal Injection product due to the severe drug shortage. Minutes of that meeting are not available at this time, but an email summarizing the meeting noted the following:

- Compliance had no concerns with the Holol manufacturing site (noting the April inspection with no issues)

- ONDQA will review the submitted COA, release specs, and test procedures and will work with OGD to discuss any major quality or BE concerns with the submitted ANDA
- Katherine Delorenzo and the Division are reviewing the labeling and the DHPL
- Wade Ackerman is vetting the Orphan Drug Exclusivity issue with OCC
- I am following up with the company to discuss the distribution plan and request a side by side comparison label of the imported product (with the Multiple Myeloma indication included) with Doxil

A follow up meeting is planned for on or about 1/4/2012 regarding this issue and consequently this consultation is being expedited in order to assist in this process with an evaluation of the serious adverse reactions and one death encountered in the study submitted to this application (Study DOX/003/08).

LABELING

Current product labeling was approved on 6/10/2008. There is a Black Box warning:

- WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION**
- 1. The use of DOXIL (doxorubicin HCl liposome injection) may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at a starting dose of 50 mg/m² every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m² or between 500-550 mg/m², the risk of cardiac toxicity for patients treated with DOXIL was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy [see Warnings and Precautions (5.1)].**
 - 2. Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoidlike infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. DOXIL should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions [see Warnings and Precautions (5.2)].**
 - 3. Severe myelosuppression may occur [see Warnings and Precautions (5.3)].**
 - 4. Dosage should be reduced in patients with impaired hepatic function [see Dosage and**

Administration (2.6) and Use in Specific Populations (8.6)].

5. Accidental substitution of DOXIL for doxorubicin HCl has resulted in severe side effects. DOXIL should not be substituted for doxorubicin HCl on a mg per mg basis [see Dosage and Administration (2.1)].

Indications and Usage

- Ovarian Cancer: for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.
- AIDS-Related Kaposi's Sarcoma: treatment of AIDS-related Kaposi's sarcoma in patients after failure of prior systemic chemotherapy or intolerance to such therapy.
- Multiple Myeloma: in combination with bortezomib is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

Off-label Indications:

Doxil is used off-label in the treatment of refractory breast cancer.

Dosage and Administration

Doxorubicin is cardiotoxic. The total lifetime dose of this drug must be carefully monitored.

Maximum dose: 550 mg/m² (maximum lifetime cumulative dose); 400 mg/m² (maximum lifetime cumulative dose) for adults having received mediastinal radiation or other cardiotoxic drugs.⁶

Due to the significant adverse reactions, such as hand-foot syndrome, hematologic toxicity, or stomatitis, doses may be delayed or reduced. Pretreatment with or concomitant use of antiemetics should be considered.

- Ovarian cancer: Usual dosage: 50 mg/m² (doxorubicin hydrochloride equivalent) IV at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related adverse reactions are observed, the rate of infusion can be increased to complete administration of the drug over 1 hour. Administer once every 4 weeks for a minimum of 4 courses. The median time to response in clinical trials was 4 months. Administer for as long as the patient does not progress, shows no evidence of cardiotoxicity, and continues to tolerate treatment.
- AIDS-related Kaposi sarcoma: Usual dosage: 20 mg/m² (doxorubicin hydrochloride equivalent) intravenously (IV) at an initial rate of 1 mg/min to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the

- administration of the drug over 1 hour. Repeat once every 3 weeks for as long as the patient responds satisfactorily and tolerates treatment.
- Multiple myeloma: Usual dosage: 30 mg/m² IV on day 4 following bortezomib (which is administered at 1.3 mg/m² bolus on days 1, 4, 8, and 11) every 3 weeks. With the first liposomal doxorubicin dose, an initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over 1 hour. Patients may be treated for up to 8 cycles, until disease progression or the occurrence of unacceptable toxicity.
 - Refractory metastatic breast cancer (off-label): 30 to 50 mg/m² IV over 1 hour every 2 to 4 weeks.

Dosage Adjustment Recommendations:

General Dosage modification:

Liposomal doxorubicin exhibits nonlinear pharmacokinetics at 50 mg/m²; therefore, dose adjustments may result in a nonproportional greater change in plasma concentration and exposure to the drug.

Patients should be carefully monitored for toxicity. Adverse reactions, such as hand-foot syndrome, hematologic toxicities, and stomatitis, may be managed by dose delays and adjustments. Following the first appearance of a grade 2 or higher adverse reaction, the dosing should be adjusted or delayed, as described in the following tables. Once the dose has been reduced, it should not be increased at a later time.¹

Dosage adjustment in Multiple Myeloma:

For patients who experience hand-foot syndrome or stomatitis, the liposomal doxorubicin dose should be modified. (See [Dosage Modification](#).) For additional bortezomib dosing and dosage adjustments, see the [Bortezomib](#) monograph.

Dosage Adjustments for Liposomal Doxorubicin and Bortezomib Combination Therapy ¹		
Patient status	Liposomal doxorubicin	Bortezomib
Fever ≥ 38°C (100.4°F) and ANC < 1,000/mm ³	Do not dose this cycle if before day 4; if after day 4, reduce next dose by 25%.	Reduce the next dose by 25%.
On any day of drug administration after day 1 of each cycle: platelet count < 25,000/mm ³ , hemoglobin < 8 g/dL, ANC < 500/mm ³	Do not dose this cycle if before day 4; if after day 4, reduce next dose by 25% in the following cycles if bortezomib is reduced for hematologic toxicity.	Do not dose; if 2 or more doses are not given in a cycle, reduce dose by 25% in following cycles.

Grade 3 or 4 nonhematologic drug-related toxicity	Do not dose until recovered to grade < 2; reduce dose by 25% for all subsequent doses.	Do not dose until recovered to grade < 2; reduce dose by 25% for all subsequent doses.
Neuropathic pain or peripheral neuropathy	No dosage adjustments.	See <u>Bortezomib</u> monograph for dosage adjustments in patients with neuropathic pain.

Dosage Adjustment According to Bilirubin Concentration:

Liposomal Doxorubicin Dosage Adjustment According to Bilirubin Concentration	
Plasma bilirubin concentration (mg/dL)	Dosage reduction (%)
1.2 to 3	50
> 3	75

Dose Modification for Hematological Toxicity:

Liposomal Doxorubicin Dose Modification for Hematological Toxicity			
Grade	ANC	Platelets	Modification
1	1,500 to 1,900	75,000 to 150,000	Resume treatment with no dose reduction.
2	1,000 to < 1,500	50,000 to < 75,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction.
3	500 to 999	25,000 to < 50,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction.
4	< 500	< 25,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose at 25% dose reduction or continue full dose with cytokine support.

Dose Modification for Hand-Foot Syndrome:

Liposomal Doxorubicin Dose Modification for Hand-Foot Syndrome		
Toxicity grade	Symptoms	Dose adjustment

1	Mild erythema, swelling, or desquamation not interfering with daily activities	Redose unless patient has experienced previous grade 3 or 4 HFS. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dosing interval.
2	Erythema, desquamation, or swelling interfering with, but not precluding, normal physical activities; small blisters or ulcerations less than 2 cm in diameter	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued. If resolved to grade 0 to 1 within 2 weeks, and if there was no prior grade 3 to 4 HFS, continue treatment at previous dose and return to original dosing interval. If patient experienced previous grade 3 or 4 toxicity, continue treatment with a 25% dose reduction and return to original dosing interval.
3	Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued.
4	Diffuse or local process causing infectious complications, or a bedridden state or hospitalization	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued.

Dose Modification for Stomatitis

Liposomal Doxorubicin Dose Modification for Stomatitis

Toxicity grade	Symptoms	Dose adjustment
1	Painless ulcers, erythema, or mild soreness	Redose unless patient has experienced previous grade 3 or 4 toxicity. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dosing interval.
2	Painful erythema, edema, or ulcers, but can eat	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued. If resolved to grade 0 to 1 within 2 weeks and there was no prior grade 3 or 4 stomatitis, continue treatment at previous dose and return to original dosing interval. If patient experienced previous grade 3 or 4 toxicity, continue treatment with a 25% dose reduction and return to original dosing interval.
3	Painful erythema, edema, or ulcers, and cannot eat	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued.
4	Requires parenteral or enteral support	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. Decrease dose by 25% and return to liposomal doxorubicin original dosing interval. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued.

Reviewer's comment: As can be seen this is a complex drug to administer. It is generally prescribed by a qualified Oncologist and administered in a hospital setting. The purpose of the liposomal encapsulation is to prolong the circulating time of drug. Since the sucrose is not a part of the encapsulated drug, but is only used to maintain isotonicity any impact that it might have on the pharmacokinetic properties of the product should be demonstrable in BE testing.

Contraindications:

- Hypersensitivity to a conventional formulation of doxorubicin or the components of liposomal doxorubicin
- Breast-feeding mothers

Warnings and Precautions:

- Cardiac toxicity
- Infusion reactions

- Myelosuppression
- Hand-Foot Syndrome
- Radiation recall therapy
- Extravasation
- Elderly: Consider 300 mg/m² as a maximum lifetime cumulative dose in patients older than 70 years of age.
- Carcinogenesis: Secondary acute myelogenous leukemia has been reported
- Toxicity potentiation: Liposomal doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with the conventional formulation of doxorubicin. Radiation-induced toxicity to the liver, mucosae, myocardium, and skin has been reported to be increased by the administration of doxorubicin.

Adverse Reactions:

The most common adverse reactions reported with liposomal doxorubicin are anemia, anorexia, asthenia, constipation, diarrhea, fatigue, fever, HFS, nausea, rash and neutropenia, stomatitis, thrombocytopenia, and vomiting. The most common serious adverse reactions observed include Mucous Membrane Disorder, Back Pain, Infection, Headache, Dyspepsia, Dizziness, Pharyngitis, Dyspnea, Cough, and Alopecia

Pregnancy Category D: Liposomal doxorubicin can cause fetal harm when administered to a pregnant woman.

Mechanism of Action:

According to the product label for Doxil® (doxorubicin HCl liposome injection) for intravenous infusion:

“The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

DOXIL is doxorubicin HCl encapsulated in long-circulating STEALTH liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH liposomes of DOXIL are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time. “

Pharmacokinetics:

According to Drug Facts and Comparisons, (Online Edition, 2011):

“Liposomal doxorubicin displayed linear pharmacokinetics over the range of 10 to 20 mg/m². Disposition occurred in 2 phases after liposomal doxorubicin administration, with a relatively short first phase (approximately 5 hours) and a prolonged second phase (approximately 55 hours) that accounted for the majority of the AUC.

The pharmacokinetics of liposomal doxorubicin at a 50 mg/m² dose is reported to be nonlinear. At this dose, the elimination half-life of liposomal doxorubicin is expected to be longer and the clearance lower compared with a 20 mg/m² dose. The exposure (AUC) is thus expected to be more than proportional at a 50 mg/m² dose compared with lower doses...

In contrast to the pharmacokinetics of doxorubicin, which display a large volume of distribution ranging from 700 to 1,100 L/m², the small steady-state volume of distribution of liposomal doxorubicin shows that liposomal doxorubicin is confined mostly to the vascular fluid volume. The plasma protein binding of liposomal doxorubicin has not been determined; the plasma protein binding of doxorubicin is approximately 70%...

The plasma clearance of liposomal doxorubicin was slow, with a mean clearance value of 0.041 L/h/m² at a dose of 20 mg/m². This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24 to 35 L/h/m²...

Because of its slower clearance, the AUC of liposomal doxorubicin, primarily representing the circulation of liposome-encapsulated doxorubicin, is approximately 2 to 3 orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin...”

Product Formulation:

Ingredients	Sun Doxorubicin	Doxil RLD
	mg/ ml	mg/ ml
Doxorubicin	2	2
MPEG-Distearoyl Phosphatidylethanolamine	3.19	3.19
Hydrogenated Soya Phosphatidyl Choline	9.58	9.58
Histidine		(b) (4)
Sucrose		
Ammonium Sulfate	2	2
Cholesterol	3.19	3.19

Reviewer’s comment: As can be seen in this, the content of sucrose in the Sun formulation exceeds the allowable 5% by (b) (4). Therefore this formulation is not qualitatively and quantitatively the same as the RLD. Acceptability of this formulation is not consistent with 21 CFR 314.94(a)(9)(iii). The decision to grant an exception is deferred to Regulatory Affairs and DBE.

Study DOX/003/08

(Study Number PKD_09_030, Protocol Number DOX_2I_1476_09):

Title: “A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Doxorubicin Hydrochloride Liposome injection, 2 mg/ml (50 mg/m² dose) of Sun Pharma Advanced Research Company Limited, India and Doxil® (Doxorubicin Hydrochloride Liposome injection), 2 mg/ml (50 mg/m² dose) of Ortho Biotech Products, LP Raritan, NJ 08869-0670, in patients with Ovarian Cancer, under fed (normal low fat breakfast) conditions.”

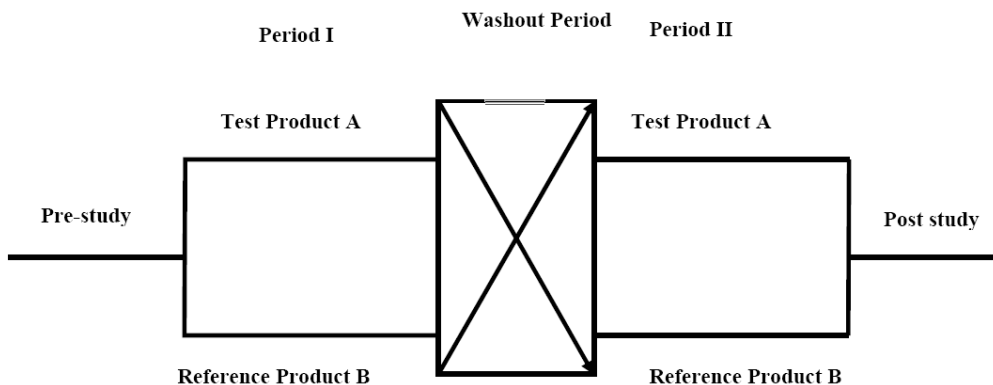
Study Objective: The objective of this study was to monitor the safety of the subjects participating in the study and to assess the bioequivalence of Doxorubicin Hydrochloride Liposome injection, 2 mg/ml (50 mg/m² dose) of Sun Pharma Advanced Research Company Limited, India and Doxil (Doxorubicin Hydrochloride Liposome injection), 2 mg/ml (50 mg/m² dose) of Ortho Biotech Products, LP Raritan, NJ 08869-0670, in patients with Ovarian Cancer, under fed (normal low fat breakfast) conditions.

Study Design: Randomized, multi centre, open label, two treatment, two period, two sequence, single dose, crossover study, with at least 28 days washout between doses, conducted under fed (normal low fat breakfast) conditions. In each of the study periods subjects were administered intravenous infusion (administered through infusion pump) of either Test or Reference product of Doxorubicin Hydrochloride, Liposome injection 2 mg/ml (50 mg/m² dose) by Intravenous Infusion after dilution over 60-minute period, 30 minutes after administration of normal low fat breakfast, according to the randomization schedule. They were subsequently fasted for a period of at least 4 hours.

The study was conducted at 5 different clinical sites in India. This is an open label study and so there was no blinding.

Reviewer’s comment: No IND for this study could be found. Since the study was conducted entirely in India prior submission of an IND was not required.

Study Schematic:



Inclusion Criteria:

1. Availability of volunteer for the entire study period and willingness to adhere to protocol requirements as evidenced by written informed consent.
2. Patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.
3. Age between 18 and 75 years.
4. No evidence of underlying disease (except ovarian cancer) during screening medical history and when physical examination was performed within 21 days prior to commencement of the study.
5. Performance ≤ 2 on the ECOG performance scale
6. Subjects whose organ and Immune system function are adequate as indicated by the following laboratory values:
 - a. Hematology
 - i. ANC $\geq 1.5 \times 10^9 /L$
 - ii. Hb ≥ 9.0 g/dL
 - iii. Platelets $\geq 100 \times 10^9 /L$
 - b. Renal
 - i. Sr. Creatinine ≤ 2.0 mg/dL
 - c. Hepatic
 - i. Total Bilirubin ≤ 1.5 mg/dL or ≤ 2 mg/dL (for liver mets)
 - ii. AST & ALT $\leq 2.5 \times$ ULN or $\leq 5 \times$ ULN (for liver mets)
 - iii. Alkaline phosphatase $\leq 5 \times$ ULN (unless bone mets are present in the absence of liver mets)
7. Female Subjects:
 - a. if of child bearing potential practicing an acceptable method of birth control for the duration of the study such as condoms, foams, jellies, diaphragm, intrauterine device (IUD), or abstinence
 - b. postmenopausal for at least 1 year.
 - c. Surgically sterile

Reviewer's comment: *These inclusion criteria are acceptable. It should be noted that the ECOG status of ≤ 2 means that the patient is at minimum 50% ambulatory and able to generally care for herself.*

Exclusion Criteria:

1. Allergy or significant history of hypersensitivity or idiosyncratic reactions to Doxorubicin Hydrochloride and/or any related compounds.
2. Cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunologic, dermatologic, musculoskeletal, neurological or psychiatric disease.

3. Use of following drugs as concurrent therapy: Paclitaxel, Progesterone, Verapamil, Cyclosporine, Dexrazoxane, Cytarabine, Phenobarbital, Streptozocin.
4. Alcohol dependence, alcohol abuse or drug abuse or addiction with any recreational drug within past one year.
5. Subjects deemed uncooperative or noncompliant.
6. Smoking (≥ 10 cigarettes/day) or consumption of tobacco products (≥ 4 chews/day).
7. Difficulty in coming for follow ups.
8. Clinically significant illness (except multiple myeloma) within 4 weeks before the start of the study.
9. Female subject who is pregnant, lactating or likely to become pregnant or have a positive pregnancy test at screening and prior to each of the two periods.
10. Positive result to HIV, HCV, RPR and HBsAg.
11. Use of enzyme-modifying drugs (such as Phenytoin, Carbamazepine, Barbiturates, Griseofulvin) in the previous 30 days before day 1 of this study
12. Abnormal 12 lead ECG, X-ray and 2D-Echocardiography finding.
13. Total cumulative dose of doxorubicin HCl approaches 550 mg/m^2 .
14. Subject having active opportunistic infection with mycobacteria, cytomegalovirus, toxoplasma, *P. carinii* or other microorganism if under treatment with myelotoxic drugs
15. Subjects who had donated 350 mL or more of blood in the previous 90 days before day 1 of this study.
16. Participation in another clinical trial within the preceding 90 days of study starts and receiving anti-cancer chemotherapy outside of a clinical trial within the preceding 30 days of study start.
17. Subjects who had:
 - a. Systolic blood pressure less than 90 mm of Hg and more than 140 mm of Hg.
 - b. Diastolic blood pressure less than 60 mm of Hg and more than 90 mm of Hg.
 - c. Pulse rate below 60/minutes or above 100/minutes.

Reviewer's comment: *These exclusion criteria are acceptable.*

Treatment administered:

The following treatments and sequences were used in this study:

Treatment A: Doxorubicin Hydrochloride Liposome Injection, 2 mg/ml (50 mg/m² dose) of Sun Pharma Advanced Research Company Limited, India.

Treatment B: Doxil® (Doxorubicin Hydrochloride Liposome injection), 2 mg/ml (50 mg/m² dose) of Ortho Biotech Products, LP Raritan, NJ

	Period I	Period II
Sequences 1	A	B
Sequences 2	B	A

Study Conduct:

Days	Screening	Period 1									Wash Out	Period 2								Post Study		
		-21 to 0	0	1	2	3	5	8	11	15		1-29	28	29	30	31	33	36	39		43	43-59
Informed Consent Form signed	X	X																				
Medical History	X	X										X										
Physical Examination	X	X			X						X			X								
Laboratory Tests	X	X**							X*		X*			X**								
Urine drug screening		X									X											
Alcohol Test		X									X											
HIV, HBsAg and anti-HCV; VDRL/RPR	X																					
Vital Signs ^a /Well Being ^b	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X			
Urine pregnancy Test	X	X									X											
Chest X-Ray	X																					
ECG Test ^c	X	X			X						X			X								
2D-Echo ^d	X										X										X	
Injection Site monitoring			X		X							X		X								
Administration of Inj. Dexamethasone, Inj. Granisetron			X									X										
Dosing			X									X										
Pharmacokinetic blood Sampling			X	X	X	X	X	X	X			X	X	X	X	X	X	X	X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [#]

** Hematology, urine and biochemistry (creatinine, urea, ALT, AST, ALP, bilirubin): *: Hematology Only, Screening laboratory reports (Hematology, biochemistry) of subject number 47 was considered as check in laboratory reports (Hematology, biochemistry) of period I.

Adverse Event Reporting Period

a. Seated Blood pressure, pulse rate were noted at check in, prior to dosing and at 1.0, 2.0, 4.0, 8.0, 12.0, 24.0 hours (±30 minutes) post-dosing and at the time of check out in each period. Oral temperature recording were noted at the time of check-in, at pre-dose 2.0, 4.0, 12.0 (±30 minutes) hours post dose and at checkout.

b. Well being was asked to all subjects at the time of check in, vitals recording and check - out and ambulatory collection of each period.

c. A 12 lead ECG was measured at check-in and check-out of both the periods

d. 2-D Echocardiography was done at check-in of period II and 30 days after dosing of period II (day 59). Subjects who were dosed for period II, 2-D Echocardiography at check-in was within normal limit. For protocol deviation refer appendix 16.2.2 (Table 16.2.2-1).

Note: Hematology investigation shall be done at least once weekly for 4 weeks after dosing of period I and period II.

Reviewer's comment: This review will defer discussion of the specifics of the pharmacokinetic parameters and variables of this study to DBE1. The MO will concentrate on the clinical conduct of the study and the specifics of the death and the adverse events of concern to DBE1.

Results:

A total of 60 patients with ovarian cancer aged between 18 to 74 years were enrolled. Fifty four (54) patients received at least one dose of medication. These constitute the safety population. Of the enrolled sixty (60) subjects, forty one (41) subjects completed both period of study and constitute the per protocol population.

Extent of Exposure:

Patients were administered single dose of Doxorubicin Hydrochloride Liposome Injection, 2 mg/ml (50 mg/m² dose) on two occasions (Period I and Period II separated by a washout period of at least 28 days),

Demographic Data:

Subject Number	Vol. ID	Age	Height	Weight	BSA	Sex	Race
		(Years)	(Cm)	(Kg)	(m ²)		
1	B-001	53	152	68	1.69	Female	Asian
2	B-002	54	156	66	1.69	Female	Asian
3	B-003	45	158	72	1.78	Female	Asian
4	B-004	55	152	48	1.42	Female	Asian
5	B-004	45	157	61	1.63	Female	Asian
6	A-005	43	150	47	1.40	Female	Asian
7	A-006	38	157	62	1.64	Female	Asian
8	A-007	49	146	55	1.49	Female	Asian
9	A-004	46	156	75	1.80	Female	Asian
10	A-008	69	156	45	1.40	Female	Asian
11	A-009	63	141	32	1.12	Female	Asian
12	A-010	61	155	43	1.36	Female	Asian
13	A-013	51	164	50	1.51	Female	Asian
14	A-012	57	154	53	1.51	Female	Asian
15	A-015	32	150	55	1.51	Female	Asian
16	A-014	44	154	41	1.32	Female	Asian
17	A-016	43	153	56	1.54	Female	Asian
18	A-011	43	154	52	1.49	Female	Asian
19	A-018	37	159	50	1.49	Female	Asian
20	A-021	64	149	54	1.49	Female	Asian
21	A-022	62	158	47	1.44	Female	Asian
22	A-023	37	158	57	1.58	Female	Asian
23	A-020	57	151	59	1.57	Female	Asian
24	A-028	49	167	65	1.74	Female	Asian
25	A-026	18	161	54	1.55	Female	Asian
26	E-001	55	148	65	1.63	Female	Asian
27	E-002	74	143	43	1.31	Female	Asian
28	E-003	48	156	52	1.50	Female	Asian
29	E-004	47	152	80	1.84	Female	Asian
30	D-011	55	151	53	1.49	Female	Asian
31	D-001	41	149	58	1.55	Female	Asian
32	D-002	36	153	49	1.44	Female	Asian
33	D-003	40	159	54	1.54	Female	Asian
34	D-004	47	165	61	1.67	Female	Asian
35	D-005	44	149	42	1.32	Female	Asian
36	A-027	27	151	52	1.48	Female	Asian
37	A-025	72	154	58	1.58	Female	Asian
38	A-029	42	154	44	1.37	Female	Asian
39	A-031	39	150	51	1.46	Female	Asian
40	A-032	47	155	47	1.42	Female	Asian
41	G-001	63	158	49	1.46	Female	Asian
42	G-002	63	155	41	1.33	Female	Asian

Subject Number	Vol. ID	Age	Height	Weight	BSA	Sex	Race
		(Years)	(Cm)	(Kg)	(m ²)		
43	G-003	58	150	67	1.67	Female	Asian
44	G-004	60	157	65	1.68	Female	Asian
45	G-006	55	149	45	1.36	Female	Asian
46	D-006	28	146	37	1.22	Female	Asian
47	D-007	55	162	56	1.59	Female	Asian
48	D-008	36	152	34	1.20	Female	Asian
49	A-030	42	148	43	1.33	Female	Asian
50	A-034	57	153	47	1.41	Female	Asian
51	D-009	45	151	73	1.75	Female	Asian
52	D-012	50	158	56	1.57	Female	Asian
53	G-009	35	150	57	1.54	Female	Asian
54	G-010	40	158	51	1.50	Female	Asian
57	A-035	57	158	58	1.60	Female	Asian
58	A-036	47	146	60	1.56	Female	Asian
59	G-007	32	157	55	1.55	Female	Asian
60	G-008	63	140	51	1.41	Female	Asian
61	A-037	60	148	53	1.48	Female	Asian
62	A-038	32	157	64	1.67	Female	Asian
	Mean	48.4	153.5	53.7	1.508		
	SD (±)	11.74	5.47	9.75	0.1469		
	Range (min)	18	140	32	1.12		
	Range (max)	74	167	80	1.84		
	CV%	24.3	3.6	18.1	9.7		

Reviewer's comment: In the above table the reported death was patient #50. Patients with serious adverse events (SAEs) were patients #1, 3, 4, 5, 15, 24, 44, 49, 59, and 63.

Dropouts:

Study No.: PKD_09_030							
Subject Number	Reason For Dropout/replacement			Period		Replaced?	Replaced With
	Cause						
1	Due to serious adverse event in period I		10:25 am 07/04/10	A	I	NO	NA
4	Due to serious adverse event in period I		02:30 pm 15/09/10	A	I	NO	NA
5	Due to serious adverse event in period I		09:45 am 15/10/10	A	I	NO	NA
6	Due to Adverse Event in period I		11:21 am 08/04/10	A	I	NO	NA
7	Due to Adverse Event before dosing in period I		11:24 am 20/04/10	NA	I	NO	NA
9	Withdrew herself without any reason, voluntarily from the study before dosing in period I		08:38 am 15/04/10	NA	I	NO	NA

11	Due to Adverse Event before dosing in period I	10:44 am 11/05/10	NA	I	NO	NA
14	Due to Adverse Event before dosing in period I	05:24 pm 25/05/10	NA	I	NO	NA
15	Due to serious adverse event in period I	05:32 pm 27/05/10	A	I	NO	NA
19	Withdrew herself without any reason, voluntarily from the study before dosing in period I	10:46 am 19/08/10	NA	I	NO	NA
21	Withdrew herself without any reason, voluntarily from the study before dosing in period II	11:47 am 28/09/10	A*	II	NO	NA
24	Due to serious adverse event before dosing in period II	03:26 pm 10/11/10	B*	II	NO	NA
25	Due to Adverse Event before dosing in period I	11:27 am 28/09/10	NA	I	NO	NA
44	Due to serious adverse event in period I	10:32 am 24/11/10	A	I	NO	NA
46	Due to Adverse Event in period I	11:00 am 30/10/10	B	I	NO	NA
49	Due to serious adverse event in period I	01:58 pm 11/11/10	B	I	NO	NA
50	Death in period I	(b) (6)	A	I	NO	NA
59	Due to serious adverse event in period I	09:32 am 30/11/10	B	I	NO	NA
62	Due to serious adverse event in period I	(b) (6)	B	I	NO	NA

Reviewer's comments:

There were 19 dropouts from this study including the one death. Ten (10) dropouts were for SAEs. In the above table it is clear that except for patients # 21 and 24 all dropouts were in Period I regardless of which drug (Test or RLD) was administered. Patient 21 withdrew prior to Period II after receiving Test in Period I and Patient 24 dropped out after a SAE following Period I in which she received the RLD.

The only apparent trend is that patients exposed to this drug (either Test or RLD) for the first time have a high rate of SAE at the initiation of therapy. This is not an unexpected occurrence given the known toxicity of doxorubicin.

The death of patient #50 was subsequent to administration of Test product in Period I.

Adverse Events:

The sponsor provided the following table of all AEs identified in this study:

Adverse Events Parameters	Test (N = 49) n (%)	Reference (N = 46) n (%)	Total (N = 54)* n (%)
Subject experiencing pretreatment AEs			
Subjects with at least 1 AE	7		7
Subjects experiencing treatment – emergent AEs			
Subjects with at least 1 AE	17 (34.7)	17 (37.0)	27 (50.0) [#]
Subjects with at least 1 SAE	6 (12.2)	5 (10.9)	11 (20.4)
Subjects with at least 1 AE leading to death	1 (2.0)	0 (0.0)	1 (1.9)
Subjects with at least 1 AE leading to withdrawal	7 (14.3)	5 (10.9)	12 (22.2)
Subjects with at least 1 AE with “definite” relationship to study drug.	3 (6.1)	2 (4.3)	5 (9.3)
Subjects with at least 1 AE with at least “probable” relationship to study drug.	9 (18.4)	8 (17.4)	13 (24.1) [#]
Subjects with at least 1 AE with at least “possible” relationship to study drug.	5 (10.2)	5 (10.9)	8 (14.8) [#]

n = number of subjects with unique AEs. A subject may fall into more than one category. Source: Appendix 16.2.7

Reviewer’s comment: In the above table on line 3 (“Subjects with at least 1 AE”) the number 7 indicates 7 patients who experienced AEs in both periods of this study (# 26, 27, 28, 29, 30, 31, and 47). None of these were SAEs. As noted in the comment above, all SAEs occurred in Period I regardless of which product was administered except for Patient #24, who dropped out prior to Period II after having received the RLD in Period I. All reported SAEs were consistent with those listed in the product label as most common SAEs including dyspnea, hypertension, anemia, chest pain, hyperhidrosis, loss of consciousness, pulse abnormal, bradycardia, hypotension, oral mucositis and fatigue

Death Report:

Patient #50 was a 57 y/o Asian female with bilateral ovarian cancer diagnosed in February 2010. She had been treated with 6 cycles of adjuvant chemotherapy including Carboplatin and Paclitaxel, but on 10/13/2010 a CT scan confirmed that her disease was progressive.

She received the Test formulation on 11/23/2010 and was discharged in reportedly good condition on (b) (6). Her actual dose as reported on the case report form (CRF) was 70.67 mg administered in a total volume of 305.36 ml over 61 minutes. At the time of discharge her vital signs showed a pulse of 78/min and BP of 100/70. CBC showed the hemoglobin to be 9.5 g/dL, WBC of 5600 cells/mm³, and platelet count of 2.95 lacs/mm³.

Subsequent to discharge the patient did not contact the investigator with any reported problems. The patient did report for all post-discharge blood samples, including those scheduled for 96 hours, 168 hours, 240 hours, and 336 hours post dose. Thus, she would have been seen last on study day 15 (12/8/2010). According to the Study Schedule,

at each visit following discharge vital signs and patient well-being were checked. There are no records of any complaints during that time period. After the patient failed to report for Period II she was called on 12/20/2010. At that time a caregiver reported that she had died in her sleep on [REDACTED] (b) (6).

Reviewer's comment: *Based on the available records and the time sequence of events following administration of the Test product it is unlikely that this death was causally related to the drug or formulation. Given the poor prognosis of advanced ovarian cancer it appears more likely that this patient succumbed to her disease.*

Discussion

Ovarian cancer is the 6th most common malignancy worldwide and is currently the most common malignancy of the female reproductive system. Prognosis for survival is poor overall. In addition to the aggressiveness of this cancer the poor accessibility of the ovary to examination results in patients being diagnosed at more advanced stages.¹ While there is active research into potential biomarkers for ovarian cancer, none have as yet been validated and put into clinical use.^{2,3}

Currently the optimal management approach for ovarian cancer involves aggressive surgical debulking of tumor followed by a platinum based chemotherapy. Prognostic indicators include age, cancer stage, and co-morbid conditions. In an extensive study by Maas, et. al. in the Netherlands a 3 year survival rate was determined since there were too few patients to determine the 5 year survival rate. They found a 3 year survival rate of 58% for patients who had no co-morbidities and were younger than 70 years of age. With any co-morbidity this rate drops to 52%.⁴ Patients whose disease recurs following initial therapy likely have more advanced disease. Estimates of 5 year survival rates in stage III and stage IV range from approximately 5% to 20%.⁵ Hatch, et. al. state that "...Ovarian Cancer that persists or recurs after primary surgery and chemotherapy is incurable when disease is large enough to be evaluated clinically. No oral or intravenous agents have been shown to significantly affect the natural course of disease in these patients."⁶

¹ Obiezu, CV, Scorilas, A, Katsaros, D, Massobrio, M, et. al., "Higher Human Kallikrein Gene 4 (KLK4) Expression Indicates Poor Prognosis of Ovarian Cancer Patients", *Clinical Cancer Research*, 2001, 7, Pp. 2380-2386.

² Ibid.

³ Kozak, KR, Amneus, MW, Pusey, SM, Su, F, et. al., "Identification of biomarkers for ovarian cancer using strong anion-exchange ProteinChips: Potential use in diagnosis and prognosis", *PNAS*, 2003, 100:21, Pp. 12343-12348.

⁴ Maas, HAAM, Kruitwagen RFP, Lemmens, VEPP, Goey, SH, Janssen-Heijnen, MLG, "The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population based study", *Gynecologic Oncology*, 2005, 97, Pp. 104-109.

⁵ Gordon, AN, Fleagle, JT, Guthrie, D, Parkin, DE, et. al., "Recurrent Epithelial Ovarian Carcinoma: A Randomized Phase III Study of Pegylated Liposomal Doxorubicin versus Topotecan", *J Clin Oncol*, 2001, 19, Pp. 3312-3322.

⁶ Hatch, KD, Beecham, JB, Blessing, JA, Creasman, WT, "Responsiveness of Patients with Advanced Ovarian Carcinoma to Tamoxifen", *Cancer*, 1991, 68, Pp. 269-271.

Doxorubicin is highly toxic anti-cancer drug which is thought to exert its effect by inhibiting synthesis of nucleic acids by binding to DNA. It is approved for the treatment of ovarian cancer patients who have failed a prior platinum based therapy. This drug may be administered intravenously as either conventional doxorubicin or in a liposomal encapsulated form. These differing products cannot be substituted on a mg/mg basis due to the considerable prolongation of the half-life of drug in the encapsulated form. Treatment with doxorubicin in any form is complex and usually carried out in a hospital setting under the direction of an experienced Oncologist. In addition to the adverse reactions known to occur with this drug, extravasation at the IV site can result in severe local reactions.

In 1983 Herman, et. al. noted that encapsulation of doxorubicin in liposomes led to a decrease in dose-limiting toxic side-effects such as cardiotoxicity and nephrotoxicity while maintaining or even increasing the anti-tumor effect.⁷ However, there is an altered distribution of doxorubicin after administration in a liposome-encapsulated form. Although a number of early studies failed to demonstrate increased cardiac, renal, or hepatic toxicity. Daemen, et. al. raised the question of whether there might be an increase in toxicity to hepatic macrophages due to the rapid clearing of liposomes from the circulation which is predominantly accomplished by macrophages in the liver, resulting in release of the entrapped drug within the cell.⁸

In their study (Rat Study) of this question they found that administration of doxorubicin free conventional liposomes did not produce any apparent effect on the liver macrophages whereas there was a significant reduction in phagocytic capacity with administration of liposomal encapsulated doxorubicin. This effect was considered to be related to the increased uptake of the encapsulated drug and not to the liposomal carrier. Therefore, the any differences in relative toxicity between conventional doxorubicin and liposomally encapsulated doxorubicin are related only to the encapsulation and not to other characteristics of the formulation.

In the study submitted to ANDA 203263 there is no indication of significant formulation differences between the Test and RLD products. The inclusion criteria for this study are consistent with the indications listed in the product label. Therefore, any patients included in this study can be assumed to have more advanced disease and to have a generally poor prognosis. In the case of the single death in the study the patient demonstrated progressive disease following 6 cycles of a platinum based regimen. This was confirmed on CT scan approximately one month prior to entry into the study. The records support that the patient tolerated the administration of the test product and was able to continue returning to the Study Site for post-administration blood drawing until about 12/8/2010. There were no reported AEs of any kind prior to her death at home on (b) (6). It is, therefore, highly unlikely that her death was related to the drug.

⁷ Herman, EH, Rahmana, A, Ferrans, VJ, Vick, JA, Schein, PS, “Prevention of chronic doxorubicin cardiotoxicity in beagles by liposomal encapsulation”, *Cancer Res*, 1983, 43, Pp. 5427-5432.

⁸ Daemen, T, Hofstede, G, Ten Kate, MT, Bakker-Woudenberg, IAJM, Sherphof, GL, “Liposomal Doxorubicin-Induced Toxicity: Depletion and Impairment of Phagocytic Activity of Liver Macrophages”, *Int J Cancer*, 1995, 61, Pp. 716-721.

Evaluation of the other reported SAEs from this study appear to have occurred almost exclusively in Period I regardless of which product was administered. Given the highly toxic nature of doxorubicin it could be inferred that these patients self-selected as intolerant of the drug. All reported SAEs are well known to be common with doxorubicin liposomal injection. All other AEs reported in this study were relatively evenly divided between the Test and RLD. It is important to note that this study was not designed to demonstrate product safety. While no opinion on the overall safety is possible from the information available, it is reasonable to infer from what is available that there is no significant difference in the safety of the Test and RLD demonstrated in this study.

Conclusions:

- The single death reported in this study appears to be unrelated to the drug product and more likely the result of the aggressive ovarian cancer that failed to respond to repeated cycles of accepted first-line therapy
- SAEs reported in this study appear to be related to individual intolerance for the highly toxic medication discovered in the 1st period of study.
- Other AEs reported appear to be evenly distributed between patients receiving Test and RLD products

References

Daemen, T, Hofstede, G, Ten Kate, MT, Bakker-Woudenberg, IAJM, Sherphof, GL, “Liposomal Doxorubicin-Induced Toxicity: Depletion and Impairment of Phagocytic Activity of Liver Macrophages”, *Int J Cancer*, 1995, 61, Pp. 716-721.

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Hatch, KD, Beecham, JB, Blessing, JA, Creasman, WT, “Responsiveness of Patients with Advanced Ovarian Carcinoma to Tamoxifen”, *Cancer*, 1991, 68, Pp. 269-271.

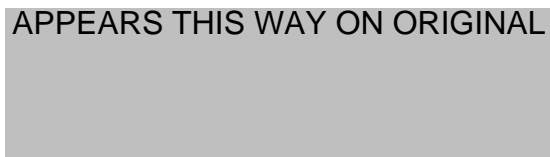
Herman, EH, Rahmana, A, Ferrans, VJ, Vick, JA, Schein, PS, “Prevention of chronic doxorubicin cardiotoxicity in beagles by liposomal encapsulation”, *Cancer Res*, 1983, 43, Pp. 5427-5432.

Kozak, KR, Amneus, MW, Pusey, SM, Su, F, et. al., “Identification of biomarkers for ovarian cancer using strong anion-exchange ProteinChips: Potential use in diagnosis and prognosis”, *PNAS*, 2003, 100:21, Pp. 12343-12348.

Maas, HAAM, Kruitwagen RFPM, Lemmens, VEPP, Goey, SH, Janssen-Heijnen, MLG, “The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population based study”, *Gynecologic Oncology*, 2005, 97, Pp. 104-109.

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/s/

BRENDA S GIERHART
01/03/2012

JOHN R PETERS
01/03/2012

Medical Consultation
Doxorubicin Hydrochloride Liposome Injection,
2 mg/mL, 10 mL and 25 mL

Re: ANDA 203263 Sun Pharma Global FZE:
Regulatory Support Branch question on safety of
formulation sucrose content

RLD: Doxil® (doxorubicin HCl liposome injection) for
intravenous infusion 2 mg/mL, 10 mL and 25 mL;
NDA 050718, approved 11/17/1995, Ortho Biotech

To: Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

Reviewer: John R Peters, M.D.
Acting Director, Division of Clinical Review (DCR),
Office of Generic Drugs

Drug Class: Anthracycline Topoisomerase Inhibitor

Chemical Name: (8S,10S)-10-[(3-amino-2,3,6-trideoxy α -L-lyxo-
hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-
trihydroxy-1-methoxy-5,12-naphthacenedione
hydrochloride)

Date Received: October 28, 2011
Review Completion Date: October 31, 2011

Recommendations:

The Division of Clinical Review (DCR) does not find that the difference in sucrose content between the RLD and Test preparations will impact the safety of the administered dose. The content of sucrose in the Sun formulation exceeds the allowable 5% by (b) (4). Therefore, it appears to the DCR that this formulation is not qualitatively and quantitatively the same as the RLD and that the sucrose is not functioning as a preservative, buffer, or antioxidant per 21 CFR 314.94(a)(9)(iii). The decision regarding the acceptability of the Sun formulation for filing is deferred to the Division of Bioequivalence 1, the Division of Chemistry and the Regulatory Support Branch.

Background Summary:

Sun Pharmaceuticals, Ltd. submitted ANDA 203263 for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL on 6/16/2011. This is the **first generic** application for Doxorubicin Hydrochloride Liposome Injection. In the

filing review of 10/6/2011 the Division of Bioequivalence (DBE) determined that “with respect to bioequivalence demonstration, the application is acceptable for filing. However, the ANDA should also be reviewed by the Division of Chemistry for the completeness and acceptability with respect to demonstration of pharmaceutical equivalence of the test product.”

There is no Chemistry Filing Review currently listed in DARRTS. In an email of 10/28/2011 the Chemistry Reviewer (Xiaobin Zhao) noted:

“1. The function of Sucrose is to maintain isotonicity. It is not part of the liposome particle composition. In other words, (b) (4) but not part of the composition in constructing the liposome structure itself.

2. According to the RLD label, "DOXIL doses up to 90 mg must be diluted in 250 mL of 5% Dextrose injection". The 90 mg dose is equivalent to 45 mL at a concentration of 2 mg/mL. Thus, the difference between (b) (4) sucrose will be further minimized after this 45mL/250 mL dilution: the RLD will have (b) (4) vs. ANDA will have (b) (4). The difference is thus less than (b) (4)%, which is not of significant safety concern for iv. Injection.

Based on the above considerations, I think the difference of sucrose concentration itself is not a REAL concern to refuse the ANDA for filing. However, during the review process, we do need to monitor if the sucrose difference will (b) (4) (b) (4) cc

On 10/28/2011 the Division of Clinical Review (DCR) was consulted by the Regulatory Support Branch regarding “whether or not the concentration in sucrose (b) (4) in RLD vs. (b) (4) in applicant) will have an effect on any safety aspect.”

According to the product label DOXIL (doxorubicin HCl liposome injection) is supplied as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each 10 ml vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/ml and each 30 ml vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/ml. Prior to intravenous administration the patient’s dose must be prepared by diluting the appropriate dosage with 5% Dextrose Injection, USP (D5W). The dose is dependent upon which condition is being treated, and ranges from 20 mg/m² to 50 mg.m². Thus in the average adult male 1.5-2.5 vials would be diluted with 375 ml or 625 ml of D5W. It is very unlikely that the (b) (4) of sucrose in the Sun formulation will have any impact on the safety of the drug following standard dilution in dose preparation.

LABELING

Current product labeling was approved on 6/10/2008. There is a Black Box warning:

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION

- 1. The use of DOXIL (doxorubicin HCl liposome injection) may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at a starting dose of 50 mg/m² every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m² or between 500-550 mg/m², the risk of cardiac toxicity for patients treated with DOXIL was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy [see *Warnings and Precautions (5.1)*].**
- 2. Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoidlike infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. DOXIL should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions [see *Warnings and Precautions (5.2)*].**
- 3. Severe myelosuppression may occur [see *Warnings and Precautions (5.3)*].**
- 4. Dosage should be reduced in patients with impaired hepatic function [see *Dosage and Administration (2.6)* and *Use in Specific Populations (8.6)*].**
- 5. Accidental substitution of DOXIL for doxorubicin HCl has resulted in severe side effects. DOXIL should not be substituted for doxorubicin HCl on a mg per mg basis [see *Dosage and Administration (2.1)*].**

Indications and Usage

- Ovarian Cancer: for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.
- AIDS-Related Kaposi's Sarcoma: treatment of AIDS-related Kaposi's sarcoma in patients after failure of prior systemic chemotherapy or intolerance to such therapy.

- Multiple Myeloma: in combination with bortezomib is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

Off-label Indications:

Doxil is used off-label in the treatment of refractory breast cancer.

Dosage and Administration

Doxorubicin is cardiotoxic. The total lifetime dose of this drug must be carefully monitored.

Maximum dose: 550 mg/m² (maximum lifetime cumulative dose); 400 mg/m² (maximum lifetime cumulative dose) for adults having received mediastinal radiation or other cardiotoxic drugs.⁶

Due to the significant adverse reactions, such as hand-foot syndrome, hematologic toxicity, or stomatitis, doses may be delayed or reduced. Pretreatment with or concomitant use of antiemetics should be considered.

- Ovarian cancer: Usual dosage: 50 mg/m² (doxorubicin hydrochloride equivalent) IV at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related adverse reactions are observed, the rate of infusion can be increased to complete administration of the drug over 1 hour. Administer once every 4 weeks for a minimum of 4 courses. The median time to response in clinical trials was 4 months. Administer for as long as the patient does not progress, shows no evidence of cardiotoxicity, and continues to tolerate treatment.
- AIDS-related Kaposi sarcoma: Usual dosage: 20 mg/m² (doxorubicin hydrochloride equivalent) intravenously (IV) at an initial rate of 1 mg/min to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over 1 hour. Repeat once every 3 weeks for as long as the patient responds satisfactorily and tolerates treatment.
- Multiple myeloma: Usual dosage: 30 mg/m² IV on day 4 following bortezomib (which is administered at 1.3 mg/m² bolus on days 1, 4, 8, and 11) every 3 weeks. With the first liposomal doxorubicin dose, an initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over 1 hour. Patients may be treated for up to 8 cycles, until disease progression or the occurrence of unacceptable toxicity.
- Refractory metastatic breast cancer (off-label): 30 to 50 mg/m² IV over 1 hour every 2 to 4 weeks.

Dosage Adjustment Recommendations:

General Dosage modification:

Liposomal doxorubicin exhibits nonlinear pharmacokinetics at 50 mg/m²; therefore, dose adjustments may result in a nonproportional greater change in plasma concentration and exposure to the drug.

Patients should be carefully monitored for toxicity. Adverse reactions, such as hand-foot syndrome, hematologic toxicities, and stomatitis, may be managed by dose delays and adjustments. Following the first appearance of a grade 2 or higher adverse reaction, the dosing should be adjusted or delayed, as described in the following tables. Once the dose has been reduced, it should not be increased at a later time.¹

Dosage adjustment in Multiple Myeloma:

For patients who experience hand-foot syndrome or stomatitis, the liposomal doxorubicin dose should be modified. (See [Dosage Modification](#).) For additional bortezomib dosing and dosage adjustments, see the [Bortezomib](#) monograph.

Dosage Adjustments for Liposomal Doxorubicin and Bortezomib Combination Therapy ¹		
Patient status	Liposomal doxorubicin	Bortezomib
Fever ≥ 38°C (100.4°F) and ANC < 1,000/mm ³	Do not dose this cycle if before day 4; if after day 4, reduce next dose by 25%.	Reduce the next dose by 25%.
On any day of drug administration after day 1 of each cycle: platelet count < 25,000/mm ³ , hemoglobin < 8 g/dL, ANC < 500/mm ³	Do not dose this cycle if before day 4; if after day 4, reduce next dose by 25% in the following cycles if bortezomib is reduced for hematologic toxicity.	Do not dose; if 2 or more doses are not given in a cycle, reduce dose by 25% in following cycles.
Grade 3 or 4 nonhematologic drug-related toxicity	Do not dose until recovered to grade < 2; reduce dose by 25% for all subsequent doses.	Do not dose until recovered to grade < 2; reduce dose by 25% for all subsequent doses.
Neuropathic pain or peripheral neuropathy	No dosage adjustments.	See Bortezomib monograph for dosage adjustments in patients with neuropathic pain.

Dosage Adjustment According to Bilirubin Concentration:

Liposomal Doxorubicin Dosage Adjustment According to Bilirubin Concentration	
Plasma bilirubin concentration (mg/dL)	Dosage reduction (%)
1.2 to 3	50
> 3	75

Dose Modification for Hematological Toxicity:

Liposomal Doxorubicin Dose Modification for Hematological Toxicity			
Grade	ANC	Platelets	Modification
1	1,500 to 1,900	75,000 to 150,000	Resume treatment with no dose reduction.
2	1,000 to < 1,500	50,000 to < 75,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction.
3	500 to 999	25,000 to < 50,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction.
4	< 500	< 25,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose at 25% dose reduction or continue full dose with cytokine support.

Dose Modification for Hand-Foot Syndrome:

Liposomal Doxorubicin Dose Modification for Hand-Foot Syndrome		
Toxicity grade	Symptoms	Dose adjustment
1	Mild erythema, swelling, or desquamation not interfering with daily activities	Redose unless patient has experienced previous grade 3 or 4 HFS. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dosing interval.
2	Erythema, desquamation, or swelling interfering	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued. If resolved to grade 0 to 1 within 2 weeks, and if there was no prior grade 3 to 4 HFS, continue treatment at previous dose and return to original dosing

	with, but not precluding, normal physical activities; small blisters or ulcerations less than 2 cm in diameter	interval. If patient experienced previous grade 3 or 4 toxicity, continue treatment with a 25% dose reduction and return to original dosing interval.
3	Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued.
4	Diffuse or local process causing infectious complications, or a bedridden state or hospitalization	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued.

Dose Modification for Stomatitis

Liposomal Doxorubicin Dose Modification for Stomatitis		
Toxicity grade	Symptoms	Dose adjustment
1	Painless ulcers, erythema, or mild soreness	Redose unless patient has experienced previous grade 3 or 4 toxicity. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dosing interval.
2	Painful erythema, edema, or ulcers,	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued. If resolved to grade 0 to 1 within 2 weeks and there was no prior grade 3 or 4 stomatitis, continue treatment at

	but can eat	previous dose and return to original dosing interval. If patient experienced previous grade 3 or 4 toxicity, continue treatment with a 25% dose reduction and return to original dosing interval.
3	Painful erythema, edema, or ulcers, and cannot eat	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued.
4	Requires parenteral or enteral support	Delay dosing up to 2 weeks or until resolved to grade 0 to 1. Decrease dose by 25% and return to liposomal doxorubicin original dosing interval. If after 2 weeks there is no resolution, liposomal doxorubicin should be discontinued.

Reviewer's comment: *As can be seen this is a complex drug to administer. It is generally prescribed by a qualified Oncologist and administered in a hospital setting. The purpose of the liposomal encapsulation is to prolong the circulating time of drug. Since the sucrose is not a part of the encapsulated drug, but is only used to maintain isotonicity any impact that it might have on the pharmacokinetic properties of the product should be demonstrable in BE testing.*

Contraindications:

- Hypersensitivity to a conventional formulation of doxorubicin or the components of liposomal doxorubicin
- Breast-feeding mothers

Warnings and Precautions:

- Cardiac toxicity
- Infusion reactions
- Myelosuppression
- Hand-Foot Syndrome
- Radiation recall therapy
- Extravasation
- Elderly: Consider 300 mg/m² as a maximum lifetime cumulative dose in patients older than 70 years of age.
- Carcinogenesis: Secondary acute myelogenous leukemia has been reported
- Toxicity potentiation: Liposomal doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with the conventional formulation of doxorubicin. Radiation-induced toxicity to the liver, mucosae, myocardium, and skin has been reported to be

increased by the administration of doxorubicin.

Adverse Reactions:

The most common adverse reactions reported with liposomal doxorubicin are anemia, anorexia, asthenia, constipation, diarrhea, fatigue, fever, HFS, nausea, rash and neutropenia, stomatitis, thrombocytopenia, and vomiting.

Pregnancy Category D: Liposomal doxorubicin can cause fetal harm when administered to a pregnant woman.

Mechanism of Action:

According to the product label for Doxil® (doxorubicin HCl liposome injection) for intravenous infusion:

“The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

DOXIL is doxorubicin HCl encapsulated in long-circulating STEALTH liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH liposomes of DOXIL are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time. “

Pharmacokinetics:

According to Drug Facts and Comparisons, (Online Edition, 2011):

“Liposomal doxorubicin displayed linear pharmacokinetics over the range of 10 to 20 mg/m². Disposition occurred in 2 phases after liposomal doxorubicin administration, with a relatively short first phase (approximately 5 hours) and a prolonged second phase (approximately 55 hours) that accounted for the majority of the AUC.

The pharmacokinetics of liposomal doxorubicin at a 50 mg/m² dose is reported to be nonlinear. At this dose, the elimination half-life of liposomal doxorubicin is expected to be longer and the clearance lower compared with a 20 mg/m² dose. The exposure (AUC) is thus expected to be more than proportional at a 50 mg/m² dose compared with lower doses...

In contrast to the pharmacokinetics of doxorubicin, which display a large volume of distribution ranging from 700 to 1,100 L/m², the small steady-state volume of distribution

of liposomal doxorubicin shows that liposomal doxorubicin is confined mostly to the vascular fluid volume. The plasma protein binding of liposomal doxorubicin has not been determined; the plasma protein binding of doxorubicin is approximately 70%...

The plasma clearance of liposomal doxorubicin was slow, with a mean clearance value of 0.041 L/h/m² at a dose of 20 mg/m². This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24 to 35 L/h/m²...

Because of its slower clearance, the AUC of liposomal doxorubicin, primarily representing the circulation of liposome-encapsulated doxorubicin, is approximately 2 to 3 orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin..."

Product Formulation:

Ingredients	Sun Doxorubicin	Doxil RLD
	mg/ ml	mg/ ml
Doxorubicin	2	2
MPEG-Distearoyl Phosphatidylethanolamine	3.19	3.19
Hydrogenated Soya Phosphatidyl Choline	9.58	9.58
Histidine		(b) (4)
Sucrose		
Ammonium Sulfate	2	2
Cholesterol	3.19	3.19

Reviewer’s comment: As can be seen in this, the content of sucrose in the Sun formulation exceeds the allowable 5% by (b) (4). Therefore this formulation is not qualitatively and quantitatively the same as the RLD. Acceptability of this formulation is not consistent with 21 CFR 314.94(a)(9)(iii). The decision to grant an exception is deferred to Regulatory Affairs and DBE.

Discussion

Doxorubicin is highly toxic anti-cancer drug which is thought to exert its effect by inhibiting synthesis of nucleic acids by binding to DNA. This drug may be administered intravenously as either conventional doxorubicin or in a liposomal encapsulated form. These differing products cannot be substituted on a mg/mg basis due to the considerable prolongation of the half-life of drug in the encapsulated form. Treatment with doxorubicin in any form is complex and usually carried out in a hospital setting under the direction of an experienced Oncologist. In addition to the adverse reactions known to occur with this drug, extravasation at the IV site can result in severe local reactions.

This consult raises the question of whether a difference in the safety profile might occur due to the (b) (4) amount of sucrose in the sponsor’s formulation for a liposomal doxorubicin. The answer to this question is dependent on the contribution of

the liposomal carrier to the toxicity of the drug and the relationship of the sucrose to the function of that carrier.

In 1983 Herman, et. al. noted that encapsulation of doxorubicin in liposomes led to a decrease in dose-limiting toxic side-effects such as cardiotoxicity and nephrotoxicity while maintaining or even increasing the anti-tumor effect.¹ However, there is an altered distribution of doxorubicin after administration in a liposome-encapsulated form. Although a number of early studies failed to demonstrate increased cardiac, renal, or hepatic toxicity. Daemen, et. al. raised the question of whether there might be an increase in toxicity to hepatic macrophages due to the rapid clearing of liposomes from the circulation which is predominantly accomplished by macrophages in the liver, resulting in release of the entrapped drug within the cell.²

In their study (Rat Study) of this question they found that administration of doxorubicin free conventional liposomes did not produce any apparent effect on the liver macrophages whereas there was a significant reduction in phagocytic capacity with administration of liposomal encapsulated doxorubicin. This effect was considered to be related to the increased uptake of the encapsulated drug and not to the liposomal carrier. Therefore, the any differences in relative toxicity between conventional doxorubicin and liposomally encapsulated doxorubicin are related only to the encapsulation and not to other characteristics of the formulation.

As noted by the chemistry reviewer, “The function of Sucrose is to maintain isotonicity. It is not part of the liposome particle composition. In other words, (b) (4), (b) (4), but not part of the composition in constructing the liposome structure itself.” In addition, it must be noted that the product requires considerable dilution in D5W prior to intravenous administration. Thus, the very small difference in the amount of sucrose present in this formulation versus the 5% allowable difference is unlikely to add further to the safety risk of the product. Evaluation of the equivalence of liposomal carriers and doxorubicin BE is deferred to the DBE.

Conclusions:

There is no evidence that the amount of sucrose in the sponsor’s formulation of liposomally encapsulated doxorubicin will have any impact on the safety profile of the product.

The content of sucrose in the Sun formulation exceeds the allowable 5% by (b) (4). Therefore this formulation is not qualitatively and quantitatively the same as the RLD. Acceptability of this formulation is not consistent with 21 CFR 314.94(a)(9)(iii). The decision to grant an exception is deferred to Regulatory Affairs and DBE.

¹ Herman, EH, Rahmana, A, Ferrans, VJ, Vick, JA, Schein, PS, “Prevention of chronic doxorubicin cardiotoxicity in beagles by liposomal encapsulation”, *Cancer Res*, 1983, 43, Pp. 5427-5432.

² Daemen, T, Hofstede, G, Ten Kate, MT, Bakker-Woudenberg, IAJM, Sherphof, GL, “Liposomal Doxorubicin-Induced Toxicity: Depletion and Impairment of Phagocytic Activity of Liver Macrophages”, *Int J Cancer*, 1995, 61, Pp. 716-721.

References

Daemen, T, Hofstede, G, Ten Kate, MT, Bakker-Woudenberg, IAJM, Sherphof, GL, “Liposomal Doxorubicin-Induced Toxicity: Depletion and Impairment of Phagocytic Activity of Liver Macrophages”, *Int J Cancer*, 1995, 61, Pp. 716-721.

Herman, EH, Rahmana, A, Ferrans, VJ, Vick. JA, Schein. PS, “ Prevention of chronic doxorubicin cardiotoxicity in beagles by liposomal encapsulation”, *Cancer Res*, 1983, 43, Pp. 5427-5432.

APPEARS THIS WAY ON ORIGINAL

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/s/

BRENDA S GIERHART
11/22/2011

JOHN R PETERS
11/23/2011

DALE P CONNER
11/23/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 203263

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ROUTING SHEET

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) CGMP

Division: **II** Team: **21** PM: **Linda Park**

Electronic ANDA:
Yes No

ANDA #: **203263**

Firm Name: **Sun Pharma Global FZE**

ANDA Name: **Doxorubicin HCl Liposome Injection USP- 2 mg/mL, 20 mg/ 10 mL, 50 mg/ 25 mL- SDV**

RLD Name: **Doxil® (doxorubicin HCl liposome injection), 2 mg/mL, 10 mL and 25 mL**

Electronic AP Routing Summary Located:

V:\Chemistry Division II\Team 21\Electronic AP-TA-NACGMPSummaries

AP/TA Letter Located:

V:\Chemistry Division II\Team 21\AP TA NACGMP CR WD Letters

Project Manager Evaluation:

Date: **1/22/13** Initials: **LP/EL**

- Previously reviewed and tentatively approved --- Date _____
 Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date <u>6/16/11</u>	Date of Application <u>6/16/11</u>	Date Acceptable for Filing <u>12/12/11</u>
Patent Certification (type) <u>PI</u>	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes ☒ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ DMF#: _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: Pending Acceptable OAI *EES Date Acceptable: 1/10/13* Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filing? Yes No Comment:
Date of Acceptable Quality (Chemistry) _____ Addendum Needed: Yes No Comment:
Date of Acceptable Bio 1/9/13 Bio reviews in DARRTS: Yes No (Volume location:)
Date of Acceptable Labeling 10/18/12 Attached labeling to Letter: Yes No Comment:
Date of Acceptable Sterility Assurance (Micro) 5/4/12
GDUFA User Fee Obligation Status Met Unmet : **Date: 11/20/12**

Methods Val. Samples Pending: Yes No ; Commitment Rcvd. from Firm: Yes No

Post Marketing Agreement (PMA): Yes No (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes No (If yes, enter dissolution information in Letter)

Routing:

Office of Management, Fee Verification, Date emailed: _____; Date OM Response: _____

Labeling Endorsement, Date emailed: 1/23/13 REMS Required: Yes No REMS Acceptable: Yes No

Regulatory Support

Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

Division

Bob West / Peter Rickman

Gregory Geba

Filed AP Routing Summary in DARRTs Notified Firm and Faxed Copy of Approval Letter Sent Email to "CDER-OGDAPPROVALS" distribution list

Reference ID: 3255287

OGD APPROVAL ROUTING SUMMARY

1. **Office of Management**

CDER Collections (cdercollections@fda.hhs.gov)

Date Emailed:

Date Verification response received from OM:

GDUFA User Fee Obligation Status Met Unmet **Date:** _____*

- Misbranding statement in letter for no Facility Fee payment
- Misbranding statement in letter for Failure to Self-ID
- Backlog fee not paid for ANDA in question statement in letter

Comments:

*NOTE: If OM verification was completed prior to the close of the fiscal year, obtain a new OM verification response for the current fiscal year.

2. **Regulatory Support Branch Evaluation**

Martin Shimer

Date: 1/23/2013

Chief, Reg. Support Branch

Initials: MHS

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)	Determ. of Involvement? Yes ☐ No ☒
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☐ No ☐ Was applicant sued w/in 45 days: Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day Is a forfeiture memo needed: Yes ☐ No ☐ If yes, has it been completed	Pediatric Exclusivity System RLD = <u>Doxil Liposomal Inj.</u> NDA# <u>50-718</u> Date Checked <u>2/2/13</u> Nothing Submitted ☒ Written request issued ☐ Study Submitted ☐
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP ☐ OTHER:	
Comments: ANDA submitted on 6/16/2011, BOS=Doxil NDA 50-718, PI cert, ODE expires 5/17/2014-Sun is carving out this exclusivity. ANDA ack for filing on 6/16/2011 (LO dated 12/12/2011), expedited review granted to this ANDA at the time Acceptance for Filing letter was issued. The ODE designation for Doxil covers the approved indication: for use in combination with bortezomib for the treatment of patients with multiple myeloma who have not previously received bortezomib and have at least one prior treatment. The claims associated with ODE have been removed from Sun's labeling. ANDA is eligible for immediate Full Approval. Approval of this product represents the first approval of a Liposomal product by OGD.	

3. **Labeling Endorsement**

Reviewer, _____ :
Date _____
Initials _____

Labeling Team Leader, _____ :
Date 2/2/13
Initials rlw/for

REMS required?
 Yes No

REMS acceptable?
 Yes No n/a

Comments:

From: Grace, John F

Sent: Thursday, January 24, 2013 7:01 PM

To: Payne, Angela; Lee, Erin

Subject: RE: ANDA 203263/doxorubicin inj/Sun

concur.

From: Payne, Angela

Sent: Wednesday, January 23, 2013 8:28 PM

To: Lee, Erin; Grace, John F

Subject: RE: ANDA 203263/doxorubicin inj/Sun

John/Lee,

The labeling approval summary#2 signed of 10/18/2012 remains acceptable. There are no new changes in DARRTS, USP or OB. No REMS.

4. ***Paragraph IV Evaluation***

PIV's Only

David Read

Date 2/2/13

Initials rlw/for

OGD Regulatory Counsel

Pre-MMA Language included

Post-MMA Language Included

Comments: N/A. There are no paragraph IV certifications associated with this ANDA. Sun has "carved-out" from its labeling all reference to the use of the drug product for the orphan drug protected indication. This is acceptable.

5. ***Quality Division Director /Deputy Director Evaluation***

Date 1/24/2013

Chemistry Div. **II (Smith)**

Initials GJS

Comments: CMC Acceptable.

OGD Office Management Evaluation

6. **Peter Rickman**

Date 2/2/13

Director, DLPS

Initials rlw/for

Para.IV Patent Cert: Yes No

Pending Legal Action: Yes No

Petition: Yes No

Entered to APTrack database

GDUFA User Fee Obligation Status Met Unmet

Press Release Acceptable

Date PETS checked for first generic drug _____

Comments: Bioequivalence review of fed BE study (low-fat breakfast) in female ovarian cancer patients found acceptable. BE was assessed based upon comparative measurements of free doxorubicin and liposomal doxorubicin in the Sun and RLD products. In-vitro dissolution testing and liposomal size distribution studies also found acceptable. Bio study sites have acceptable OSI inspection histories. Office-level bio endorsed 11/13/12, 1/9/13.

Microbiology/Sterility Assurance found acceptable for approval (Microbiology Review #2) 5/4/12.

Final-printed labeling(FPL) found acceptable for approval 10/18/12, as endorsed 1/24/13. No REMS is required.

Sun has "carved-out" from its labeling all reference to the use of the drug product for the Orphan Drug Exclusivity (ODE) - Treatment of multiple myeloma (in combination with bortezomib). This is acceptable.

CMC found acceptable for final approval (Chemistry Review #3) 1/25/13.

OR

7. **Robert L. West**

Date 2/2/13

Initials RLWest

Deputy Director, OGD

Para.IV Patent Cert: Yes No

Pending Legal Action: Yes No

Petition: Yes No

Entered to APTrack database

GDUFA User Fee Obligation Status Met Unmet

Press Release Acceptable

Date PETS checked for first generic drug _____

Comments: There are no patents listed in the current "Orange Book" for this drug product. Also, as noted above, Sun has successfully addressed the RLD holder's orphan drug exclusivity (ODE). No additional exclusivity is currently listed in the "Orange Book" for this drug product.

A response to the pending Citizen Petition, Press release and Information Advisories are currently being cleared by ORP/ORA. Approval of this ANDA will be coordinated with the issuance/release of those documents.

GDUFA User Fee obligations have been met by the applicant.

This is a first-generic ANDA approval that was granted "expedited review" status because of nationwide drug shortage issues associated with the unavailability of the RLD product.

This ANDA is recommended for final approval. The actual approval will occur once agency agreement has reached for the proposed Press Release and Information Advisory, as well as concurrent with issuance of the Citizen Petition.

8. ***OGD Director Evaluation***

Gregory Geba

Comments: RLWest for Gregory P. Geba, M.D., M.P.H. 2/3/13.

First Generic Approval

PD or Clinical for BE

Special Scientific or Reg. Issue

Press Release Acceptable

Comments:

9. Project Manager

Date 2-4-13

Initials LP

GDUFA User Fee Obligation Status Met Unmet

Check Communication and Routing Summary into DARRTS

EES DATA:

Establishment Evaluation System ORACLE

File Edit Search Navigate Options Help Window

Application Drawer

Application Establishments **Status** Milestones Comments Contacts Product

Application: Subtype: Sponsor:
 Drug Name:

FEI / CFN	Establishment Name	Profile Code	Last Milestone Name	Last Compliance			OA Ale
				Date	Status	Date	
☒ 3002809586	SUN PHARMACEUTICAL IN	SVS	OC RECOMMENDATION	10-JAN-2013	AC	10-JAN-2013	
☐ 3007512695	SUN PHARMACEUTICAL AD	CTL	OC RECOMMENDATION	29-NOV-2012	AC	29-NOV-2012	(b) (4)

Overall Compliance:

Date	Recommendation	Overall Re-eval Date
10-JAN-2013	ACCEPTABLE	09-SEP-2014

OAI Alert Comments

start | [Taskbar Icons] | 9:35 AM

- [Tobacco Products](#)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

- 
-  1
-  2

- [FDA Home](#)³
- [Drug Databases](#)⁴
- [Orange Book](#)⁵

-
Patent and Exclusivity Search Results from query on Appl No 050718 Product 002 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N050718	002	ODE	May 17, 2014

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/s/

ERIN M LEE
02/04/2013

LINDA M PARK
02/04/2013

Record of Telephone Conversation

On January 17, 2013, a teleconference was made with Sun Pharmaceutical Global FZE to communicate the following minor chemistry deficiencies related to ANDA 203263 (Doxorubicin HCl liposome injection, 2 mg/mL, 10 mL and 25 mL): 1. [REDACTED] (b) (4) The agent acknowledged the deficiency and stated that they will respond ASAP, with a possibility of responding tomorrow.	ANDA Number: 203263
	Product Name: Doxorubicin HCl liposome injection, 2 mg/mL, 10 mL and 25 mL
	Firm Name: Sun Pharma
	Firm Representative: Robert Kurkiewicz
	Phone Number: 313-556-4105 (does not work) Called cell phone: [REDACTED] (b) (6)
	FDA Representative: Xiaobin Zhao, Ph.D.
	Signatures: Xiaobin Zhao

CC: ANDA 203263

V:\FIRMSAM\ \TELECONS\ 203263 .doc

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/s/

XIAOBIN ZHAO
01/17/2013

FRANK J NICE
01/18/2013



ANDA 203263

COMPLETE RESPONSE

Caraco Pharmaceutical Laboratories Ltd.
US Agent for Sun Pharma Global FZE
Attention: Robert Kurkiewicz
1150 Elijah McCoy Drive
Detroit, MI 48202

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 16, 2011, received June 16, 2011, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Doxorubicin Hydrochloride Liposome Injection USP, 2 mg/mL, packaged in 10 mL and 25 mL single use vials.

We acknowledge receipt of your amendments dated November 3, 2011; March 7, March 20, April 9, May 10, June 29, July 4, July 5, July 27, August 4, September 26, and October 5, 2012.

We have completed our review of this ANDA and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below represent MINOR deficiencies.

1.  (b) (4)
2. 
3. 
4. 

5.

(b) (4)

6.

7.

8.

9.

10

11

12

13

BIOEQUIVALENCE

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledge on the cover sheet. The following deficiencies have been identified:

Between 8/27/2012 and 9/4/2012, the Office of Scientific Investigations (OSI) inspected the clinical site, NRR Hospital, Bangalore, India, which was used as one of the clinical sites for your fed bioequivalence (BE) study of the current application. A Form 483 was issued to the site following the inspection.

Please address the following inspection findings cited in the Form 483 and their impact on the integrity of the BE study results:

- Failure to maintain possession and/or control of investigational product test and reference retention samples.
- Failure to assure that an Ethics Committee complying with applicable regulatory requirements and following their own written procedures was responsible for the initial and continuing review and approval of a clinical study.
- Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study related activities.
- There was no statement in the informed consent for screening document that described the extent, if any, to which confidentiality of records identifying the subjects would be maintained; and that noted the possibility that regulatory agencies might inspect the records.
- Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the clinical investigation.

Please provide any necessary supporting documents in your response.

MICROBIOLOGY

The Division of Microbiology has no further questions at this time.

LABELING

The Division of Labeling has no further questions at this time since their last review dated October 18, 2012. Please check the DRUGS@FDA website before your next submission and submit any revised labeling, as necessary.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a MINOR AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION- MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Chemistry, Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

If you have any questions, call Linda Park, Regulatory Project Manager, at (240) 276-8536.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST on behalf of GREGORY P GEBA

11/14/2012

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

BIOEQUIVALENCE AMENDMENT

ANDA 203263

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Sun Pharma Global FZE

TEL: 313-556-4105

ATTN: Robert Kurkiewicz

FAX: 248-926-0231

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on June 16, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Doxorubicin hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL.

Reference is also made to the amendments submitted on August 4, 2012.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response**.

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:

*Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810*

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA: 203263
APPLICANT: Sun Pharma Global FZE
DRUG PRODUCT: Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL (10 mL and 25 mL)

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledge on the cover sheet.

The following deficiencies have been identified:

1. Although the imported batches were accepted by the Agency for importation purpose, you have been informed in the past that the acceptance criteria for importation should not be considered the same as the criteria for the ANDA approval. Please note that the quality testing program for the imported lots is more limited then that used to support the approval of an application. Therefore, it is not acceptable to justify the proposed in vitro drug release specifications for the test product based on the in vitro drug release data of the imported lots.

Based on the additional in vitro drug release data submitted for the 25 mL vial of the test product, Lot No. JK93743A, in the amendment dated Aug 04, 2012, the release specifications previously recommended by the Agency (based on the release data of the test bio-lot, Lot No. - JK93496) were confirmed, and therefore, no change in the recommended specifications is justified.

However, per our consultation with the Division of Chemistry II (DCII), Office of Generic Drugs, you may consider submitting in vitro release data from **at least** 3 fresh imported lots (in place of any 3 other fresh test lots) to justify your proposed specifications at the time points of 1.5 hours, 3 hours and 5 hours, provided that the complete Manufacturing, Chemistry and Controls (CMC) data and records for these 3 imported lots (or any 3 other fresh test lots) are submitted, reviewed and accepted by the Division of Chemistry, Office of Generic Drugs. The CMC records for these test lots should demonstrate that they are manufactured and tested under the same approved manufacturing site, conditions, specifications, controls, and are pharmaceutically equivalent to the test lot used in the bioequivalence study. Please contact the DCII for the

information concerning additional testing necessary for these selected imported lots.

Alternatively, please acknowledge your acceptance of the following FDA-recommended method and specifications stated in the previous letter dated July 25, 2012.

The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus (b) (4)

(Model No: (b) (4)) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner (b) (4)

(b) (4) The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr:	NMT	(b) (4) %
1.5 hr:		(b) (4) %
3 hr:		%
5 hr:		%
7 hr:	NLT	(b) (4) %

- The Office of Regulatory Affairs (ORA) conducted an audit of the in vitro bioequivalence study for the current ANDA. A Form 483 was issued following the inspection of the study site, Sun Pharmaceutical Industries Ltd., Halol-Baroda Highway Halol-389350 Gujarat India between June 11-13, 2012. The DBI has reviewed the inspection report by the ORA pertinent to the in vitro bioequivalence study and found the following objectionable findings by the ORA could potentially compromise the integrity of the in vitro study results.

"The calibration of (b) (4) Laser Diffraction instrument was inadequate"

For particle size measurements, samples from each vial of test or reference product were poured into a cuvette and the particle size was determined using the defined parameters. Due to the (b) (4) the inspector suspects that the refractive index should have been (b) (4) and the viscosity should have been (b) (4) for the suspending medium. The parameter of (b) (4) for refractive index of liposome particles was not verified.

The D10, D50, D90, and span values in particle size distributions reported in the in vitro study were calculated from scattered light signals by the (b) (4) DLS software. (b) (4)

The particle size data for D10, D50, D90, and span in the in vitro bioequivalence (BE) study should be evaluated only after the refractive index, viscosity of the suspending medium and the refractive index of liposome particles can be confirmed.

Please address the above findings, and provide any appropriate supporting documentation in your response.

3. In our previous letter dated July 25, 2012, we informed you that *"if and when the RLD product becomes available, additional comparative characterization testing may be requested by the Agency, as appropriate, to obtain more complete information on the in vitro release of the test product, as compared with the reference product."* In the current amendment, you responded by noting that you have submitted in vitro release testing for both 10-mL and 25 mL vials of the test and RLD product, using your proposed method. Since your proposed in vitro release testing method has been accepted by the DBI for your test product, the in vitro release testing data as submitted by you thus far are considered adequate for your application at this time, given the current shortage of the RLD product. However, in order to confirm the comparability of in vitro release characteristics between the test and the RLD products, under other relevant in vitro release testing conditions, for instance, the Agency may request additional in vitro comparative characterization testing in the future, if and when the RLD product becomes available.

4. Please provide appropriate documentation and evidence that the reference lot, Doxil Liposomal Injection, Lot No. JK93496 used in your BE study, was US-approved and marketed product. The documentation may include but may not be limited to purchase invoice, package labeling etc.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

DALE P CONNER
09/24/2012

OFFICE OF GENERIC DRUGS

Product Quality Memo

Date: August 10, 2012

To: Doxorubicin Hydrochloride Liposome Injection (ANDA 203263) Review Team

From: Xiaobin (Ben) Zhao, Ph.D. (240-276-8552, xiaobin.zhao@fda.hhs.gov)

Through:

Radhika Rajagopalan (240-276-8546, radhika.rajagopalan@fda.hhs.gov)

Glen Smith (240-276-8580, glen.smith@fda.hhs.gov)

Subject: Chemistry, Manufacturing, and Controls (CMC) Considerations for Doxorubicin HCl Liposome Manufacturing and Quality

PURPOSE

This Product Quality Memo (PQM) is written to summarize the CMC information relevant to the Office of Compliance (OC) evaluations of the two manufacturing sites of Doxorubicin Hydrochloride Liposome Injection (LipoDox): (1) Sun Pharmaceutical Industries Ltd.-Halol (CFN# 3003789481), and (2) Sun Pharma Advanced Research Company Ltd. (CFN # 3007512695).

BACKGROUND

Doxorubicin hydrochloride liposome injection (LipoDox) is doxorubicin hydrochloride encapsulated in PEGylated liposomes for intravenous administration. It is an extended-release injectable formulation. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. Liposomal encapsulation can prolong the circulation of doxorubicin relative to those of the unencapsulated drug. LipoDox is indicated for the treatment of ovarian cancer and AIDS-related Kaposi's Sarcoma.

Sun Pharma Global FZE submitted ANDA 203263 with a reference to Doxil® (Doxorubicin HCl liposome injection), 2 mg/mL, 10 mL and 25 mL (NDA# 050718) as the RLD. The original application has been reviewed. On 4/23/2012, we requested the firm to include more raw material controls on (b) (4) add several in process control (IPC) tests during the manufacturing process, and revise the drug product specifications. On 7/6/2012, the firm responded to the deficiencies and the minor amendment is currently under review by the OGD.

According to the ANDA, the drug product is manufactured at

Sun Pharmaceutical Industries Ltd.-Halol

Halol-Baroda High way, Halol,

Gujarat, India-389 350

Contact: Mr. Sudhir Valia

Tele. No. +91-22-28212115, 28212128; Fax No. +91-22-28212010

Product Quality Memo

The firm also stated that several tests will be performed at the Analytical development laboratory of Sun Pharma Advanced Research Company Ltd. (SPARC), Vadodara located at following address:

Sun Pharma Advanced Research Company Ltd.
Tandalja
Vadodara- 390 020, India.
Telephone:91-265-6615500

The drug product composition contains doxorubicin HCl, hydrogenated soya phosphatidyl choline (HSPC), methoxy polyethylene glycol distearoyl phosphatidylethanolamine (MPEG-DSPE), cholesterol, histidine, ammonium sulfate, sucrose (b) (4), HCl, NaOH, (b) (4). The drug product is manufactured (b) (4)

The manufacturing flow diagram is included in **Attachment 1**. The intended commercial batch size and exhibit batch size are (b) (4). The manufacturing equipments used include: (b) (4)

The firm provided master batch records for JK93496 and JK93743 for the 10 mL and 25 mL strength, respectively. The drug product specifications have been recently revised and the updated copies are provided in **Attachment 2**. In the recent amendment, the firm updated the 24 month long term stability data for both strengths: 10 mL: JK 93371A, JK 93496A, JK 93699A; and 25 mL: JK 93743A, JKJ0142A, JKJ0322A.

POINTS TO CONSIDER

The followings are for the team's consideration during the pre-approval inspection (PAI). The reviewer's risk assessment is provided for each point.

1. Lipid analysis and excipient control

Lipid excipients are critical in the liposome formulation. Information concerning the chemistry, manufacturing and control of the lipid components should be provided at the same level of detail expected for a drug substance.¹ In the recent amendment, the firm provided (b) (4). The reviewer would appreciate an inspectional review of the method validation reports. For excipients control, the firm (b) (4) at the SPARC site. This site should be covered during the inspection.

2. Manufacturing process

¹ Draft Guidance on Doxorubicin Hydrochloride, OGD, 2010.
<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM199635.pdf>

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/s/

XIAOBIN ZHAO
08/13/2012

RADHIKA RAJAGOPALAN
08/13/2012

FRANK J NICE
08/13/2012

BIOEQUIVALENCE AMENDMENT

ANDA 203263

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Sun Pharma Global FZE

TEL: 313-556-4105

ATTN: Robert Kurkiewicz

FAX: 248-926-0231

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on June 16, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Doxorubicin hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL.

Reference is also made to the amendments submitted on April 9, 2012, May 10, 2012, June 29, 2012 and July 4, 2012.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response**.

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:

*Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810*

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

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ANDA: 203263
APPLICANT: Sun Pharma Global FZE
DRUG PRODUCT: Doxorubicin Hydrochloride Injection, Liposomal, 2 mg/mL (10 mL and 25 mL)

The Division of Bioequivalence I (DBI) has completed its review of your submission acknowledge on the cover sheet.

The following deficiency has been identified:

The in vitro drug release testing using your proposed method with Bottle Rotating Apparatus is acceptable. Based on the data submitted for the test lot used in the in vivo bioequivalence study, the DBI has recommended appropriate specifications for the test product. Please acknowledge your acceptance of the following method and specifications:

The in vitro drug release testing should be conducted in 90 mL of Phosphate Buffer, pH 6.4 at 52°C ± 0.5°C, using Bottle Rotating Apparatus at 12 rpm.

The testing should be performed using (b) (4) Bottle Rotating Apparatus (b) (4) (b) (4) using 100 mL cylinder glass bottles (b) (4) with cap with (b) (4) liner (b) (4). The calibration procedure for the rotating apparatus, the drug release testing procedure and the analytical method should be as specified in your SOP QCI-157/02 for Calibration Procedure (Operation and Calibration Procedure of Bottle Rotating Apparatus, effective date 01/25/2011), and SOP for In Vitro testing (Finished Product-Analytical Test Procedure (Code No. BFE1548, Spec No. 0011548, Revision No. 4, CC No. JKK/F101, effective date 04/03/2012), respectively.

The test product should meet the following specification:

0.5 hr:	NMT	(b) (4) %
1.5 hr:		(b) (4) %
3 hr:		%
5 hr:		%
7 hr:	NLT	(b) (4) %

Please note the following:

1. You may request revision of the above FDA-recommended release specifications by submitting additional in vitro release data from fresh test lots, for which the validation has been reviewed and accepted by the Division of Chemistry, Office of Generic Drugs (OGD): The Manufacturing, Chemistry and Controls (CMD) records for these test lots should be submitted to the chemistry review division, and demonstrate that they are manufactured under the same approved manufacturing site, conditions, specifications, controls, and are pharmaceutically equivalent to the test lot used in the bioequivalence study. We note that at the present time, the evaluation of the proposed finished product specifications for the test product by the OGD chemistry division is ongoing.

2. Due to the reported limited availability of the reference listed drug (RLD) product, Doxil[®], the Agency has not requested a complete comparative characterization of the in vitro release profile for the test versus the RLD product at this time. However, if and when the RLD product becomes available, additional comparative characterization testing may be requested by the Agency, as appropriate, to obtain more complete information on the in vitro release of the test product, as compared with the reference product.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

DALE P CONNER
07/25/2012

OSI Consult
Request for Biopharmaceutical Inspections

Date	07/20/2012
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	Sam H. Haidar, Ph.D., R.Ph. Chief, Bioequivalence Investigations Branch Division of Bioequivalence and GLP Compliance Office of Scientific Investigations
Consulting Office/Division	OGD/DB1
Project Manager	Ramson, Teresa
Application Type	PEPFAR? ☐ Yes ☐ No ☐ NDA ☐ BLA ☒ ANDA
Application Number	203263
Drug Product	Doxorubicin hydrochloride Liposome Injection
Sponsor Name	Sun Pharma Global FZE
Sponsor Address	Office # 43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U.A.E
US Agent (if applicable)	Robert Kurkiewicz Sun Pharmaceutical industries Ltd. (C/O Caraco)
US Agent Address	1150 Elijah Mccoy Drive, Detroit, MI 48202
Electronic Submission	☒ Yes ☐ No
PDUFA Due Date Action Goal Date	This is a drug shortage product, therefore the Action Goal Date is as soon as possible
OSI Review Requested By	Dale P. Conner, Pharm.D.

Inspection Request Detail (All fields should be fill out completely)			
Study #1			
Study Number	PKD_09_030		
Study Title	Fed		
Study Type	☒ In vivo BE	☐ In vitro BE	☐ Permeability ☐ Others (specify)
☒ Inspection Request - Clinical Site		☐ Inspection Request - Analytical Site	
Facility #1 Name: Dr. G. Vishwanathan Speciality Hospitals Address: #27, Babu road Trichy, Tamilnadu (Tel) (Fax)		Facility #1 Name: Address: (Tel) (Fax)	
Clinical Investigator:		Principal Analytical Investigator:	
(email)		(email)	
Facility #2 Name: (if applicable) Address: (Tel) (Fax) Clinical Investigator:		Facility #2 Name: (if applicable) Address: (Tel) (Fax) Principal Analytical Investigator:	
(email)		(email)	
Check one: ☒ Routine inspection ☐ For cause		Check one: ☐ Routine inspection ☐ For cause	
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>			
☒ Study Report: (location, eg., 5.3.1.2)		☒ Validation Report: (eg., 5.3.1.2)	
		☒ Bioanalytical Report: (eg., 5.3.1.4)	

Study #2				
Study Number	DOX/003/08			
Study Title	Pilot Fed			
Study Type	☒ In vivo BE	☐ In vitro BE	☐ Permeability	☐ Others (specify)
☒ Inspection Request - Clinical Site			☐ Inspection Request - Analytical Site	
Facility #1 Name: Same as above Address: (Tel) (Fax)			Facility #1 Name: Address: (Tel) (Fax)	
Clinical Investigator: (email)			Principal Analytical Investigator: (email)	
Facility #2 Name: (if applicable) Address: (Tel) (Fax) Clinical Investigator: (email)			Facility #2 Name: (if applicable) Address: (Tel) (Fax) Principal Analytical Investigator: (email)	
Check one: ☐ Routine inspection ☐ For cause			Check one: ☒ Routine inspection ☐ For cause	
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>				
☒ Study Report: (location, eg., 5.3.1.2)			☒ Validation Report: (eg., 5.3.1.2) ☒ Bioanalytical Report: (eg., 5.3.1.4)	

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

I. Appendix

Specific Items To be Addressed During the Inspection

The Division of Bioequivalence I (DBI) is requesting new sites inspection for the clinica sites:

1. Dr. G. Vishwanathan Speciality Hospitals
#27, Babu road, Trichy, Tamilnadu- 620 008, India

(In the review of the original submission it was mistakenly stated that it's pending a new site OSI inspection for this clinical site. However there is no history of OSI inspection for this site. Therefore we are requesting an inspection of this site in addition to the sites requested previously on 2/26/2012 for this same ANDA 203263)

Please note that this ANDA falls into the Drug Shortage expedited review category.

Please see Suman Dandamudi's review checked into DARRTS on 7/20/2012 for more details on this inspection request.

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/s/

TERESA V RAMSON
07/23/2012

DALE P CONNER
07/24/2012

Telephone Fax

ANDA 203263

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7620 Standish Place
Rockville, MD 20855
Angela.payne@fda.hhs.gov



TO: Sun Pharma Global FZE

TEL: 313-556-4105

ATTN: Robert Kurkiewicz, Sun Pharmaceutical
Industries

FAX: 248-926-0231

FROM: Angela Payne

Dear Applicant:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Doxorubicin Hydrochloride liposome Injection.

Pages (including cover): 3

ee attached labeling comments.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

***Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855***

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

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**REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number:	203263	Date of Submission:	6/16/2011
Applicant's Name:	Sun Pharma Global FZE		
Established Name:	Doxorubicin Hydrochloride liposome Injection,; 2 mg/mL ; 20 mg/10 mL and 50 mg/ 25 mL) SDV.		

LABELING COMMENTS:

1. **CONTAINER:** (2 mg/mL: 10 mL and 25 mL)
 - a. Add "Must be diluted" to the main panel prior to "for intravenous...."
 - b. Please add "cytotoxic agent".
 - c. This product is light sensitive, please add "Retain vial in carton until time of use"
 - d. Relocate the refrigerate statement to the main panel as seen with the reference product.
 - e. Place "LIPOSOMAL FORMULATION. DO NOT SUBSTITUE" in large red shaded box and place prior to the route of administration statement on the main panel.
 - f. Please use color schemes that are similar to the reference listed drug's color scheme to differentiate your product strengths. We note this color scheme should be different than the non-liposomal (regular injection) product that is on the market.
 - g. Please provide the reference product labels that properly depict the color scheme for comparison with your label.
2. **CARTON (1s):** See comments under CONTAINER.
3. **PROFESSIONAL INSERT:**
 - a. GENERAL COMMENTS- Please retain same table numbering system that appears in the reference listed drug's labeling. (example... your table 4 is numbered table 5 in the RLD labeling. Renumber your tables.
 - b. DESCRIPTION, Section 11 - "...30 mL" should read "...25 mL". Do not include the size of the vial but rather the fill volume which is " 25 mL".

- c. HOW SUPPLIED section.... Revise the Each 30 mL vial contains 50 mg doxorubicin... to Each 25 mL vial containers.....[do not use the vial size]

Revise your labels and labeling, as instructed above, and submit final print electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or if appropriate your last submission) with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JOHN F GRACE
07/23/2012
for Wm Peter Rickman

Electronic Log Book

Electronic Log Book ID 2434
Contact: Sun Pharmaceutical Industries Ltd.
Contact Person: Robert Kurkiewicz

Reason: Outgoing, FDA Request for Information
Contact Type: Email

Category: ANDA
ANDA/Control/Protocol #: 203263

FDA Contact: Teresa Ramson

Contact Time and Date 6/25/2012 at 2:44:52 PM

Subject: Bioequivalence

Query

Please see attached for additional telephone amendment request for ANDA 203263, Doxorubicin. As usual, please respond to me via email or fax within 7 to 10 business days and also send in a formal copy as well.

I. We are requesting additional comparative in vitro testing using one of our originally recommended methods (described below).

Apparatus: Circulating water bath
Medium: 98% FBS containing 80 mM ammonium chloride, pH 6.0
Temperature: 47 ± 0.5 C
Volume: 3 mL
Time Point: 0, 0.5, 1, 2, 3, 4 and 5 hrs

Procedure:

1. The sample size should be 3 mL, i.e., 30 L of the drug product should be added to 2.97 mL of the FBS containing 80 mM of ammonium chloride at pH 6.0.
2. Adjustment to pH 6.0 should be done during the reagent preparation and again after adding the drug product.
3. For each time point, a separate tube of sample should be used.
4. There should be no agitation during sample incubation. However, at the end of incubation, the sample tubes should be mixed well prior to removing each aliquot for further analysis.
5. At the end of incubation, the sample tubes should be placed on ice for at least 5 minutes before sample analysis.

We are aware that you have limited supply of RLD product and these lots might have been expired at this time. However it is important that we obtain the comparative profile of two products using this method for our information purpose.

II. In the amendment dated April 9, 2012, you have submitted

the stability testing results of doxorubicin drug substance in FBS medium, pH 6.5 at 47C. Please conduct additional stability testing study of drug substance in the FBS medium (98% FBS containing 80 mM ammonium chloride), pH 6.0 at 47C.

Response

The firm was asked to respond within 7 to 10 business days.

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/s/

TERESA V RAMSON
06/25/2012

Electronic Log Book

Electronic Log Book ID 2426
Contact: Sun Pharma Global FZE
Contact Person: Robert Kurkiewicz

Reason: Outgoing, FDA Request for Information
Contact Type: Email

Category: ANDA
ANDA/Control/Protocol #: 203263

FDA Contact: Teresa Ramson

Contact Time and Date 6/21/2012 at 9:52:38 AM

Subject: Bioequivalence

Query
Hello,

Please respond to the following "Telephone Amendment" request within 7 to 10 business days for ANDA 203263, Doxorubicin hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL.

The in vitro release testing conducted using your own proposed method, (b) (4)

(b) (4) Please submit the following:

Any reference such as scientific literature or your in-house studies to support the (b) (4)

(b) (4) .

Optimization study for (b) (4)

Validation data to demonstrate (b) (4)

You can send the response via email or fax to me then send in a formal copy.

Thanks,

Teresa

Response

The firm was requested to respond within 7 to 10 days.

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/s/

TERESA V RAMSON
06/21/2012

Electronic Log Book

Electronic Log Book ID 2168
Contact: Sun Pharma Global FZE
Contact Person: Robert Kurkiewicz

Reason: Outgoing, FDA Request for Information
Contact Type: Email

Category: ANDA
ANDA/Control/Protocol #: 203263

FDA Contact: Teresa Ramson

Contact Time and Date 5/3/2012 at 11:29:42 AM

Subject: Bioequivalence

Query

Hi Robert,

Attached please find a telephone amendment request for Sun Pharma's Doxorubicin, ANDA 203263. Please respond to this request within 7 to 10 business days and address it to Bioequivalence. You may fax the response or email it to me, but also send in an official copy.

ANDA No 203263
Drug Name Doxorubicin hydrochloride Liposome Injection
Strength 2 mg/mL, 10 mL and 25 mL
Applicant Sun Pharma Global FZE
Point of Contact Robert Kurkiewicz
Telephone Number 313-556-4105
Fax Number: 248-926-0231
Submission Date June 16, 2011 (Original Submission)
April 05, 2012 (Amendment)

As the Bottle Rotating Apparatus is not an official compendial apparatus, the DBI request the following information for your proposed in vitro drug release (leakage) testing apparatus:

1. Please submit the model and manufacturer of the apparatus. Please also submit the standard operating procedure and detailed information concerning the calibration of the instrument.
2. Please provide the physical descriptions including size, shape, material composition and manufacturer of the 100 mL glass bottles used for in vitro drug release testing.
3. Please provide photographs of your apparatus and bottles.

Response

The firm was requested to respond within 7 to 10 business days.

APPEARS THIS WAY ON
ORIGINAL

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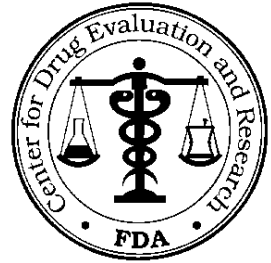
/s/

TERESA V RAMSON
05/04/2012

QUALITY DEFICIENCY - MINOR

ANDA 203263

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



TO: Sun Pharma Global FZE

TEL: 732.839.9400

ATTN: Vincent Andolina

FAX: 732.917.0780

FROM: Frank J. Nice

FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 16, 2011, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL.

Reference is also made to your amendments dated November 3, 2011 and March 20, 2012.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

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7620 Standish Place
Rockville, Maryland 20855***

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ANDA: 203263

APPLICANT: Sun Pharma Global FZE

DRUG PRODUCT: Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

The following are deficiencies related to **Drug Substance**:

1.

(b) (4)

The following are deficiencies related to **Manufacture**:

2.

3.

4.

(b) (4)

Following this page, 4 Pages Withheld in Full as (b)(4)

2.

3.

4.

(b) (4)

Sincerely,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

RADHIKA RAJAGOPALAN

04/23/2012

For Glen Smith,

OSI Consult
Request for Biopharmaceutical Inspections

Date	02/16/2012
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	Sam H. Haidar, Ph.D., R.Ph. Chief, Bioequivalence Investigations Branch Division of Bioequivalence and GLP Compliance Office of Scientific Investigations
Consulting Office/Division	OGD/DB1
Project Manager	Ramson, Teresa
Application Type	PEPFAR? ☐ Yes ☐ No ☐ NDA ☐ BLA ☒ ANDA
Application Number	203263
Drug Product	Doxorubicin hydrochloride Liposome Injection
Sponsor Name	Sun Pharma Global FZE
Sponsor Address	Office # 43, Block Y, SAIF Zone, P. O. Box # 122304, Sharjah, U.A.E
US Agent (if applicable)	Vincent Andolina Sun Pharmaceutical Industries, Inc., 270 Prospect Plains Road Cranbury, NJ 08512
US Agent Address	Sun Pharmaceutical Industries, Inc., 270 Prospect Plains Road Cranbury, NJ 08512
Electronic Submission	☒ Yes ☐ No
PDUFA Due Date Action Goal Date OSI Review Requested By	Dale P. Conner, Pharm.D.

Inspection Request Detail (All fields should be fill out completely)			
Study #1			
Study Number	PKD_09_030		
Study Title	Fed		
Study Type	☒ In vivo BE	☐ In vitro BE	☐ Permeability ☐ Others (specify)
☒ Inspection Request - Clinical Site		☐ Inspection Request - Analytical Site	
Facility #1 Name: NRR Hospital Address: Chikkasandra, Bangalore-560090 (India) (Tel) (Fax)	Facility #1 Name: Address: (Tel) (Fax)		
Clinical Investigator: (email)	Principal Analytical Investigator: (email)		
Facility #2 Name: (if applicable) Address: (Tel) (Fax) Clinical Investigator: (email)	Facility #2 Name: (if applicable) Address: (Tel) (Fax) Principal Analytical Investigator: (email)		
Check one: ☒ Routine inspection ☐ For cause	Check one: ☐ Routine inspection ☐ For cause		
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>			
☒ Study Report: (location, eg., 5.3.1.2)	☒ Validation Report: (eg., 5.3.1.2) ☒ Bioanalytical Report: (eg., 5.3.1.4)		

Study #2				
Study Number	FDD-02/10-11/001			
Study Title	In-Vitro Liposome Size Distribution Testing Site			
Study Type	☐ In vivo BE	☒ In vitro BE	☐ Permeability	☐ Others (specify)
☐ Inspection Request - Clinical Site		☒ Inspection Request - Analytical Site		
Facility #1 Name: (or indicate if same as above) Address: (Tel) (Fax)	Facility #1 Name: Sun Pharmaceutical India Ltd. Address: Halol-Baroda Highway Halol-389350 Gujarat India (Tel) (Fax)			
Clinical Investigator: (email)	Principal Analytical Investigator: (email)			
Facility #2 Name: (if applicable) Address: (Tel) (Fax) Clinical Investigator: (email)	Facility #2 Name: (if applicable) Address: (Tel) (Fax) Principal Analytical Investigator: (email)			
Check one: ☐ Routine inspection ☐ For cause	Check one: ☒ Routine inspection ☐ For cause			
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>				
☒ Study Report: (location, eg., 5.3.1.2)		☒ Validation Report: (eg., 5.3.1.2) ☒ Bioanalytical Report: (eg., 5.3.1.4)		

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

I. Appendix

Specific Items To be Addressed During the Inspection

The Division of Bioequivalence I (DBI) is requesting new sites inspection for the clinical and analytical sites:

1. DB I requests new-site inspection for NRR Hospital, Bangalore India.
2. For in vitro liposome size distribution testing, the site was Sun Pharmaceutical India Ltd. Halol-Baroda Highway, Halol-389350 Gujarat India. This site has not been inspected for such testing. Therefore, the DB I requests a routine OSI inspection for this site.

Please note that this ANDA falls into the Drug Shortage expedited review category.

Please see Shrinivas Neurkar's review checked into DARRTS on 2/16/2012 for more details on this inspection request.

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/s/

TERESA V RAMSON
02/16/2012

DALE P CONNER
02/16/2012

BIOEQUIVALENCE AMENDMENT

ANDA 203263

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Sun Pharma Global FZE

TEL: 313-556-4105

ATTN: Robert Kurkiewicz

FAX: 248-926-0231

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on June 16, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Doxorubicin hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ page(s). This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

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Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810*

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

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ANDA: 203263
APPLICANT: Sun Pharma Global FZE
DRUG PRODUCT: Doxorubicin Hydrochloride Injection, Liposomal,
2 mg/mL (10 mL and 25 mL)

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The deficiencies below have been identified.

Bioanalytical Report:

1. You have provided multiple summary tables of calibration curve (CC) and quality control (QC) data for the analytes of free doxorubicin and liposome encapsulated doxorubicin. Please provide justification for submitting multiple summary tables, instead of one overall summary of the interday accuracy and precision of all the CC's and QC data from the study sample analyses.

In Vitro Liposome Size Distribution Testing

2. Please submit in vitro liposome size distribution testing data in **electronic SAS Transport files** using the following table format for verification analysis by the DBE.

PRODUCT	LOT	VIAL	D10	D50	D90	SPAN
TEST	1234	1				
		2				
		3				
		4				
		5				
		6				
		7				
		8				
		9				
		10				

3. It did not appear that you conducted cross-validation study for confirmation of the extraction method to estimate only liposomal doxorubicin in the presence of free doxorubicin. Please provide the cross-validation data.

Dissolution Testing

4. You have submitted *in vitro* drug release testing data using your proposed testing method with bottle rotating apparatus. However, currently the DBE does not encourage the use of non-compendial apparatus in *in vitro* drug release testing. Since the bottle rotating apparatus is not considered a compendial apparatus, your proposed method is considered incomplete at this time. Please submit all detailed information concerning the development, optimization and validation of your proposed test method for a full evaluation.

5. In addition, please conduct the following *in vitro* drug release testing. Please note that this recommended method does not employ any dissolution apparatus.

The comparative testing should be conducted on the test and reference product, using one dosage unit (vial) (10 mL of 2 mg/mL) per replicate and six samples taken per unit for six different time points: Six samples of 1 mL of the vial content should be transferred to six separate glass tubes containing the medium of 98% fetal bovine serum with 80 mM NH₄Cl at pH 6.0, to obtain the final sample volume of 100 mL. The resulting drug concentration should be 20 microgram/mL of liposomal doxorubicin. These glass tubes should be incubated at 47°C without agitation. From these six glass tubes, the amount of doxorubicin released from the liposome should be determined at the following six time points: 0 hr, 0.5 hr, 1 hr, 2 hrs, 3 hrs and 4 hrs. The testing should be replicated for 12 dosage vials per each test and the reference drug product.

The individual percent doxorubicin release data from each vial at each time point should be submitted, as well as the mean data from 12 vials at each time point for each product (% mean and % CV) over the period of 0 to 4 hours for the test and RLD from 12 dosage units.

Please submit a complete validation data and report for the above-recommended test method.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

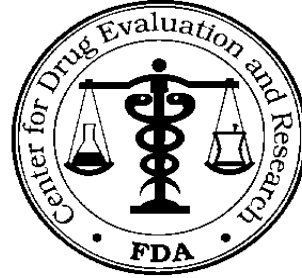
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/s/

DALE P CONNER
02/16/2012

FAX – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855 (240-276-8408)



TO: Robert Kurkiewicz	FROM: Bonnie McNeal
Sun Pharmaceutical Industries Ltd	Microbiology Project Manager
PHONE: 313-556-4105	PHONE: (240) 276-8831
FAX: 248-926-0231	FAX: (240) 276-8725

Total number of pages, excluding this cover sheet: _____

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Rockville, Maryland 20855**

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Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for **ANDA 203263 for Doxorubicin Hydrochloride Liposomal Injection, 2 mg/mL**. The submission reviewed was submitted on June 16, 2011. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter. Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application. If you have questions, feel free to call Bonnie McNeal or Mark Anderson.

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LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 203263 APPLICANT: Sun Pharmaceutical Industries, Inc.

DRUG PRODUCT: Doxorubicin Hydrochloride Liposomal Injection

A. Microbiology Deficiencies:

1.

2.

3.

4.



(b) (4)

5.

6.

(b) (4)

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

(b) (4)

Please clearly identify your amendment to this facsimile as “RESPONSE TO MICROBIOLOGY DEFICIENCIES”. The “RESPONSE TO MICROBIOLOGY DEFICIENCIES” should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

CDR Paul Dexter, M.S.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

PAUL L DEXTER
02/08/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20852

To:	John R Peters, M.D., Acting Director for Division of Clinical Review, Office of Generic Drugs
From:	Suman Dandamudi, Reviewer, Team 8, Division of Bioequivalence I, Office of Generic Drugs
Through:	Hoainhon Nguyen, Acting Deputy Director, Division of Bioequivalence (DBE) 1, Office of Generic Drugs
Re:	Clinical Consultation Request on Death and other Serious Adverse Events Reported in the Bioequivalence (BE) Study of ANDA 203263 Sun's Doxorubicin Hydrochloride Liposome Injection – Expedited due to Drug Shortage

Introduction:

Currently, Doxorubicin Hydrochloride Liposomal Injection is a medically necessary drug that is in serious short supply. The RLD product, Doxil, the only approved doxorubicin HCl liposomal injection product, is currently not being manufactured due to manufacturing issues, and its supply is very limited. The Drug Shortage Program (DSP) is now considering importation of Sun's Doxorubicin HCl Liposomal Injection, which is the subject of the only pending ANDA for the drug product. In response to the drug shortage, the FDA uses enforcement discretion for the limited importation of the foreign version until the shortage of the FDA-approved drug is resolved. As a part of the consideration for importation of Sun's product, the DSP has asked all OGD review divisions to conduct a preliminary review of the data submitted in ANDA 203263 to identify any major quality or BE problems or concerns which may affect the importation decision (Please see the email concerning the DSP's request). The deadline for the responses by the review divisions is January 4th, 2011.

Sun Pharmaceuticals submitted ANDA 203263 that contains a bioequivalence (BE) study (administered intravenously while a normal low fat breakfast was served) comparing the test product, Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL (50 mg/ m² dose), to the corresponding reference product, Ortho Biotech's Doxil® Liposome Injection, 2 mg/mL (50 mg/ m² dose). ANDA 203263 was accepted for filing on December 12th, 2011. Although the bioequivalence review has begun immediately following the ANDA filing, due to the complexity of the drug dosage form which is also the first generic version to be reviewed by the DBE, the full BE review has not yet been completed at this time, and is ongoing. A preliminary bioequivalence review has not identified any obvious bioequivalence-related issues. However, based on the clinical report of the study, some serious adverse reactions including one death were reported. To be sure that these serious adverse reactions are not directly related to the test formulation and that

they are not considered as a major safety concern that could affect the importation decision, we request your expedited clinical evaluation of these AEs.

Issue:

DBE requests your opinion on one death that occurred during the study. In addition, DBE also requests your opinion on the other serious adverse events reported for the BE study of the above ANDA. This is a two-way crossover study. A total of 54 patients with ovarian cancer received at least one dose of the study medication. Of these, eleven patients (1, 3, 4, 5, 15, 24, 44, 49, 50, 59 and 62) experienced serious adverse events and were dropped from the study. One death (patient 50) occurred during the study. The adverse events that occurred for the other patients than mentioned above were mild to moderate in intensity.

As per the firm, "Patient 50 received test formulation, Liposomal Doxorubicin on Nov 23, 2010 and checked out on [REDACTED] (b) (6). At discharge her condition was normal. Her vitals (pulse rate 78/min, BP 100/70) and CBP (Hb: 9.5 g/dL, total WBC count= 5600 cells/cumm, platelet count= 2.95 lacs/cmm) were normal. Patient was called for cycle II on Dec 20, 2010. Through telephone patient attender informed that she was passed away in her sleep on [REDACTED] (b) (6) at her residence". In the Case report Form it was written that the "***Patient 50 was diagnosed with cancer of bilateral ovaries in Feb 2010. She had received six cycles of adjuvant chemotherapy (Carboplatin Injection 450 mg and Paclitaxel Injection 250 mg). Her last CT was on Oct 13, 2010. The disease was progressive after using platinum based chemotherapy***". This serious adverse event was judged unrelated to Doxorubicin HCl Liposome Injection (SPARC Ltd.), communicated to sponsor and ethics committee on Dec 21, 2010 (see the attached CRF for patient 50) Since the serious adverse event (death) occurred in patient 50 was after the administration of the test product, DBE is concerned about the safety of the test formulation.

The other patients that experienced serious adverse events were 1, 3, 4, 5, 15, 24, 44, 49, 59 and 62. Patients 1, 3, 4, 5, 15, 44, 50 experienced the serious AEs when the test formulation was administered, and patients 24, 49, 59 and 62 experienced the serious AEs while the reference formulation was administered. The serious adverse events experienced by the patients after the administration of the test formulation were dyspnoea, hypertension, anemia, chest pain, hyperhidrosis, loss of consciousness, pulse abnormal, bradycardia, hypotension, oral mucositis and fatigue. The serious adverse events experienced by the patients after the administration of the reference formulation were chest pain, breathlessness, bradycardia, tachycardia, sweating, giddiness, and thrombocytopenia.

Subjects with Serious Adverse Events:

Patient 1: Patient was administered Doxorubicin HCl liposome injection (A) diluted in 5% Dextrose as per study protocol. The study drug infusion was started at 10:16 am (7th April 2010) with a flow rate, infusing 1mg/min doxorubicin as per study protocol. After the start of infusion, patient developed severe breathlessness at 10:16 am (7th April 2010).

The study drug administration was discontinued immediately and patient was shifted to Intensive care Unit. The patient was dropped from the study. Patient's vital recordings were pulse: 118/min, B.P: 180/110Hg, SPO2: 82% (without O2), Patient was under observation for rest of the day and patient improved from her condition. Adverse event was resolved completely at 11:45 am on 7th April 2010 and patient was discharged at 12:30 pm on (b) (6). The firm stated that this serious adverse event was probable related to Doxorubicin HCl liposome injection (SPARC Ltd), communicated to sponsor on 7 April 2010 and ethics Committee on 7 April 2010.

Patient 3: The patient was administered with test product Doxorubicin HCl liposome injection (2 mg/ml). The infusion started at 9:40 am on 14th July 2010. On (b) (6) (b) (6) the patient complained of severe weakness and fatigability, oral mucositis and decrease oral intake. Her vital examinations were normal. She was admitted to the hospital and given intravenous fluids (Dextrose saline with multivitamin and normal saline), folic acid and treatment for mucositis. Adverse event was resolved completely on 28th August 2010, by 10.30 am. The firm stated that this serious adverse event was probably related to Doxorubicin HCl liposome injection (SPARC Ltd), communicated to sponsor on and ethics Committee on 26th August 2010. As the adverse event was resolved, the patient was not dropped from the study.

Patient 4: The patient was administered with test product Doxorubicin HCl liposome injection (2 mg/ml). The infusion started at 10:04 am on 7th August 2010. Patient developed anemia on 27th August 2010. Patient was treated with Granulocyte Colony Stimulating Factor (G-CSF) and Packed Cell Volume (PCV) as her total blood count was decreased. The firm stated that on 14th September 2010, the adverse event was resolved. However the adverse event was recorded as SAE and patient was dropped from the study on 15th September 2010. The firm stated that this serious adverse event was probably related to Doxorubicin HCl liposome injection (SPARC Ltd), communicated to sponsor on 15 September 2010 and ethics Committee on 27 August 2010.

Patient 5: The patient was administered with test product Doxorubicin HCl liposome injection (2 mg/ml). The infusion started at 9:45 am on 15th October 2010. After approximately 4 minutes patient developed acute breathlessness and tachycardia, hence the infusion was stopped immediately. Patient's pulse was 120/min, B.P: 150/100 mmHg, SpO2: 85%. Patient was treated with O 2 inhalation and hydrocortisone sodium succinate Injection. The patient was then normal and well. The adverse event was recorded as SAE and patient was dropped from the study. The firm stated that this serious adverse event was probably related to Doxorubicin HCl liposome injection (SPARC Ltd), communicated to sponsor on 15 October 2010 and ethics Committee on 15 October 2010.

Patient number 15: Patient was dosed 75.69 mg of doxorubicin HCl liposome dose diluted in 250ml of 5% dextrose USP. The infusion rate was 1mg/min for first 10 minutes. Infusion started at 09:45 hrs at the rate of 228.18 ml/hr. After two minutes of infusion, the patient complained of chest pain and infusion was stopped immediately. The Investigator observed sweating, loss of consciousness, and nonpalpable pulse, DC shock was administered by an external defibrillator and Dexamethasone Injection (8mg), Hydro

cortisone Injection(100mg), Rantac Injection (50 mg) were administered intravenously. Patient regained consciousness and her condition improved after 3 minutes. She was kept under observation and her general condition gradually improved .She was evaluated and discharged on [REDACTED] (b) (6) At the time of discharge, patient condition was normal. The event was judged possibly related to Doxorubicin HCl liposome injection (SPARC Ltd) due to the fact that the patient had no prior history or risk factors for cardiac disease, was completely asymptomatic and ambulatory prior to treatment in this study. This event was considered as a serious adverse event, communicated to Sponsor and Ethics Committee on May 27, 2010.

Patient 44: Patient was dosed 83.36 mg of Doxorubicin HCl Liposome dose diluted in 250ml of 5% dextrose USP. The infusion was started at 10:00 hrs at the rate of 3.48 ml/min after pre-medicated with Dexamethasone Injection 8 mg IV and Granisetron Injection 2 mg IV. A few minutes after start of infusion, the patient complained of chest pain and infusion was stopped immediately. The patient had bradycardia (pulse rate 38/minute), and hypotension (blood pressure systolic 90 mm Hg, diastolic 60 mm Hg), and the respiratory rate was 16/minute. Atropine Injection (2 ml), Hydrocortisone Sodium Injection (100 mg) and Adrenaline Bitrate Injection (1 mg) were administered intravenously. Patient regained consciousness after 21 minutes and was kept under observation. Her general condition gradually improved. She was discharged from the hospital on [REDACTED] (b) (6) at 11:35 hrs. At the time of discharge, her vital parameters and general condition were within normal limits. This serious adverse event was judged possibly related to Doxorubicin HCl Liposome injection (SPARC Ltd), communicated to sponsor and ethics Committee on 24 Nov 2010.

Patient 24: Patient was pre-medicated with Dexamethasone Injection 8 mg IV and Granisetron Injection 2 mg IV before start of infusion. Infusion started 10:00 hrs and completed at 11:04 hrs. The subject was planned to receive Liposomal Doxorubicin HCl on 19 October 2010 for period II. But check in lab report on [REDACTED] (b) (6) showed her platelet count to be very low (-22000/mm³). It was considered as severe thrombocytopenia (low platelet count). The patient was hospitalized and kept under strict surveillance. Patient treated with intravenous Filagrastim Injection (300 mcg) on date 21, 24 & 26 Sep 2010 and also received 6 unit of platelet rich plasma on date 20 Sep 2010. At the time of discharge, her vital parameters and general condition was normal. This event was initially considered as Adverse Event from 19 Oct 2010, but due to prolonged hospitalization it is considered as SAE and resolved on 10 Nov 2010. This serious adverse event was judged unrelated to Doxil® Injection, 2 mg/ml (50 mg/m² dose) Doxil®, communicated to sponsor and ethics committee on 13 Nov 2010.

Patient 49: Patient was dosed 66 mg of Doxil® Injection diluted in 250ml of 5% dextrose USP. Infusion was started at 10:00 hrs at the rate of 4.8 ml/min after premedicated with Dexamethasone Injection 8 mg IV and Granisetron Injection 2 mg IV before start of infusion. Immediately after start of infusion, patient complained of chest pain and breathlessness. Infusion was stopped immediately – after 1.56 min of start of infusion. Investigator also noticed sweating and tachycardia. On examination patients pulse was 86, blood pressure was Systolic 110 (mm/Hg), diastolic 70(mm/Hg),

respiratory rate was 20 /min. Patient was treated with intravenous injections of Dexamethasone (8 mg), Hydrocortisone (100 mg), Ranitidine (50 mg), Atropine (0.6 mg) and Chlorpheniramine maleate (45.5 mg). Patients condition improved with this treatment within next 30-min. She was kept under observation and was discharged on (b) (6). At the time of discharge, her vital parameters and general condition were within normal limits. This serious adverse event was judged possibly related to Doxil® Injection, communicated to sponsor on 09 Nov 2010 and ethics committee on 10 Nov 2010.

Patient 59: Patient was dosed 77.52 mg of Doxil® diluted in 250 ml of 5% dextrose USP. Infusion was started at 10:00 hrs at the rate of 3.72 ml/min after pre-medication with Dexamethasone Injection 8 mg IV and Granisetron Injection 2 mg IV. Two minutes after start of infusion, the patient complained of chest pain, breathlessness, feeling dizzy, and therefore infusion was stopped immediately. On examination the pulse rate was 28/min and respiratory rate was 14/min. Atropine Sulfate Injection 0.6 mg/ ml, Hydrocortisone Sodium Injection 100 mg and Pheniramine Injection Maleate 44.50 mg/2 ml were administered intravenously immediately. Patient regained consciousness after 3 minutes and was kept under observation. Her general condition gradually improved. She was discharged from the hospital on (b) (6) at 19:10 hrs. At the time of discharge, her vital parameters and general condition were within normal limits. This serious adverse event was judged possibly related to Doxil® Injection, communicated to sponsor and ethics committee on 30 Nov 2010.

Patient 62: Patient was dosed 83.53 mg of Doxil® diluted in 250 ml of 5% dextrose USP. Infusion was started at 10:45 hrs at the rate of 3.49 mL/min after pre-medication with Dexamethasone Injection 8 mg IV and Granisetron Injection 2 mg IV. Immediately after start of infusion, patient complained of chest pain and breathlessness. Infusion was stopped after 1.39 min of start of infusion. Investigator also noticed sweating and tachycardia. On examination pulse rate was 92/min, blood pressure systolic was 100 mm Hg and diastolic was 70 mm Hg, and respiratory rate was 20/min. Intravenous injection of Dexamethasone (8 mg), Hydrocortisone (200 mg), Ranitidine (50 mg) and Chlorpheniramine maleate (45.5 mg) were administered. Patient's condition improved in next 45 min. She was kept under observation and discharged from the hospital on (b) (6). At the time of discharge, her vital parameters and general condition were within normal limits. This serious adverse event was judged possibly related to Doxil®, communicated to sponsor on 14 Dec 2010 and ethics Committee on 15 Dec 2010.

Because of the death and the other serious adverse events experienced by the patients after the administration of test formulation during the fed BE study, the DBE is concerned about the safety of the test formulation.

Please find the Case Report Forms (CRF) for the above patients in Module 5.3.1.2.24 of the EDR submission for ANDA 203263.

Serious Adverse Events:

Patient Number	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	Cause	Action Taken	Toxicity Grade (I-VCTC Version 4)
		Investigators Term	Preferred Term									
1	A	Breathlessness (Dyspnea)	Dyspnoea	07/04/10	10:16 am	10:16 to 10:17 am 07/04/10	07/04/10 11:45 am	3	1	2	4,5	4
		Hypertension	Hypertension									1
4	A	Anemia	Anaemia	27/08/10	03:40 pm	10:04 to 11:08 am 07/08/10	08/09/10 05:20 pm	3	1	2	4,5	3
5	A	Dyspnea	Dyspnoea	15/10/10	09:45 am	09:45 to 09:49 am 15/10/10	15/10/10 09:58 am	1	1	3	4,5	1
		Hypertension	Hypertension							2		2
15	A	Chest pain	Chest pain	27/05/10	9:47 am	09:45 to 09:47 am 27/05/10	27/05/10 09:50 am	3	1	1	4,5	3
		Sweating	Hyperhidrosis									
		Loss of consciousness	Loss of consciousness									
		Pulse abnormal	Pulse abnormal									
3	A	Oral mucositis	Oral mucositis	(b) (6)	01:10 pm	09:40 to 10:41 am 12/08/10	28/08/10 02:30 pm	1	1	3	4	1
		Fatigue	Fatigue		01:00 pm		28/08/10 10:30 am	3	3	2		2
24	B*	Thrombocytopenia	Thrombocytopenia	19/10/10	08:21 am	10:00 to 11:04 am* 21/09/10	10/11/10 10:08 am	3	1	4	4,5	4
44	A	Discomfortness all over body	Discomfort	24/11/10	10:32 am	10:30 to 10:32 am 24/11/10	(b) (6) 11:35 am	3	NA	3	4, 5	3

		Bradycardia	Bradycardia									
		Hypotension	Hypotension									
		Chest discomfortness	Chest discomfort									
49	B	Chest pain	Chest pain	09/11/10	10:02 am	10:00 to 10:02 am 9/11/10	09/11/2010 10:23 am	3	NA	3	4,5	3
		breathlessness	Dyspnoea									
50	A	Cancer with bilateral ovaries	Ovarian cancer	(b) (6)	NA	09:30 to 10:31 am 23/11/10	#	3	NA	4	5	5
59	B	Breathing difficulty	Dyspnoea	30/11/10	09:30 am	09:30 to 09:32 am 30/11/10	(b) (6) 07:10 pm	3	NA	3	4,5	3
		Giddiness	Giddiness									
		Discomfortness all over body	Discomfortness all over body									
		Bradycardia	Bradycardia									
62	B	Chest pain	Chest pain	14/12/10	10:47 am	10:45:00 to 10:46:39 am 14/12/10	14/12/10 11:38 am	3	NA	3	4,5	3
		Breathlessness	Dyspnoea									
		Tachycardia	Tachycardia									
		Sweating	Hyperhidrosis									

Treatment: A = Test, B = Reference

Intensity : 1 = Mild, 2 = Moderate, 3 = Severe

Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4 = Medication, 5 = Withdrawn

Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous.

Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.

Toxicity Grade (I-VCTC Version 4) 1= Mild, 2 = Moderate, 3 = Severe, 4 = Life threatening or disabling, 5 = Death related to AE.
Version 4)

Other Adverse Events

Subject Number	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	Cause	Action Taken	Toxicity Grade (1-V/CTC Version 4)
		Investigators Term	Preferred Term									
4	A	Oral mucositis	Stomatitis	14/08/10	11:20 am	10:04 to 11:08 am 07/08/10	19/08/10 02:20 pm	1	1	2	4	1
		Vomiting	Vomiting						2	2		
		Body ache	Pain						3	4		
		Epigastric burning	Dyspepsia						1	2		
5	A	Dyspnea	Dyspnoea	15/10/10	09:45 am	09:45 to 09:49 am 15/10/10	15/10/10 09:58 am	1	1	3	4,5	1
		Hypertension	Hypertension						2	2		2
6	A	Observed Anaphylactic reaction	Anaphylactic reaction	08/04/10	09:31 am	09:30 to 09:31 am 08/04/10	08/04/10 10:30 am	1	1	3	4,5	2
26	B	Anaemia	Anaemia	02/11/10	03:00 pm	09:45 to 10:48 am 23/10/10	19/11/10 08:30 pm	1	3	2	1	1
		Leucopenia	Leukopenia	06/11/10	03:00 pm							
27	A	Anaemia	Anaemia	03/11/10	03:00 pm	10:00 to 11:00 am 30/10/10	14/03/11 01:20 pm	1	3	2	1	2
28	B	Generalized body ache	Pain	10/11/10	08:00 am	10:35 to 11:36 am 08/11/10	12/11/10	1	3	3	1	2
		Leucopenia	Leukopenia	30/11/10	04:00 pm		06/12/10 09:45 am			1		1

29	B	Leucopenia	Leukopenia	25/11/10	06:00 pm	10:55 to 11:56 am 15/11/10	23/03/11 NA	1	3	2	1	1, 2, 3
		Thrombocytopenia	Thrombocytopenia	29/11/10	07:00 pm		07/12/10 04:00 pm					1
		Neutropenia	Neutropenia				12/12/10 04:00 pm					2
30	B	Thrombocytopenia	Thrombocytopenia	14/01/11	NA	11:00 to 12:01 pm 21/12/10	25/01/11 NA	1	1	2	3, 4	2
		Neutropenia	Neutropenia	25/01/11			29/01/11 NA					1
31	A	Vomiting	Vomiting	26/08/10	08:30 pm	11:00 to 11:59	27/08/10	1	2	1	2	2
46	B	Anaphylactic (allergic) reaction	Anaphylactic reaction	30/10/10	10:00:30 am	10:00:00 to 10:00:30 am 30/10/10	30/10/10 10:05:02 am	3	1	1	4, 5	3
47	A	Gastritis	Gastritis	17/11/10	05:50 am	10:45 to 11:46	17/11/10 12:06 pm	2	2	4	4	2
54	B	Breathing difficult	Dyspnoea	27/12/10	09:42 am	09:40 to 09:42 am and 10:05 to 11:06 am 27/12/10	27/12/10 09:48 am	2	1	2	4	2
		Giddiness	Dizziness				27/12/10 09:50 am					
		Low pulse	Heart rate decreased				27/12/10 09:45 am					
Treatment: A = Test, B = Reference												
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe												
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4 = Medication, 5 = Withdrawn												
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous.												
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.												
Toxicity Grade (I-VCTC Version 4) 1= Mild, 2 = Moderate, 3 = Severe, 4 = Life threatening or disabling, 5 = Death related to AE. Version 4)												

Period II

Subject Number	Drug Treatment	Adverse Events		Onset Date	Onset Time	Time of Dose/Date	Resolve Date/Time	Intensity	Occurrence	Cause	Action Taken	Toxicity Grade (I-VCTC Version 4)
		Investigators Term	Preferred Term									
13	B*	Total WBC count less	White blood cell count decreased	16/06/10	06:12 pm	09:30 to 10:31 am* 20/05/10	18/06/10 7: 21 pm	1	1	2	2	1
18	A*	Anaemia	Anaemia	13/08/10	08:30 am	09:30 to 10:31 am* 14/07/10	14/08/10 06:23 pm	1	1	2	4	1
23	A*	Low hemoglobin	Haemoglobin decreased	11/10/10	07:54 pm	09:30 to 10:32 am* 14/09/10	13/10/10 06:36 pm	1	1	2	2,4	1
26	A	Headache	Headache	20/11/10	07:30 pm	09:45 to 10:47 am 20/11/10	20/1 1/10	1	1	2	4	1
		Anaemia	Anaemia	22/11/10	06:00 pm		13/12/10 05:00 pm		3		1	
27	B	Anaemia	Anaemia	29/11/10	07:30 pm	10:00 to 11:00 am 30/11/10	14/03/11 01:20 pm	1	3	2	1	2
		Leucopenia	Leukopenia	14/12/10	04:30 pm		27/12/10 05:00 pm					
28	B*	Anaemia	Anaemia	06/12/10	09:45 am	10:35 to 11:36 am* 08/11/10	AE on-going Lost to follow up	1	3	2	1	1, 2
29	A	Thrombocytopenia	Thrombocytopenia	27/12/10	05:00 pm	10:55 to 11:56 am 13/12/10	05/01/11 1 11:35	1	3	1	1	1
		Hyperpigmentation	Skin hyperpigmentation	29/12/10	11:35 am		07/05/11 1 12:15 pm	1	3	2	1	1
		Neuropathy	Neuropathy peripheral	29/12/10	11:35 am		1	3	2	1	2	
		Neutropenia	Neutropenia	05/01/11	05:00 pm		12/01/11 NA	1	3	1	1	1

30	A	Anemia	Anaemia	13/02/11	NA	11:00 to 12:01 pm 29/01/11	21/02/11	2	NA	3	3,4	2
		Leucocytopenia	Leukopenia					1				1
31	B	Vomiting	Vomiting	22/09/10	05:08 am	11:00 to 11:59 am 20/09/10	22/09/10 06:30 am	2	2	3	2,4	1
		Diarrhoea	Diarrhoea		05:26 am			1	1			
32	B	Vomiting	Vomiting	16/10/10	09:00 pm	11:00 to 12:03 pm 28/09/10	17/10/10 10:30 am	2	3	4	2,3,4	1
		Sore-throat pain	Oropharyngeal pain		10:30 pm		16/10/10 11:45 pm	1	NA			
47	B	Mucositis	Mucosal inflammation	14/12/10	03:00 pm	10:45 to 11:46 am 01/12/10	17/12/10 07:00 am	2	3	4	4	2
48	A	Vomiting	Vomiting	13/12/10	02:40 pm	11:15 to 12:16 pm 04/12/10	13/12/10 04:00 pm	1	1	4	4	1
		Nausea	Nausea				13/12/10 06:00 pm		2			
61	B*	Low hemoglobin level	Haemoglobin decreased	11/01/11	08:24 am	10:30 to 11:31 am* 14/12/10	13/01/11 03:24 pm	1	1	2	4,2	1
Treatment: A = Test, B = Reference												
Intensity : 1 = Mild, 2 = Moderate, 3 = Severe												
Action Taken: 1=None, 2 = Increased Surveillance, 3 = Follow up, 4 = Medication, 5 = Withdrawn												
Occurrence: 1= Single Episode, 2 = Intermittent, 3 = Continuous.												
Cause (Relation to Drug): 1 = Definite, 2 = Probable, 3 = Possible, 4 = Unlikely.												
Toxicity Grade (I-VCTC Version 4) 1= Mild, 2 = Moderate, 3 = Severe, 4 = Life threatening or disabling, 5 = Death related to AE. Version 4)												

Background:

Section I: Drug Product Information

Test Product	Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL
Reference Product	Doxil® Liposomal Injection, 20 mg/10 mL and 50 mg/25 mL
RLD Manufacturer	Ortho Biotech
NDA No.	050718
RLD Approval Date	November 17, 1995 (20 mg/10 mL) June 13, 2000 (50 mg/25 mL)
Indication	Doxil® is indicated • For the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy. • For treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy. • In combination with bortezomib is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

PK/PD Information

Bioavailability	DOXIL displayed linear pharmacokinetics over the range of 10 to 20 mg/m². Disposition occurred in two phases after DOXIL administration, with a relatively short first phase (≈ 5 hours) and a prolonged second phase (≈ 55 hours) that accounted for the majority of the area under the curve (AUC). The pharmacokinetics of DOXIL at a 50 mg/m² dose is reported to be nonlinear. At this dose, the elimination half-life of DOXIL is expected to be longer and the clearance lower compared to a 20 mg/m² dose. The exposure (AUC) is thus expected to be more than proportional at a 50 mg/m² dose when compared with the lower doses.
Food Effect	N/A
Metabolism	Doxorubicinol, the major metabolite of doxorubicin, was detected at very low levels (range of 0.8 to 26.2 ng/mL) in the plasma of patients who received 10 or 20 mg/m ² DOXIL.
Excretion	The plasma clearance of DOXIL was slow, with a mean clearance value of 0.041 L/h/m² at a dose of 20 mg/m². This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24 to 35 L/h/m². Because of its slower clearance, the AUC of DOXIL, primarily representing the circulation of liposome-encapsulated doxorubicin, is approximately two to three orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin HCl as reported in the literature.
Half-life	5 hours (first phase) and 55 hours (second phase)

Drug Specific Issues (if any)	Boxed Warning: WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION 1. The use of DOXIL (doxorubicin HCl liposome injection) may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at a starting dose of 50 mg/m² every 4 weeks. At all cumulative anthracycline doses between 450–500 mg/m² or between 500–550 mg/m², the risk of cardiac toxicity for patients treated with DOXIL was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy. 2. Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. DOXIL should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions. 3. Severe myelosuppression may occur. 4. Dosage should be reduced in patients with impaired hepatic function. 5. Accidental substitution of DOXIL for doxorubicin HCl has resulted in severe side effects. DOXIL should not be substituted for doxorubicin HCl on a mg per mg basis. Doxil is a pregnancy category D drug, can cause fetal harm when administered to a pregnant woman.

Section II: Conclusion:

Considering death occurred for patient 50 is after the administration of the test product, the DBE asks if the serious adverse event associated with the test formulation should be of a safety concern.

Request for Preliminary Reviews by the Drug Shortage Program:

From: Bina, Christine
Sent: Monday, December 19, 2011 5:32 PM
To: Jensen, Valerie E; Saliba, Jouhayna; Dill, Susie; Santiago, Israel; Gould, Catherine; Patel, Has Mukh B; Chidambaram, Nallaperum; Mesmer, Deborah; Delorenzo, Katherine; Hughes, Monica L; Keegan, Patricia; Thakur, Emily; Schmuff, Norman R; Jones, Karen; Gootenberg, Joseph; Stone, Jennifer; Jaworski, David J; Greenberg, Harvey A; Ackerman, Wade; Batista, Huascar R; Fritsch, William; Godwin, Francis; Rose, Merideth; Motta, Rosa; Simmons, Kim-Chi; Webber, Keith; Yu, Lawrence; Shimer, Martin; Conner, Dale P; Nguyen, Hoainhon T; Jetton, Timothy; Zhao, Xiaobin; Arroyo, Rafael E; Tracey, Joseph; Aldridge, Allison; Rajagopalan, Radhika; Bina, Christine
Cc: Koo, Ellen; Peters, John (CDER); Nerurkar, Shriniwas G; Dandamudi, Suman; Smith, Glen J; Snyder, Kerri
Subject: RE: Follow-up Meeting on Possible Importation of Sun's Doxorubicin Liposomal Product

Follow Up Flag: Follow up
Flag Status: Red

I spoke with Sun's US Agent, Bob Kurkiewicz late Friday afternoon to request additional labeling of their Doxorubicin Liposomal product (Lipodox). This labeling has been submitted and is posted at the following link:

\\cdsnas\cder_email_attachments\Drug-Shortage\doxorubicin\Sun\Labeling

Sun is very interested in filling the drug shortage gap and was asking if they could start manufacturing a batch of Doxorubicin Liposomal. I told him I would get back with him after I receive more information, but expected to have a final answer on regulatory discretion the first week in January.

I just wanted to follow up with everyone and ask if there have been any major issues identified with Sun's proposed product?

Thanks,

Christine

From: Bina, Christine
Sent: Friday, December 16, 2011 3:52 PM
To: Bina, Christine; Jensen, Valerie E; Saliba, Jouhayna; Dill, Susie; Santiago, Israel; Gould, Catherine; Patel, Has Mukh B; Chidambaram, Nallaperum; Mesmer, Deborah; Delorenzo, Katherine; Hughes, Monica L; Keegan, Patricia; Thakur, Emily; Schmuff, Norman R; Jones, Karen; Gootenberg, Joseph; Stone, Jennifer; Jaworski, David J; Greenberg, Harvey A; Ackerman, Wade; Batista, Huascar R; Fritsch, William; Godwin, Francis; Rose, Merideth; Motta, Rosa; Simmons, Kim-Chi; Webber, Keith; Yu, Lawrence; Shimer, Martin; Conner, Dale P; Nguyen, Hoainhon T; Jetton, Timothy; Zhao, Xiaobin; Arroyo, Rafael E; Tracey, Joseph; Aldridge, Allison; Rajagopalan, Radhika; Bina, Christine
Cc: Koo, Ellen; Peters, John (CDER); Nerurkar, Shriniwas G; Dandamudi, Suman; Smith, Glen J; Snyder, Kerri
Subject: RE: Follow-up Meeting on Possible Importation of Sun's Doxorubicin Liposomal Product

Thank you all for attending the meeting today to discuss the importation of Sun's Doxorubicin Liposome Injection.

As we discussed:

- Compliance had no concerns with the Holol manufacturing site (noting the April inspection with no issues)
- ONDQA will review the submitted COA, release specs, and test procedures and will work with OGD to discuss any major quality or BE concerns with the submitted ANDA
- Katherine Delorenzo and the Division are reviewing the labeling and the DHPL
- Wade Ackerman is vetting the Orphan Drug Exclusivity issue with OCC
- I am following up with the company to discuss the distribution plan and request a side by side comparison label of the imported product (with the Multiple Myeloma indication included) with Doxil

Please provide your responses by Wednesday January 4th or sooner if possible. Also, let me know if I have missed anything here.

Thanks again for all your efforts!

Christine

~~*~*~*~*~*~*~*~*

The firm submitted a proposed Dear Healthcare Professional letter, Labeling, COA, Release Specs, and Test Procedures for the product. The information can be accessed at the following link :

\\cdsnas\cder_email_attachments\Drug-Shortage\doxorubicin\Sun

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

/s/

SUMAN DANDAMUDI
12/20/2011

SHRINIWAS G NERURKAR
12/20/2011

HOAINHON N CARAMENICO
12/20/2011

ANDA FILING CHECKLIST
(CTD or eCTD FORMAT)
FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 203263
 APPLICANT: SUN PHARMA GLOBAL FZE
 RELATED APPLICATION(S):

DRUG NAME: DOXORUBICIN HYDROCHLORIDE LIPOSOME
 DOSAGE FORM: INJECTION, 2 MG/ML, 10ML AND 25ML (SINGLE DOSE VIAL)

LETTER DATE: **JUNE 16, 2011**
 RECEIVED DATE: JUNE 16, 2011

- P-IV
 FIRST GENERIC
 EXPEDITED REVIEW REQUEST (Approved/Denied)
 PEPFAR

Electronic or Paper Submission: Gateway
 LIPOSOMAL (b)(4) #

Type II DMF# DOXORUBICIN HYDROCHLORIDE

BASIS OF SUBMISSION:

NDA/ANDA: 50-718
FIRM: ORTHO BIOTECH PRODUCTS, LP
RLD: DOXIL

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

CHEM Team: DC1 TM 12 ☒ Activity	Bio Team: DBE 1 TM4: Nilufer Tampal ☒ Activity
CHEM Team Leader: Bing Cai ☒ No Assignment Needed in DARRTS	Bio PM: Diana Solana Sodeinde ☐ FYI
CHEM RPM: Eunjung (Esther) Chuh ☒ FYI	Clinical Endpoint Team: (No) ☐ Activity
DMF Review Team Leader: Aloka Srinivasan ☒ FYI	
Labeling Reviewer: Payne, Angela ☒ Activity	Micro Review: Random Micro Team 1 ☒ Activity

Regulatory Reviewer: Date: 10/11/11	Recommendation: ☒ FILE ☐ REFUSE to RECEIVE

Comments: EC- 3 YES
 Therapeutic Code: 4010800 ANTITUMOR ANTIBIOTICS
 On Cards: YES
 Archival copy: GATEWAY (ELECTRONIC DATA)
 Sections: I

- For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: <http://www.fda.gov/cder/regulatory/ersr/ectdl.htm>
- For a Comprehensive Table of Contents Headings and Hierarchy please go to: <http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>
- For more CTD and eCTD informational links see the final page of the ANDA Checklist

Reference ID: A3056058
 Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage

1. Edit Application Property Type in DARRTS where applicable for

- a. First Generic Received
 Yes No
- b. Market Availability
 Rx OTC
- c. Pepfar
 Yes No
- d. Product Type
 Small Molecule Drug
- e. USP Drug Product (at time of filing review)
 Yes No

2. Edit Submission Patent Records

Yes

3. Edit Contacts Database with Bioequivalence Recordation where applicable

Yes

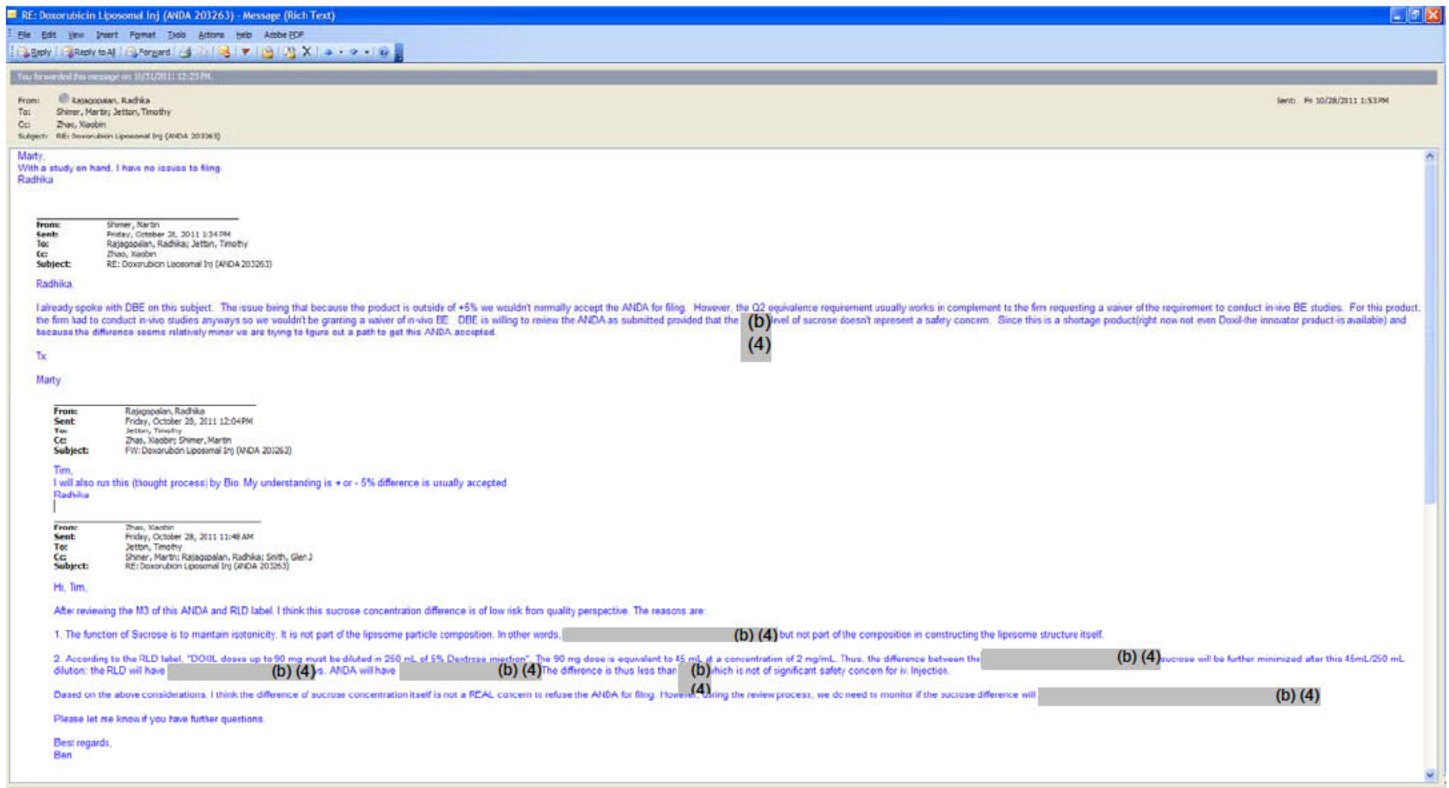
4. EER (in Draft)

Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. Vincent Andolina 609-495-2808

ANDA is being accepted since it isn't entirely clear what the quantitative amount of sucrose is in the RLD. The approved FDA label for this product does not include a concentration level for Sucrose. This is odd since Sucrose is a tonicity agent with the amount present required to be in the RLD label. Labels for this drug which are marketed outside of the United States indicated that approximately 94 mg/mL of Sucrose is present (b) (4). However, Sun submitted information to the ANDA which indicates that there is significant variability in the amount of Sucrose present in Doxil. After two internal OGD meetings held on 12/2(K. Webber, Lawrence Yu, Dale Connor, Hoai Caramenico, Harvey Greenberg, Tim Jetton and myself) and 12/9/2011(Lawrence Yu, Dale Connor, Hoai Caramenico, Radhika Rajagopalan, Xiaobin Zhao, Tim Jetton and myself) it was decided that this ANDA could be filed. Sun has provided sufficient evidence from a filing perspective to indicate that their product meets the requirements for filing at 21 CFR 314.94(a)(9)(iii). Furthermore, this ANDA will automatically be granted expedited review due to a pending shortage of this drug product. -Martin H. Shimer 12/12/2011.



MODULE 1: ADMINISTRATIVE

		COMMENT (S)
1.1	Signed and Completed Application Form (356h) (Rx/OTC Status) Yes (original signature)	RX YES
1.1.2	Establishment Information: Yes 1. Drug Substance Manufacturer 2. Drug Product Manufacturer 3. Outside Testing Facility(ies)	
1.2	Cover Letter Yes	
1.2.1	Form FDA 3674 (PDF) B	
*	Table of Contents (paper submission only) Yes	
1.3.2	Field Copy Certification (N/A for E-Submissions) N/A (original signature)	
1.3.3	Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) Yes 2. List of Convictions statement (original signature) Yes	
1.3.4	Financial Certifications Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) Yes Disclosure Statement (Form FDA 3455) N/A	

1.3.5

Patent Information

Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations

Patent Certification

1. Patent number(s)
2. Paragraph: (Check all certifications that apply)
MOU PI PII PIII PIV (Statement of Notification)
3. Expiration of Patent(s): NA
 - a. Pediatric exclusivity submitted? Select
 - b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: State marketing intentions? YES

The screenshot shows a web browser window displaying the FDA's Orange Book search results. The page title is "Patent and Exclusivity Search Results" and the URL is "http://www.accessdata.fda.gov/scripts/cder/ob/obca/patexchew.cfm?Appl_No=050718&Product_No=001&table=OB_Rx". The page content includes the FDA logo, navigation links, and the search results for the query "Appl No 050718 Product 001 in the OB_Rx list". The results show that there are no unexpired patents for this product in the Orange Book Database. A table lists the application number (N050718), product number (001), exclusivity code (ODE), and exclusivity expiration date (May 17, 2014). The page also provides links to view patent use codes and exclusivity codes, and information about the update frequency of the data.

U.S. Department of Health & Human Services
www.hhs.gov

FDA U.S. Food and Drug Administration
A-Z Index Search

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

FDA Home

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 050718 Product 001 in the OB_Rx list.

There are no unexpired patents for this product in the Orange Book Database.

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N050718	001	ODE	May 17, 2014

[View a list of all patent use codes](#)
[View a list of all exclusivity codes](#)

[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through October, 2011
Patent and Generic Drug Product Data Last Updated: December 08, 2011

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[FOIA](#) | [Accessibility](#) | [No FEAR Act](#)

1.4.1	References Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Yes b. Type II DMF# DOXORUBICIN HYDROCHLORIDE LIPOSOME (b) (4) # c. Type III DMF authorization letter(s) for container closure Yes 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) Yes	
1.12.4	Request for Comments and Advice - Proprietary name requested N/A If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes Select 2. No - contact the firm to submit the request as a separate electronic amendment.	
1.12.11	Basis for Submission NDA#: 50-718 Ref Listed Drug: DOXIL Firm: ORTHO BIOTECH PRODUCTS, LP ANDA suitability petition required? Select If Yes, provide petition number and copy of approved petition ANDA Citizen's Petition Required? Select If Yes, provide petition number and copy of petition	

MODULE 1: ADMINISTRATIVE (Continued)

		COMMENT (S)
1.12.12	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use x 2. Active ingredients x 3. Inactive ingredients x 4. Route of administration x 5. Dosage Form x 6. Strength x	
1.12.14	Environmental Impact Analysis Statement (cite 21CFR 25.31, if applicable) Yes	
1.12.15	Request for Waiver Request for Waiver of In-Vivo BA/BE Study(ies) No	
1.14.1	Draft Labeling (Multi Copies N/A for E-Submissions) 1.14.1.1 4 copies of draft for paper submission only (each strength and container) Yes 1.14.1.2 1 side by side labeling comparison of containers and carton with all differences visually highlighted and annotated Yes 1.14.1.3 1 package insert (content of labeling) and SPL submitted electronically Yes	
1.14.3	Listed Drug Labeling 1.14.3.1 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated Yes 1.14.3.3 RLD package insert, 1 RLD label and 1 RLD container label Yes	

MODULE 2: SUMMARIES

		COMMENT (S)
2.3	Quality Overall Summary (QOS) E-Submission: PDF Yes Word Processed e.g., MS Word Yes A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ Question based Review (QbR) Yes 2.3.S Drug Substance (Active Pharmaceutical Ingredient) Yes 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability 2.3.P Drug Product Yes 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	
2.7	Clinical Summary (Bioequivalence) Model BE Data Summary Tables E-Submission: PDF Select Word Processed: e.g., MS Word Yes 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods 2.7.1.1 Background and Overview Table 1. Submission Summary Yes Table 4. Bioanalytical Method Validation Yes Table 6. Formulation Data Yes 2.7.1.2 Summary of Results of Individual Studies Table 5. Summary of In Vitro Dissolution Yes 2.7.1.3 Comparison and Analyses of Results Across Studies Table 2. Summary of Bioavailability (BA) Studies Yes Table 3. Statistical Summary of the Comparative BA Data Yes 2.7.1.4 Appendix Select 2.7.4.1.3 Demographic and Other Characteristics of Study Population Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Yes 2.7.4.2.1.1 Common Adverse Events Table 8. Incidence of Adverse Events in Individual Studies Yes	

MODULE 3: 3.2.S DRUG SUBSTANCE

		COMMENT (S)
3.2.S.1	General Information (Do not refer to DMF) Yes 3.2.S.1.1 Nomenclature 3.2.S.1.2 Structure 3.2.S.1.3 General Properties	
3.2.S.2	Manufacturer Drug Substance (Active Pharmaceutical Ingredient) 1. Name and Full Address(es) of the Facility(ies) yes 2. Contact name, phone and fax numbers, email address Yes 3. Specify Function or Responsibility Yes 4. Type II DMF number for API (b) (4) 5. CFN or FEI numbers (b) (4)	
3.2.S.3	Characterization Yes Provide the following in tabular format: 1. Name of Impurity(ies) 2. Structure of Impurity(ies) 3. Origin of Impurity(ies)	
3.2.S.4	Control of Drug Substance (Active Pharmaceutical Ingredient) 3.2.S.4.1 Specification Yes Testing specifications and data from drug substance manufacturer(s) 3.2.S.4.2 Analytical Procedures Yes 3.2.S.4.3 Validation of Analytical Procedures (API that is USP or reference made to DMF, must provide verification of USP or DMF procedures) Yes 1. Spectra and chromatograms for reference standards and test samples Yes 2. Samples-Statement of Availability and Identification of: a. Drug Substance Yes b. API lot number(s) 200709 & 230909 3.2.S.4.4 Batch Analysis 1. COA(s) specifications and test results from drug substance mfr(s) Yes 2. Applicant certificate of analysis No 3.2.S.4.5 Justification of Specification Yes	
3.2.S.5	Reference Standards or Materials (Do not refer to DMF) Yes	
3.2.S.6	Container Closure Systems Yes	
3.2.S.7	Stability 1. Retest date or expiration date of API Yes	

MODULE 3: 3.2.P DRUG PRODUCT

		COMMENT (S)
3.2.P.1	Description and Composition of the Drug Product - Unit composition with indication of the function of the inactive ingredient(s) Yes - Inactive ingredients and amounts are appropriate per IIG (per/dose justification) Select - Conversion from % to mg/dose values for inactive ingredients (if applicable) Select - Elemental iron: provide daily elemental iron calculation or statement of adherence to 21CFR73.1200 (calculation of elemental iron intake based on maximum daily dose (MDD) of the drug product is preferred if this section is applicable) Select - Injections: If the reference listed drug is packaged with a drug specific diluent then the diluent must be Q1/Q2 and must be provided in the package configuration Select	

Statement of Composition

Strength	2 mg/mL (10 mL and 25 mL)	
Components	mg/mL	%w/v
Doxorubicin Hydrochloride, USP	2.00	0.200
Hydrogenated Soya Phosphatidyl Choline	9.58	0.958
MPEG-Distearoyl Phosphatidylethanolamine	3.19	0.319
Cholesterol ^{(b) (4)} NF	3.19	0.319
Ammonium Sulphate, NF	*1	
Histidine USP		(b) (4)
Sucrose, NF		
Sodium Hydroxide, NF	(b) (4)*2	
Hydrochloric Acid, NF	*2	(b) (4)

*1 Ammonium Sulphate is (b) (4) approximately 2 mg per mL. (b) (4)

*2 Used for pH adjustment (b) (4)

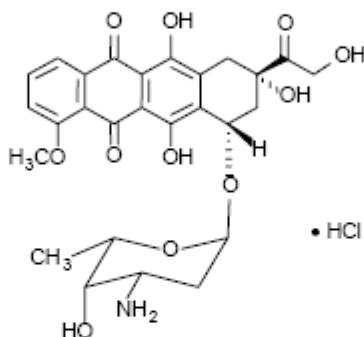
P.I. for RLD follows:

11 DESCRIPTION

DOXIL (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in STEALTH[®] liposomes for intravenous administration.

Doxorubicin is an anthracycline topoisomerase inhibitor isolated from *Streptomyces peucetius* var. *caesius*.

Doxorubicin HCl, which is the established name for (8S,10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride, has the following structure:



The molecular formula of the drug is C₂₇H₂₉NO₁₁·HCl; its molecular weight is 579.99.

DOXIL is provided as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The STEALTH[®] liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the STEALTH[®] liposomes.

20

No inf

No information on sucrose concentration was contained on the RLD package insert, and LXMAIN is not always 100% accurate therefore we asked the applicant to provide information on how they arrived at their sucrose level (see chart below). Also taken into consideration was the fact that President Obama has issued an executive order with respect to “shortage drugs” which applies to this drug. This led to chemistry evaluating the formulation, in relation to osmolality. The information provided by the applicant gave justification of their levels.

Doxil [®]			Sun's Proposed product			
Strength	Lot #	Sucrose content(mg/mL) (b) (4)	Strength	Lot #	Sucrose content(mg/mL) (b) (4)	
10 mL	0706845	(b) (4)	10 mL	JK93699	(b) (4)	
	JK93496					
	0709500		(b) (4)	25 mL	JKJ0322	(b) (4)
					JKJ0142	
0543472	(b) (4)		JK93743	(b) (4)		
0729032						
25 mL	0710167					

Results of Osmolality of Sun's proposed product and RLD summarized in below table indicates that isotonicity of Sun's proposed product is comparable with that of RLD

Oracle Developer Forms Runtime - Web

Action Edit Query Block Record Field Help Window

DPRF: Drug Product Query System (18-Aug-1992)

N 050718 PRODUCT DETAILS

Prod: 002 TE: Rx/OTC: RX Trade: DOXIL

Received: 16-DEC-1999 Approval: APPEP / 13-JUN-2000 Discontinued: Withdrawal:

Current: Dosage Form(s): INJECTION, SUSPENSION, LIPOSOMAL Route(s) of Administration: INTRAVENOUS

Part: 01

Ingredient Name	POTENCY	Type
DOXORUBICIN HYDROCHLORIDE	50MG/25ML	ACTIVE
CHOLESTEROL	3.19MG/25ML	INACTIVE
AMMONIUM SULFATE	2MG/25ML	INACTIVE
HISTIDINE	(b) (4) 25ML	INACTIVE
HYDROCHLORIC ACID	ADJUST PH	INACTIVE

UP/DOWN: Move to previous/next product RETURN: Move cursor to next field
(P)F2: Help (P)F6: Export to Excel
(P)F4: Return to previous screen Ctrl+H: Previous Field

Record: 1/7 <OSC>

DPRF: Drug Product Query System (18-Aug-1992)

N 050718 PRODUCT DETAILS

Prod: 001 TE: Rx/OTC: RX Trade: DOXIL

Received 01-JUN-1995 APPEF / Approval 17-NOV-1995 Discontinued Withdrawal

Current Dosage Form(s) INJECTION, SUSPENSION, LIPOSOMAL Route(s) of Administration INTRAVENOUS
Part 01

Table with 3 columns: Ingredient Name, POTENCY, Type. Rows include HYDROCHLORIC ACID, SODIUM HYDROXIDE, HYDROGENATED SOY, N-(CARBAMOYL-METHOXY PEG-40)-1,2-DISTEAROYL-CEPHALIN SODIUM, and SUCROSE.

UP/DOWN: Move to previous/next ingredient RETURN: Move cursor to potency
Ctrl+H: Previous Field
(P)F2: Help (P)F4: Return to previous screen

3.2.P.2	Pharmaceutical Development Pharmaceutical Development Report Yes	
3.2.P.3	Manufacture 3.2.P.3.1 Drug Product (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es) of the Facility(ies) yes 2. Contact name, phone and fax numbers, email address Yes 3. Specify Function or Responsibility Yes 4. CGMP Certification (from both applicant and drug product manufacturer if different entities) Yes 5. CFN or FEI numbers 3003789481 & 3007512695 3.2.P.3.2 Batch Formula Yes 3.2.P.3.3 Description of Manufacturing Process and Process Controls 1. Description of the Manufacturing Process Yes 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified same 3. Master packaging records for intended marketing container(s) Yes 4. If sterile product (b) (4) 5. Reprocessing Statement (cite 21CFR 211.115, submitted by the drug product manufacturer and the applicant, if different entities) Yes 3.2.P.3.4 Controls of Critical Steps and Intermediates Yes 3.2.P.3.5 Process Validation and/or Evaluation 1. (b) (4) 2. (b) (4)	
3.2.P.4	Controls of Excipients (Inactive Ingredients) Source of inactive ingredients identified Yes 3.2.P.4.1 Specifications 1. Testing specifications (including identification and characterization) Yes 2. Suppliers' COA (specifications and test results) Select 3.2.P.4.2 Analytical Procedures Yes 3.2.P.4.3 Validation of Analytical Procedures Yes 3.2.P.4.4 Justification of Specifications: 1. Applicant COA Yes	

MODULE 3: 3.2.P DRUG PRODUCT (Continued)

		COMMENT (S)
3.2.P.5	Controls of Drug Product 3.2.P.5.1 Specification(s) Yes 3.2.P.5.2 Analytical Procedures Yes 3.2.P.5.3 Validation of Analytical Procedures (if using USP procedure, must provide verification of USP procedure) Yes Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Yes 2. Lot number(s) and strength of Drug Product(s) JK93496 & JK93743 3.2.P.5.4 Batch Analysis Certificate of Analysis for Finished Dosage Form Yes 3.2.P.5.5 Characterization of Impurities Yes 3.2.P.5.6 Justification of Specifications Yes	
3.2.P.7	Container Closure System 1. Summary of Container/Closure System (if new resin, provide data) Yes 2. Components Specification and Test Data Yes 3. Packaging Configuration and Sizes yes 4. Container/Closure Testing (recommended additional testing for all plastic) Select a. Solid Orals: water permeation, light transmission Select b. Liquids: leachables, extractables, light transmission Select 5. Source of supply and suppliers address Yes	
3.2.P.8	3.2.P.8.1 Stability (Finished Dosage Form) 1. Stability Protocol submitted Yes 2. Expiration Dating Period ^(b)₍₄₎ month 3.2.P.8.2 Post-approval Stability and Conclusion Post Approval Stability Protocol and Commitments Yes 3.2.P.8.3 Stability Data 1. Accelerated stability data a. four (4) time points 0,1,2,3 Yes -OR- b. three (3) time points 0,3,6 (if 3 time points for accelerated stability data are submitted then provide 3 exhibit batches along with 12 months of room temperature stability data –Refer to Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products November 2003, Section B) Select 2. Batch numbers on stability records the same as the test batch Yes	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Substance)

		COMMENT (S)
3.2.R Drug Substance	3.2.R.1.S Executed Batch Records for drug substance (if available) No 3.2.R.2.S Comparability Protocols N/A 3.2.R.3.S Methods Validation Package Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

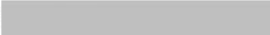
MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Product)

		COMMENT (S)
3.2.R Drug Product	3.2.R.1.P.1 Executed Batch Records Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation Select ***see below*** Bulk Package Reconciliation required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: - Bulk Package Label (1.14.1) Select - Bulk Package Stability (accelerated stability data [0,1,2,3] -OR- room temperature [0,3,6]) (3.2.P.8) Select - Bulk Package Container and Closure information (3.2.P.7) Select 3.2.R.1.P.2 Information on Components Yes 3.2.R.2.P Comparability Protocols No 3.2.R.3.P Methods Validation Package Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

10 mL vials:

Product :Doxorubicin Hydrochloride Injection 2 mg/ml ,10 ml

Batch No. : JK93496

Batch size :  (b) (4)



20 mL vials:

Product :Doxorubicin hydrochloride Injection 2 mg/ml, 25 ml

Batch No. : JK93743

Batch size : (b) (4)



MODULE 5: CLINICAL STUDY REPORTS

		COMMENT (S)
5.2	Tabular Listing of Clinical Studies Select	

5.3.1 (complete study data)	Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (check proportionality of multiple strengths) Select b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v)) 2. Lot Numbers and strength of Products used in BE Study(ies) 3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)	
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select 2. Summary Bioequivalence tables: Table 10. Study Information Select Table 12. Dropout Information Select Table 13. Protocol Deviations Select 5.3.1.3 In Vitro-In-Vivo Correlation Study Reports 1. Summary Bioequivalence tables Select Table 11. Product Information Select Table 16. Composition of Meal Used in Fed Bioequivalence Study Select 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Select Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Select Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples Select Case Report Forms should be placed under the study to which they pertain, and appropriately tagged. Refer to The eCTD Backbone File Specification for Study Tagging //www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf	
5.4	Literature References	
	Possible Study Types:	
Study Type	IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	FASTING AND FED
Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80,1.25) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select	
Study Type	IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) Select 1. Study(ies) meets BE criteria (90% CI of 80-125) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	

Study Type	NASALLY ADMINISTERED DRUG PRODUCTS 1. Solutions (Q1/Q2 sameness) Select a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study Select 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select b. In-Vivo BE Study with Clinical End Points Select 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p < 0.05$) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select	
Study Type	IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) Select 2. Pivotal Study (study meets BE criteria 90%CI of 80-125) Select	
Study Type	TRANSDERMAL DELIVERY SYSTEMS 1. In-Vivo PK Study Select a. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) Select b. In-Vitro Dissolution Select c. EDR Email: Data Files Submitted Select 2. Adhesion Study Select 3. Skin Irritation/Sensitization Study Select	

Updated 05/16/2011

The screenshot displays the Oracle AS Forms Services interface for an Establishment Evaluation System. The main window shows a table with the following data:

FEI / CFR	Establishment Name	Profile Code	Last Milestone Name	Last Compliance Date	Status	OAI Alert Date	EER Re-eval Date
1052809586	SUN PHARMACEUTICAL THE SVS DRAFT	(b) (4)		12-DEC-2011		(b) (4)	

Below the table, there are sections for 'Overall Compliance' and 'OAI Alert Comments'. The 'Overall Compliance' section includes fields for Date, Recommendation, and Overall Re-eval Date. The 'OAI Alert Comments' section has a text area for entering details.

The Oracle AS Forms Services logo is overlaid on the bottom half of the screenshot.

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

/s/

TIMOTHY G JETTON
12/12/2011

MARTIN H Shimer
12/12/2011

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA/SUPPLEMENT #: 203263
 DRUG: Doxorubicin HCl Liposome

APPLICANT: Sun Pharma Global FZE
 DATE OF SUBMISSION: June 16, 2011

The Office of Generic Drugs MaPP # 5240.1 lists the following criteria for granting expedited review status to a supplemental abbreviated new drug application. At least one of the criteria must be met.

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative
2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.
 - a) Catastrophic events such as explosion, fire storms damage.
 - b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:
 - ◆ Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
 - ◆ Relocation of a facility or change in an existing facility because of a catastrophic event (see item 2.a)
3. AGENCY NEED.
 - a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
 - b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
 - c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
 - d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant ☒ Deny ☐	
Chemistry Team Leader (sign as needed)	Grant ☒ Deny ☐	
Micro Team Leader (sign as needed)	Grant ☒ Deny ☐	
Labeling Team Leader (sign as needed)	Grant ☒ Deny ☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant ☒ Deny ☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: SELECT TEAM #

- a) When expedited review is denied, notify the applicant by telephone
 DATE

ENTER FORM INTO DFS

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/s/

TIMOTHY G JETTON
12/12/2011

MARTIN H Shimer
12/12/2011



ANDA 203263

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharma Global FZE
Attention: Robert Kurkiewicz
1150 Elijah McCoy Drive
Detroit, MI 48202

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated November 2, 2011 and your correspondence dated November 3, 2011.

NAME OF DRUG: Doxorubicin Hydrochloride Liposomal Injection, 2 mg/mL,
10 mL and 25 mL vial

DATE OF APPLICATION: June 16, 2011

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 16, 2011

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Esther Chuh
Project Manager
240-276-8530

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

MARTIN H Shimer
12/12/2011
Signing for Wm Peter Rickman

MEMORANDUM

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

DATE : October 28, 2011

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 203263 for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL to determine if the application is substantially complete for filing.

Sun Pharma Global FZE has submitted ANDA 203263 for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL, 10 mL and 25 mL. In order to accept an ANDA, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Sun Pharma Global FZE on June 16, 2011 for its Doxorubicin Hydrochloride product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

EDWARD WASHINGTON
10/28/2011

MEMORANDUM

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

DATE : July 18, 2011

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 203263 for Doxorubicin Hydrochloride Liposomal Injection, 2mg/mL, 10 mL and 25 mL to determine if the application is substantially complete for filing.

Sun Pharma Global FZE has submitted ANDA 203263 for Doxorubicin Hydrochloride Liposomal Injection, 2mg/mL, 10 mL and 25 mL. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Sun Pharma Global FZE on June 29, 2011 for its Doxorubicin Hydrochloride Liposomal product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

EDA E HOWARD
07/18/2011