

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 208657

Name: DOXOurbicin Hydrochloride Liposome Injection
20mg/10ml

Sponsor: Dr. Reddy's Laboratories Inc

Approval Date: June 15, 2017

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APPLICATION NUMBER:
ANDA208657Orig1s000
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APPLICATION NUMBER:

ANDA 208657

APPROVAL LETTER



ANDA 208657

ANDA APPROVAL

Dr. Reddy's Laboratories, Inc.
U.S. Agent for Dr. Reddy's Laboratories Limited
107 College Road East
Princeton, NJ 08540
Attention: Srinivasa Rao
Vice President and Head, Regulatory Affairs- North America

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on October 8, 2015, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL) Single-dose Vials.

Reference is also made to the complete response letter issued by this office on December 27, 2016, and to your amendments received on February 16, March 22, and May 11, 2017.

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 Office of Bioequivalence has determined your Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL) Single-dose Vials to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Doxil Liposome Injection, 20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL), of Janssen Research and Development, LLC.

Under section 506A of FD&C 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 and 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 FD&C Act.

REPORTING REQUIREMENTS

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

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those

responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

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.

The Electronic Common Technical Document (eCTD) is CDER’s standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

CAPT Carol A. Holquist, RPh
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



Carol
Holquist

Digitally signed by Carol Holquist
Date: 5/15/2017 04:53:03PM
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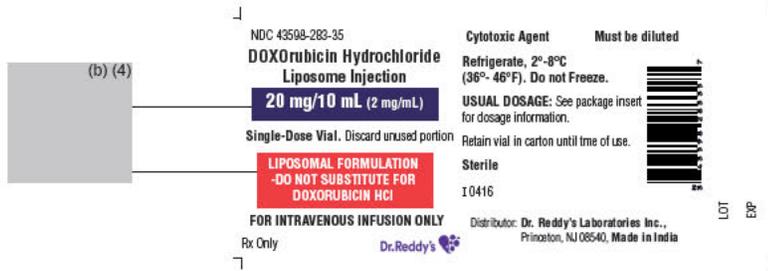


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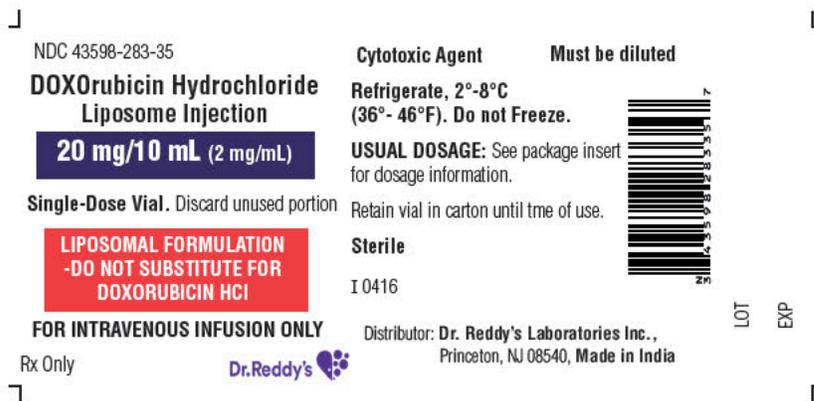
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LABELING

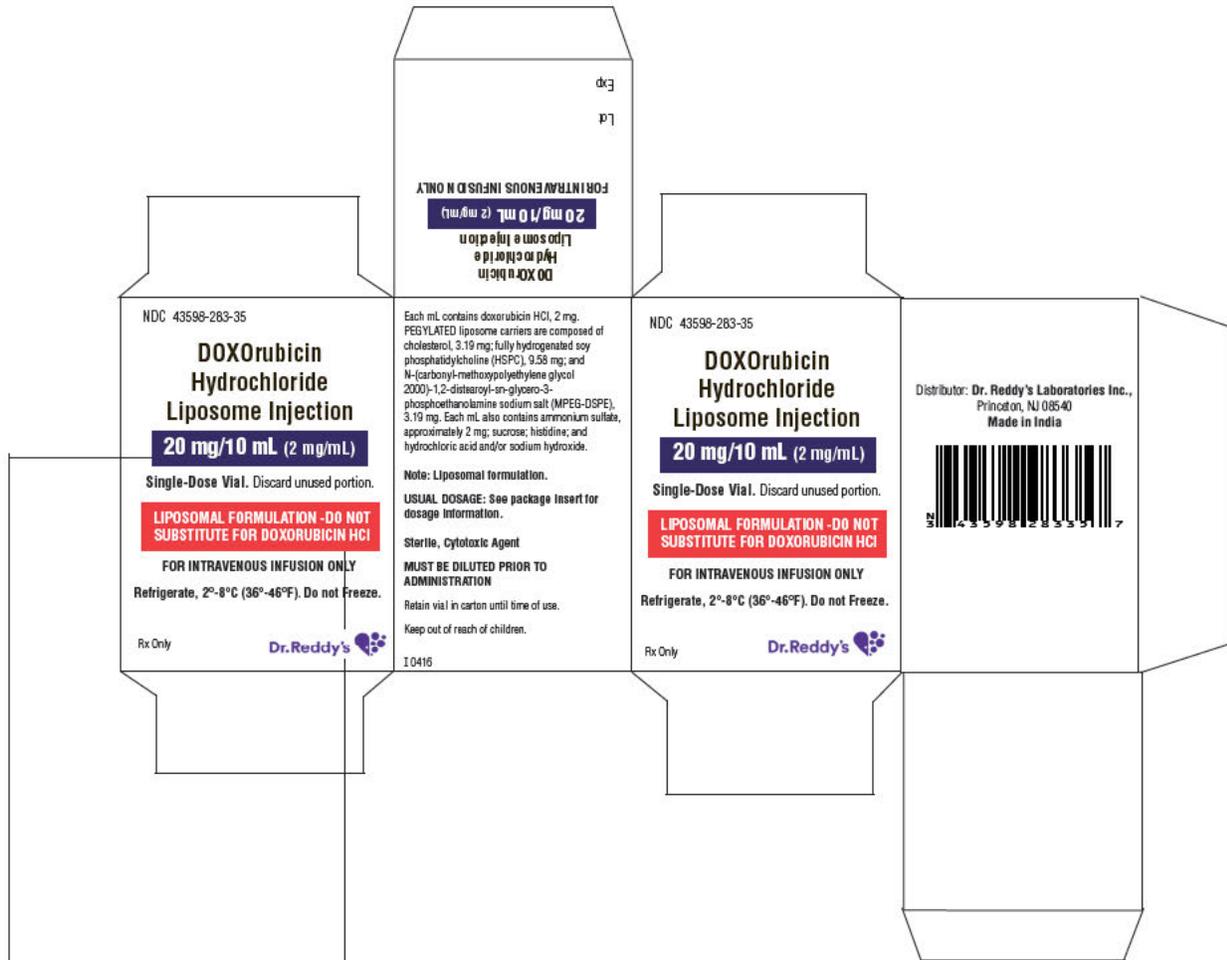
Revised Vial Label for Doxorubicin Hydrochloride Liposome Injection 20 mg/10 mL (2 mg/mL)
 Label Size: 70 mm x 32 mm



150% of Actual Size



**Revised Vial Carton for
Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL - (2 mg/mL)
Actual Label Size: 40 mm x 35 mm x 55 mm**



(b) (4)

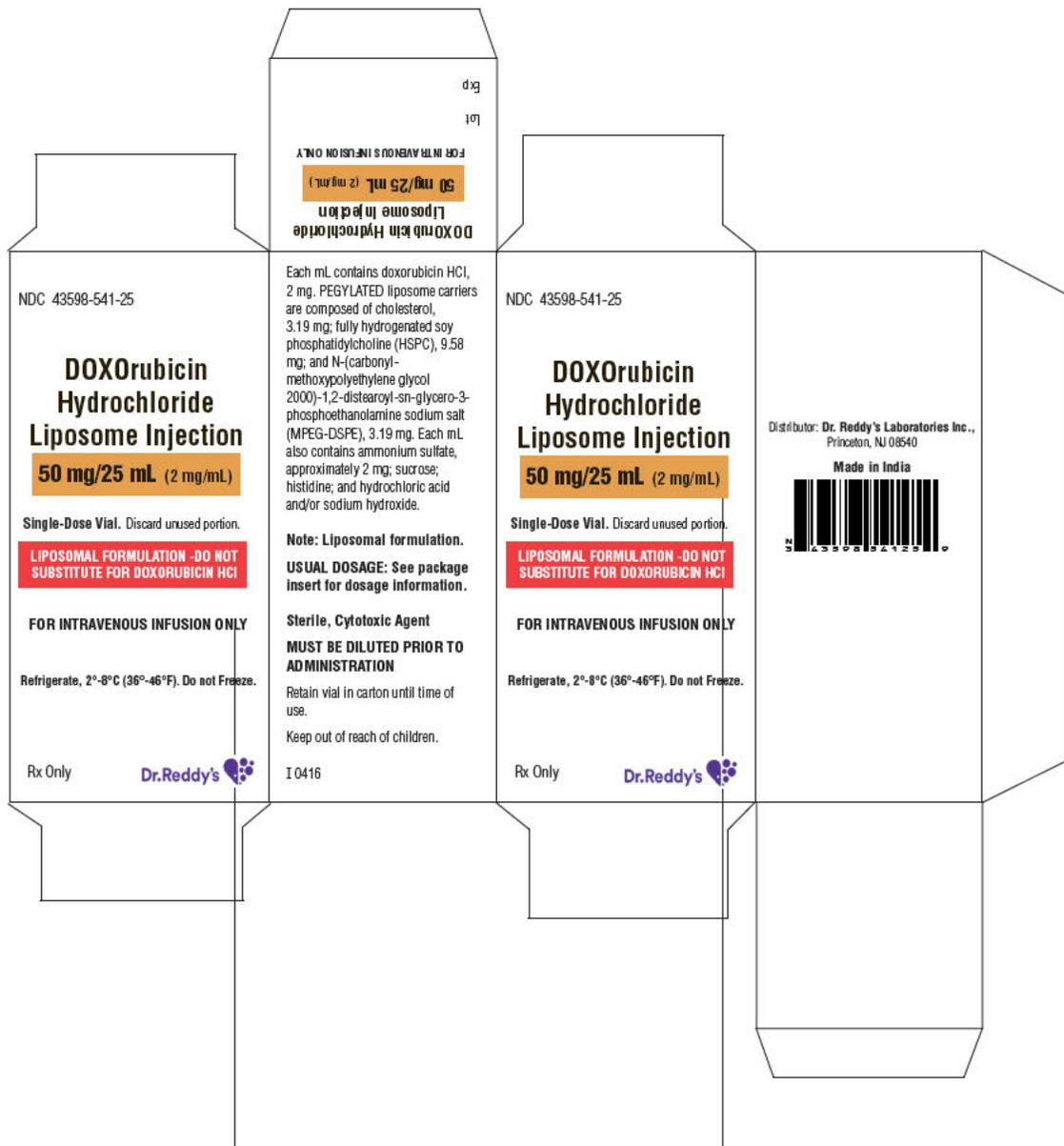
Revised Vial Label for Doxorubicin Hydrochloride Liposome Injection 50 mg/25 mL (2 mg/mL)
 Label Size: 78 mm x 50 mm



150% of Actual Size



**Revised Vial Carton for
Doxorubicin Hydrochloride Liposome Injection, 50 mg/25 mL - (2 mg/mL)
Actual Label Size: 40 mm x 35 mm x 85 mm**



(b) (4)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION safely and effectively. See full prescribing information for DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION.

DOXORUBICIN HYDROCHLORIDE liposome injection, for intravenous use
Initial U.S. Approval: 1995

WARNING: CARDIOMYOPATHY and INFUSION RELATED REACTIONS
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 HCl approaches 550 mg/m². The risk of cardiomyopathy may be increased at lower cumulative doses with mediastinal irradiation (5.1).
• Acute infusion-related reactions occurred in 11% of patients with solid tumors. Serious, life-threatening, and fatal infusion reactions have been reported. Medications/emergency equipment to treat such reactions should be available for immediate use (5.2).

RECENT MAJOR CHANGES

Boxed Warning	01/2015
Dosage and Administration (2)	01/2015
Contraindications (4)	01/2015
Warnings and Precautions (5)	01/2015

INDICATIONS AND USAGE
Doxorubicin hydrochloride liposome injection is an anthracycline topoisomerase II 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.
• **Multiple Myeloma (1.3)**
In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior 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).
• **Ovarian cancer:** 50 mg/m² IV every 4 weeks (2.2)
• **AIDS-related Kaposi’s Sarcoma:** 20 mg/m² IV every 3 weeks (2.3)
• **Multiple Myeloma:** 30 mg/m² IV on day 4 following bortezomib (2.4)

DOSAGE FORMS AND STRENGTHS
Doxorubicin hydrochloride (HCl) liposomal injection: Single-dose vials: 20 mg/10 mL and 50 mg/25 mL (3)

CONTRAINDICATIONS
• Hypersensitivity reactions to doxorubicin HCl 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 (5.3)
• Embryofetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus. Use effective contraception (5.5, 8.1, 8.3)

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

To report SUSPECTED ADVERSE REACTIONS, contact Dr. Reddy’s Laboratories Inc., at 1-888-375-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS
• Lactation: Discontinue breastfeeding (8.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2016

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1.2 AIDS-Related Kaposi’s Sarcoma
1.3 Multiple Myeloma
2 DOSAGE AND ADMINISTRATION
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FULL PRESCRIBING INFORMATION

WARNING: CARDIOMYOPATHY and INFUSION-RELATED REACTIONS

- **Doxorubicin hydrochloride liposome injection can cause myocardial damage, including congestive heart failure, as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². In a clinical study of 250 patients with advanced cancer who were treated with doxorubicin hydrochloride liposome injection, the risk of cardiotoxicity was 11% when the cumulative anthracycline dose was between 450 to 550 mg/m². Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. The risk of cardiomyopathy may be increased at lower cumulative doses in patients with prior mediastinal irradiation [see Warnings and Precautions (5.1)].**
- **Acute infusion-related reactions consisting of, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension occurred in 11% of patients with solid tumors treated with doxorubicin hydrochloride liposome injection. Serious, life-threatening and fatal infusion reactions have been reported [see Dosage and Administration (2.6) and Warnings and Precautions (5.2)].**

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.

1.3 Multiple Myeloma

Doxorubicin hydrochloride liposome injection, 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 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

Do not substitute doxorubicin hydrochloride liposome injection for doxorubicin HCl injection.

Do not administer as an undiluted suspension or as an intravenous bolus [see Warnings and Precautions (5.2)].

2.2 Ovarian Cancer

The recommended dose of doxorubicin hydrochloride liposome injection is 50 mg/m² intravenously over 60 minutes every 28 days until disease progression or unacceptable toxicity.

2.3 AIDS-Related Kaposi's Sarcoma

The recommended dose of doxorubicin hydrochloride liposome injection is 20 mg/m² intravenously over 60 minutes every 21 days until disease progression or unacceptable toxicity.

2.4 Multiple Myeloma

The recommended dose of doxorubicin hydrochloride liposome injection is 30 mg/m² intravenously over 60 minutes on day 4 of each 21-day cycle for eight cycles or until disease progression or unacceptable toxicity. Administer doxorubicin hydrochloride liposome injection after bortezomib on day 4 of each cycle [see *Clinical Studies (14.3)*].

2.5 Dose Modifications for Adverse Reactions

Do not increase doxorubicin hydrochloride liposome injection after a dose reduction for toxicity

Table 1: Recommended Dose Modifications for Hand-Foot Syndrome, Stomatitis, or Hematologic Adverse Reactions

Toxicity	Dose Adjustment
Hand-Foot Syndrome (HFS)	
Grade 1: Mild erythema, swelling, or desquamation not interfering with daily activities	<ul style="list-style-type: none"> • If no previous Grade 3 or 4 HFS: no dose adjustment. • If previous Grade 3 or 4 HFS: delay dose up to 2 weeks, then decrease dose by 25%.
Grade 2: Erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter	<ul style="list-style-type: none"> • Delay dosing up to 2 weeks or until resolved to Grade 0-1. • Discontinue doxorubicin hydrochloride liposome injection if no resolution after 2 weeks. • If resolved to Grade 0-1 within 2 weeks: <ul style="list-style-type: none"> o <u>And</u> no previous Grade 3 or 4 HFS: continue treatment at previous dose. o <u>And</u> previous Grade 3 or 4 toxicity: decrease dose by 25%.
Grade 3: Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	<ul style="list-style-type: none"> • Delay dosing up to 2 weeks or until resolved to Grade 0-1, then decrease dose by 25%. • Discontinue doxorubicin hydrochloride liposome injection if no resolution after 2 weeks.
Grade 4: Diffuse or local process causing infectious complications, or a bed ridden state or hospitalization	<ul style="list-style-type: none"> • Delay dosing up to 2 weeks or until resolved to Grade 0-1, then decrease dose by 25%. • Discontinue doxorubicin hydrochloride liposome injection if no resolution after 2 weeks.
Stomatitis	
Grade 1: Painless ulcers, erythema, or mild soreness	<ul style="list-style-type: none"> • If no previous Grade 3 or 4 toxicity: no dose adjustment. • If previous Grade 3 or 4 toxicity: delay up to 2 weeks then decrease dose by 25%.
Grade 2: Painful erythema, edema, or ulcers, but can eat	<ul style="list-style-type: none"> • Delay dosing up to 2 weeks or until resolved to Grade 0-1. • Discontinue doxorubicin hydrochloride liposome injection if there is no resolution after 2 weeks. • If resolved to Grade 0-1 within 2 weeks: <ul style="list-style-type: none"> o <u>And</u> no previous Grade 3 or 4 stomatitis: resume treatment at previous dose. o <u>And</u> previous Grade 3 or 4 toxicity: decrease dose by 25%.
Grade 3: Painful erythema, edema, or ulcers, and cannot eat	<ul style="list-style-type: none"> • 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, discontinue doxorubicin

	hydrochloride liposome injection.
Grade 4: Requires parenteral or enteral support	<ul style="list-style-type: none"> • 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, discontinue doxorubicin hydrochloride liposome injection.
Neutropenia or Thrombocytopenia	
Grade 1	No dose reduction
Grade 2	Delay until ANC \geq 1,500 and platelets \geq 75,000; resume treatment at previous dose
Grade 3	Delay until ANC \geq 1,500 and platelets \geq 75,000; resume treatment at previous dose
Grade 4	Delay until ANC \geq 1,500 and platelets \geq 75,000; resume at 25% dose reduction or continue previous dose with prophylactic granulocyte growth factor

Table 2: Recommended Dose Modifications of Doxorubicin Hydrochloride Liposome Injection for Toxicity When Administered in Combination With Bortezomib

Toxicity	Doxorubicin Hydrochloride Liposome Injection
Fever \geq 38°C and ANC $<$ 1,000/mm ³	<ul style="list-style-type: none"> • Withhold dose for this cycle if before Day 4; • Decrease dose by 25%, if after Day 4 of previous cycle.
On any day of drug administration after Day 1 of each cycle: <ul style="list-style-type: none"> • Platelet count $<$25,000/mm³ • Hemoglobin $<$8 g/dL • ANC $<$500/mm³ 	<ul style="list-style-type: none"> • Withhold dose for this cycle if before Day 4; • Decrease dose by 25%, if after Day 4 of previous cycle AND if bortezomib is reduced for hematologic toxicity.
Grade 3 or 4 non-hematologic drug related toxicity	Do not dose until recovered to Grade $<$ 2, then reduce dose by 25%.

For neuropathic pain or peripheral neuropathy, no dosage adjustments are required for doxorubicin hydrochloride liposome injection. Refer to bortezomib manufacturer’s prescribing information.

2.6 Preparation and Administration

Preparation

Dilute doxorubicin hydrochloride liposome injection doses up to 90 mg in 250 mL of 5% Dextrose Injection, USP prior to administration. Dilute doses exceeding 90 mg in 500 mL of 5% Dextrose Injection, USP prior to administration. Refrigerate diluted doxorubicin hydrochloride liposome injection at 2°C to 8°C (36°F to 46°F) and administer within 24 hours.

Administration

Inspect parenteral drug products 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.

Do not use with in-line filters.

Administer the first dose of doxorubicin hydrochloride liposome injection at an initial rate of 1 mg/min. If no infusion-related adverse reactions are observed, increase the infusion rate to complete the administration of the drug over one hour [see *Warnings and Precautions (5.2)*]. Do not rapidly flush the infusion line.

Do not mix doxorubicin hydrochloride liposome injection with other drugs.

Management of Suspected Extravasation

Discontinue doxorubicin hydrochloride liposome injection for burning or stinging sensation or other evidence indicating perivenous infiltration or extravasation. Manage confirmed or suspected extravasation as follows:

- Do not remove the needle until attempts are made to aspirate extravasated fluid
- Do not flush the line
- Avoid applying pressure to the site
- Apply ice to the site intermittently for 15 min 4 times a day for 3 days
- If the extravasation is in an extremity, elevate the extremity

2.7 Procedure for Proper Handling and Disposal

Doxorubicin hydrochloride liposome injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹ If doxorubicin hydrochloride liposome injection comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

3 DOSAGE FORMS AND STRENGTHS

Doxorubicin hydrochloride liposome injection: Single-dose vials contain 20 mg/10 mL and 50 mg/25 mL doxorubicin HCl as a translucent, red liposomal dispersion.

4 CONTRAINDICATIONS

Doxorubicin hydrochloride liposome injection is contraindicated in patients who have a history of severe hypersensitivity reactions, including anaphylaxis, to doxorubicin HCl [see *Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Doxorubicin HCl can result in myocardial damage, including acute left ventricular failure. The risk of cardiomyopathy with doxorubicin HCl is generally proportional to the cumulative exposure. The relationship between cumulative doxorubicin hydrochloride liposome injection dose and the risk of cardiac toxicity has not been determined.

In a clinical study in 250 patients with advanced cancer who were treated with doxorubicin hydrochloride liposome injection, the risk of cardiotoxicity was 11% when the cumulative anthracycline dose was between 450 to 550 mg/m². Cardiotoxicity was defined as >20% decrease in resting left ventricular ejection fraction (LVEF) from baseline where LVEF remained in the normal range or a >10% decrease in LVEF from baseline where LVEF was less than the

institutional lower limit of normal. Two percent of patients developed signs and symptoms of congestive heart failure without documented evidence of cardiotoxicity.

Assess left ventricular cardiac function (e.g. MUGA or echocardiogram) prior to initiation of doxorubicin hydrochloride liposome injection, during treatment to detect acute changes, and after treatment to detect delayed cardiotoxicity. Administer doxorubicin hydrochloride liposome injection to patients with a history of cardiovascular disease only when the potential benefit of treatment outweighs the risk.

5.2 Infusion-Related Reactions

Serious and sometimes life-threatening infusion-related reactions characterized by one or more of the following symptoms can occur with doxorubicin hydrochloride liposome injection: 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. The majority of infusion-related events occurred during the first infusion. Of 239 patients with ovarian cancer treated with doxorubicin hydrochloride liposome injection in Trial 4, 7% of patients experienced acute infusion-related reactions resulting in dose interruption. All occurred during cycle 1 and none during subsequent cycles. Across multiple studies of doxorubicin hydrochloride liposome injection monotherapy including this and other studies enrolling 760 patients with various solid tumors, 11% of patients had infusion-related reactions.

Ensure that medications to treat infusion-related reactions and cardiopulmonary resuscitative equipment are available for immediate use prior to initiation of doxorubicin hydrochloride liposome injection. Initiate doxorubicin hydrochloride liposome injection infusions at a rate of 1 mg/min and increase rate as tolerated [*see Dosage and Administration (2.6)*]. In the event of an infusion-related reaction, temporarily stop the drug until resolution then resume at a reduced infusion rate. Discontinue doxorubicin hydrochloride liposome injection infusion for serious or life-threatening infusion-related reactions.

5.3 Hand-Foot Syndrome (HFS)

In Trial 4, the incidence of HFS was 51% of patients in the doxorubicin hydrochloride liposome injection arm and 0.9% of patients in the topotecan arm, including 24% Grade 3 or 4 cases of HFS in doxorubicin hydrochloride liposome injection-treated patients and no Grade 3 or 4 cases in topotecan-treated patients. HFS or other skin toxicity required discontinuation of doxorubicin hydrochloride liposome injection in 4.2% of patients.

HFS was generally observed after 2 or 3 cycles of treatment but may occur earlier. Delay doxorubicin hydrochloride liposome injection for the first episode of Grade 2 or greater HFS [*see Dosage and Administration (2.5)*]. Discontinue doxorubicin hydrochloride liposome injection if HFS is severe and debilitating.

5.4 Secondary Oral Neoplasms

Secondary oral cancers, primarily squamous cell carcinoma, have been reported from post-marketing experience in patients with long-term (more than one year) exposure to doxorubicin

hydrochloride liposome injection. These malignancies were diagnosed both during treatment with doxorubicin hydrochloride liposome injection and up to 6 years after the last dose. Examine patients at regular intervals for the presence of oral ulceration or with any oral discomfort that may be indicative of secondary oral cancer.

The altered pharmacokinetics and preferential tissue distribution of liposomal doxorubicin that contributes to enhanced skin toxicity and mucositis compared to free doxorubicin may play a role in the development of oral secondary malignancies with long-term use.

5.5 Embryofetal Toxicity

Based on animal data, doxorubicin hydrochloride liposome injection can cause fetal harm when administered to a pregnant woman. At doses approximately 0.12 times the recommended clinical dose, doxorubicin hydrochloride liposome injection was embryotoxic and abortifacient in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during and for 6 months after treatment with doxorubicin hydrochloride liposome injection [see *Use in Specific Populations (8.1) and (8.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Cardiomyopathy [see *Warnings and Precautions (5.1)*]
- Infusion-Related Reactions [see *Warnings and Precautions (5.2)*]
- Hand-Foot Syndrome [see *Warnings and Precautions (5.3)*]
- Secondary Oral Neoplasms [see *Warnings and Precautions (5.4)*]

The most common adverse reactions (>20%) observed with doxorubicin hydrochloride liposome injection are asthenia, fatigue, fever, nausea, stomatitis, vomiting, diarrhea, constipation, anorexia, hand-foot syndrome, rash and neutropenia, thrombocytopenia and anemia.

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice.

The safety data reflect exposure to doxorubicin hydrochloride liposome injection in 1310 patients including: 239 patients with ovarian cancer, 753 patients with AIDS-related Kaposi's sarcoma, and 318 patients with multiple myeloma.

The following tables present adverse reactions from clinical trials of single-agent doxorubicin hydrochloride liposome injection in ovarian cancer and AIDS-Related Kaposi's sarcoma.

Patients With Ovarian Cancer

The safety data described below are from Trial 4, which included 239 patients with ovarian cancer treated with doxorubicin hydrochloride liposome injection 50 mg/m² once every 4 weeks for a minimum of four courses in a randomized, multicenter, open-label study. In this trial, patients received doxorubicin hydrochloride liposome injection for a median number of 3.2

months (range 1 day to 25.8 months). The median age of the patients is 60 years (range 27 to 87), with 91% Caucasian, 6% Black, and 3% Hispanic or Other.

Table 3 presents the hematologic adverse reactions from Trial 4.

Table 3: Hematologic Adverse Reactions in Trial 4

	Doxorubicin Hydrochloride Liposome Injection Patients (n=239)	Topotecan Patients (n=235)
Neutropenia		
500 -<1000/mm ³	8%	14%
<500/mm ³	4.2%	62%
Anemia		
6.5 -<8 g/dL	5%	25%
< 6.5 g/dL	0.4%	4.3%
Thrombocytopenia		
10,000 -<50,000/mm ³	1.3%	17%
<10,000/mm ³	0%	17%

Table 4 presents the non-hematologic adverse reactions from Trial 4.

Table 4: Non-Hematologic Adverse Reactions in Trial 4

Non-Hematologic Adverse Reaction 10% or Greater	Doxorubicin Hydrochloride Liposome Injection (%) treated (n=239)		Topotecan (%) treated (n=235)	
	All grades	Grades 3-4	All grades	Grades 3-4
<i>Body as a Whole</i>				
Asthenia	40	7	52	8
Fever	21	0.8	31	6
Mucous Membrane Disorder	14	3.8	3.4	0
Back Pain	12	1.7	10	0.9
Infection	12	2.1	6	0.9
Headache	11	0.8	15	0
<i>Digestive</i>				
Nausea	46	5	63	8
Stomatitis	41	8	15	0.4
Vomiting	33	8	44	10
Diarrhea	21	2.5	35	4.2
Anorexia	20	2.5	22	1.3
Dyspepsia	12	0.8	14	0
<i>Nervous</i>				
Dizziness	4.2	0	10	0
<i>Respiratory</i>				
Pharyngitis	16	0	18	0.4
Dyspnea	15	4.1	23	4.3

Cough increased	10	0	12	0
<i>Skin and Appendages</i>				
Hand-foot syndrome	51	24	0.9	0
Rash	29	4.2	12	0.4
Alopecia	19	N/A	52	N/A

The following additional adverse reactions were observed in patients with ovarian cancer with doses administered every four weeks (Trial 4).

Incidence 1% to 10%

Cardiovascular: vasodilation, tachycardia, deep vein thrombosis, hypotension, cardiac arrest.

Digestive: oral moniliasis, mouth ulceration, esophagitis, dysphagia, rectal bleeding, ileus.

Hematologic and Lymphatic: ecchymosis.

Metabolic and Nutritional: dehydration, weight loss, hyperbilirubinemia, hypokalemia, hypercalcemia, hyponatremia.

Nervous: somnolence, dizziness, depression.

Respiratory: rhinitis, pneumonia, sinusitis, epistaxis.

Skin and Appendages: pruritus, skin discoloration, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, dry skin, herpes simplex, fungal dermatitis, furunculosis, acne.

Special Senses: conjunctivitis, taste perversion, dry eyes.

Urinary: urinary tract infection, hematuria, vaginal moniliasis.

Patients With AIDS-Related Kaposi's Sarcoma

The safety data described is based on the experience reported in 753 patients with AIDS-related Kaposi's sarcoma (KS) enrolled in four open-label, uncontrolled trials of doxorubicin hydrochloride liposome injection administered at doses ranging from 10 to 40 mg/m² every 2 to 3 weeks. Demographics of the population were: median age 38.7 years (range 24 to 70); 99% male; 88% Caucasian, 6% Hispanic, 4% Black, and 2% Asian/other/unknown. The majority of patients were treated with 20 mg/m² of doxorubicin hydrochloride liposome injection every 2 to 3 weeks with a median exposure of 4.2 months (range 1 day to 26.6 months). The median cumulative dose was 120 mg/m² (range 3.3 to 798.6 mg/m²); 3% received cumulative doses of greater than 450 mg/m².

Disease characteristics were: 61% poor risk for KS tumor burden, 91% poor risk for immune system, and 47% poor risk for systemic illness; 36% were poor risk for all three categories; median CD4 count 21 cells/mm³ (51% less than 50 cells/mm³); mean absolute neutrophil count at study entry approximately 3,000 cells/mm³.

Of the 693 patients with concomitant medication information, 59% were on one or more antiretroviral medications [35% zidovudine (AZT), 21% didanosine (ddI), 16% zalcitabine (ddC), and 10% stavudine (D4T)]; 85% received PCP prophylaxis (54% sulfamethoxazole/trimethoprim); 85% received antifungal medications (76% fluconazole); 72% received antivirals (56% acyclovir, 29% ganciclovir, and 16% foscarnet) and 48% patients received colony-stimulating factors (sargramostim/filgrastim) during their course of treatment.

Adverse reactions led to discontinuation of treatment in 5% of patients with AIDS-related Kaposi's sarcoma and included myelosuppression, cardiac adverse reactions, infusion-related reactions, toxoplasmosis, HFS, pneumonia, cough/dyspnea, fatigue, optic neuritis, progression of a non-KS tumor, allergy to penicillin, and unspecified reasons. Tables 5 and 6 summarize adverse reactions reported in patients treated with doxorubicin hydrochloride liposome injection for AIDS-related Kaposi's sarcoma in a pooled analysis of the four trials.

Table 5: Hematologic Adverse Reactions 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 < 500/mm ³	46% 11%	49% 13%
Anemia < 10 g/dL < 8 g/dL	58% 16%	55% 18%
Thrombocytopenia < 150,000/mm ³ < 25,000/mm ³	61% 1.4%	61% 4.2%

*This includes a subset of subjects who were retrospectively identified as having disease progression on prior systemic combination chemotherapy (at least 2 cycles of a regimen containing at least 2 of 3 treatments: bleomycin, vincristine or vinblastine, or doxorubicin) or as being intolerant to such therapy.

**This includes only subjects with AIDS-KS who had available data from the 4 pooled trials.

Table 6: Non-Hematologic Adverse Reactions Reported in $\geq 5\%$ 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	18%	17%
Asthenia	7%	10%
Fever	8%	9%
Alopecia	9%	9%
Alkaline Phosphatase Increase	1.3%	8%
Vomiting	8%	8%
Diarrhea	5%	8%
Stomatitis	5%	7%
Oral Moniliasis	1.3%	6%

*This includes a subset of subjects who were retrospectively identified as having disease progression on prior systemic combination chemotherapy (at least 2 cycles of a regimen containing at least 2 of 3 treatments: bleomycin, vincristine or vinblastine, or doxorubicin) or as being intolerant to such therapy.

**This includes only subjects with AIDS-KS who had available adverse event data from the 4 pooled trials.

The following additional adverse reactions were observed in 705 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: mouth ulceration, 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.

Patients With Multiple Myeloma

The safety data described are from 318 patients treated with doxorubicin hydrochloride liposome injection (30 mg/m²) administered on day 4 following bortezomib (1.3 mg/m² i.v. bolus on days 1, 4, 8 and 11) every 3 weeks, in a randomized, open-label, multicenter study (Trial 6). In this trial, patients in the doxorubicin hydrochloride liposome injection + bortezomib combination group were treated for a median number of 4.5 months (range 21 days to 13.5 months). The population was 28 to 85 years of age (median age 61), 58% male, 90% Caucasian, 6% Black, and 4% Asian and Other. Table 7 lists adverse reactions reported in 10% or more of patients treated with doxorubicin hydrochloride liposome injection in combination with bortezomib for multiple myeloma.

Table 7: Frequency of Treatment-Emergent Adverse Reactions Reported in ≥10% Patients Treated for Multiple Myeloma With Doxorubicin Hydrochloride Liposome Injection in Combination With Bortezomib

Adverse Reaction	Doxorubicin Hydrochloride Liposome Injection + bortezomib (n=318)		Bortezomib (n=318)	
	Any (%)	Grade 3-4	Any (%)	Grade 3-4
Blood and lymphatic system disorders				
Neutropenia	36	32	22	16
Thrombocytopenia	33	24	28	17
Anemia	25	9	21	9
General disorders and administration site conditions				
Fatigue	36	7	28	3
Pyrexia	31	1	22	1
Asthenia	22	6	18	4
Gastrointestinal disorders				
Nausea	48	3	40	1
Diarrhea	46	7	39	5
Vomiting	32	4	22	1
Constipation	31	1	31	1
Mucositis/Stomatitis	20	2	5	<1
Abdominal pain	11	1	8	1
Infections and infestations				
Herpes zoster	11	2	9	2
Herpes simplex	10	0	6	1
Investigations				
Weight decreased	12	0	4	0
Metabolism and Nutritional disorders				
Anorexia	19	2	14	<1
Nervous system disorders				
Peripheral Neuropathy ¹	42	7	45	11
Neuralgia	17	3	20	4
Paresthesia/dysesthesia	13	<1	10	0
Respiratory, thoracic and				

mediastinal disorders

Cough	18	0	12	0
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Skin and subcutaneous tissue disorders

Rash ²	22	1	18	1
Hand-foot syndrome	19	6	<1	0

¹ Peripheral neuropathy includes the following adverse reactions: peripheral sensory neuropathy, neuropathy peripheral, polyneuropathy, peripheral motor neuropathy, and neuropathy NOS.

² Rash includes the following adverse reactions: rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, exfoliative rash, and rash generalized.

6.2 Postmarketing 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: muscle spasms

Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism (in some cases fatal)

Hematologic disorders: Secondary acute myelogenous leukemia

Skin and subcutaneous tissue disorders: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Secondary oral neoplasms: [see Warnings and Precautions (5.4)].

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with doxorubicin hydrochloride liposome injection.

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy**Risk Summary

Based on findings in animals, doxorubicin hydrochloride liposome injection can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, doxorubicin hydrochloride liposome injection was embryotoxic in rats and abortifacient in rabbits following intravenous administration during organogenesis at doses approximately 0.12 times the recommended clinical dose [see Data]. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data*Animal Data*

Doxorubicin hydrochloride liposome injection was embryotoxic at doses of 1 mg/kg/day in rats and was embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about 0.12

times the recommended dose of 50 mg/m² human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

8.2 Lactation

Risk Summary

It is not known whether doxorubicin hydrochloride liposome injection is present 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 breastfeeding during treatment with doxorubicin hydrochloride liposome injection.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Doxorubicin hydrochloride liposome injection can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during and for 6 months after treatment with doxorubicin hydrochloride liposome injection.

Males

Doxorubicin hydrochloride liposome injection may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during and for 6 months after treatment with doxorubicin hydrochloride liposome injection [*see Non-clinical Toxicology (13.1)*].

Infertility

Females

In females of reproductive potential, doxorubicin hydrochloride liposome injection may cause infertility and result in amenorrhea. Premature menopause can occur with doxorubicin HCl. Recovery of menses and ovulation is related to age at treatment.

Males

Doxorubicin hydrochloride liposome injection may result in oligospermia, azoospermia, and permanent loss of fertility. Sperm counts have been reported to return to normal levels in some men. This may occur several years after the end of therapy [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of doxorubicin hydrochloride liposome injection conducted in patients with either epithelial ovarian cancer (Trial 4) or with AIDS-related Kaposi's sarcoma (Trial 5) did not contain sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

In Trial 6, of 318 patients treated with doxorubicin hydrochloride liposome injection in combination with bortezomib for multiple myeloma, 37% were 65 years of age or older and 8% 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. Reduce doxorubicin hydrochloride liposome injection for serum bilirubin of 1.2 mg/dL or higher.

10 OVERDOSAGE

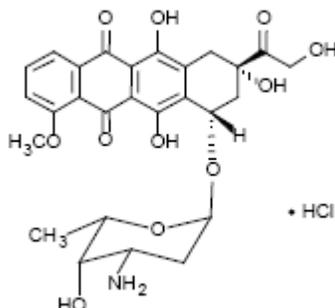
Acute overdosage with doxorubicin HCl causes increased risk of severe mucositis, leukopenia, and thrombocytopenia.

11 DESCRIPTION

Doxorubicin hydrochloride liposome injection is doxorubicin hydrochloride (HCl), an anthracycline topoisomerase II inhibitor, that is encapsulated in PEGYLATED liposomes for intravenous use.

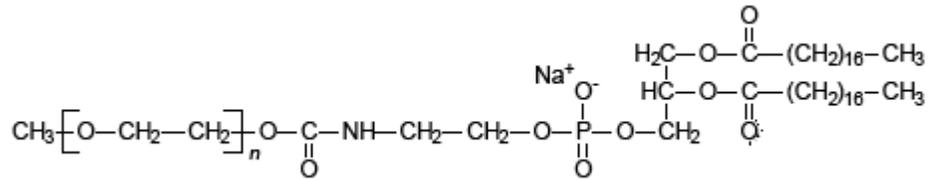
The chemical name of doxorubicin HCl is (8S,10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxohexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride. The molecular formula is $C_{27}H_{29}NO_{11} \cdot HCl$; its molecular weight is 579.99.

The molecular structure is:



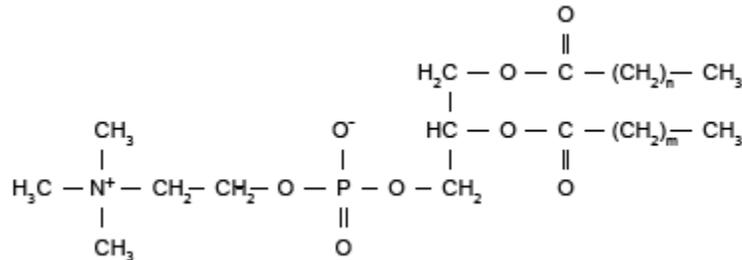
Doxorubicin hydrochloride liposome injection is a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single-dose vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The PEGYLATED liposome carriers are composed of cholesterol, 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and N-(carbonyl-methoxypolyethylene 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:



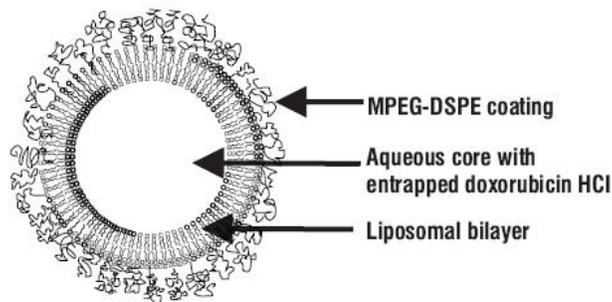
n=ca. 45

HSPC has the following structural formula:



m,n=14 or 16

Representation of a PEGYLATED liposome:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active ingredient of doxorubicin hydrochloride liposome injection is doxorubicin HCl. 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.

12.3 Pharmacokinetics

The pharmacokinetic parameters for total doxorubicin following a single dose of doxorubicin hydrochloride liposome injection infused over 30 minutes are presented in Table 8.

Table 8: Pharmacokinetic Parameters of Total Doxorubicin from Doxorubicin Hydrochloride Liposome Injection in Patients With AIDS-Related Kaposi’s Sarcoma

Parameter (units)	Dose	
	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 ± 0.120
AUC (mcg/mL•h)	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. Relative to doxorubicin hydrochloride liposome injection doses at or below 20 mg/m², the pharmacokinetics of total doxorubicin following a 50 mg/m² doxorubicin hydrochloride liposome injection dose are nonlinear. At this dose, the elimination half-life of doxorubicin hydrochloride liposome injection is longer and the clearance lower compared to a 20 mg/m² dose.

Distribution:

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.

In contrast to doxorubicin, which displays a large volume of distribution (range 700 to 1100 L/m²), the small steady state volume of distribution of liposomal doxorubicin suggests that doxorubicin hydrochloride liposome injection is largely confined to vascular fluid. Doxorubicin becomes available after the liposomes are extravasated. Plasma protein binding of doxorubicin hydrochloride liposome injection has not been determined; the plasma protein binding of doxorubicin is approximately 70%.

Metabolism:

Doxorubicinol, the major metabolite of doxorubicin, was detected at concentrations of 0.8 to 26.2 ng/mL in the plasma of patients who received 10 or 20 mg/m² doxorubicin hydrochloride liposome injection.

Elimination:

The plasma clearance of total doxorubicin from doxorubicin hydrochloride liposome injection was 0.041 L/h/m² at a dose of 20 mg/m². Following administration of doxorubicin HCl, the plasma clearance of doxorubicin is 24 to 35 L/h/m².

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Mutagenicity or carcinogenicity studies have not been conducted with doxorubicin hydrochloride liposome injection, however doxorubicin was shown to be mutagenic in the *in vitro* Ames assay, and clastogenic in multiple *in vitro* assays (CHO cell, V79 hamster cell, human lymphoblast, and SCE assays) and the *in vivo* mouse micronucleus assay. The possible adverse effects on fertility in animals have not been adequately evaluated. Doxorubicin hydrochloride liposome injection resulted in mild to moderate ovarian and testicular atrophy in mice after administration of a single dose of 36 mg/kg (about 2 times the 50 mg/m² human dose on a mg/m² basis). Decreased testicular weights and hypospermia were observed in rats after repeat doses \geq 0.25 mg/kg/day (about 0.03 times 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 0.4 times 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 (Trials 1, 2, and 3). One hundred forty-five of these patients were refractory to both paclitaxel-and platinum-based chemotherapy regimens, defined as disease progression while on treatment or relapse within 6 months of completing treatment. Patients received doxorubicin hydrochloride liposome injection at 50 mg/m² every 3 or 4 weeks for 3 to 6+ cycles in the absence of dose-limiting toxicity or disease progression.

The median age at diagnosis ranged from 52 to 64 years in the 3 studies, and the range was 22 to 85. Most patients had International Federation of Obstetricians and Gynecologists (FIGO) stage III or IV disease (ranging from 83% to 93%). Approximately one third of the patients had three or more prior lines of therapy (ranging from 22% to 33%).

The primary outcome measure was confirmed response rate based on Southwestern Oncology Group (SWOG) criteria for patients refractory to both paclitaxel-and a platinum-containing regimen. Secondary efficacy parameters were time to response, duration of response, and time to progression.

The response rates for the individual single arm trials are given in Table 9 below.

Table 9: Response Rates in Patients With Refractory Ovarian Cancer From Single Arm Ovarian Cancer Trials

	Trial 1 (U.S.) N=27	Trial 2 (U.S.) N=82	Trial 3 (non-U.S.) N=36
Response Rate	22.2%	17.1%	0%
95% Confidence Interval	8.6% -42.3%	9.7% -27%	0% -9.7%

In a pooled analysis of Trials 1 to 3, the response rate for all patients refractory to paclitaxel and platinum agents was 13.8% (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.

In Trial 4, a randomized, multicenter, open-label, trial in 474 patients with epithelial ovarian cancer after platinum-based chemotherapy, patients were randomized to receive either doxorubicin hydrochloride liposome injection 50 mg/m² every 4 weeks (n=239) or topotecan 1.5 mg/m² daily for 5 consecutive days every 3 weeks (n=235). Patients were stratified according to platinum sensitivity (response to initial platinum-based therapy and a progression-free interval of greater than 6 months off treatment) and the presence of bulky disease (tumor mass greater than 5 cm in size). The primary outcome measure was time to progression (TTP). Other endpoints included overall survival and objective response rate.

Of the 474 patients, the median age at diagnosis was 60 years (range 25 to 87), 90% were FIGO stage III and IV; 46% were platinum sensitive; and 45% had bulky disease.

There was no statistically significant difference in TTP between the two arms. Results are provided in Table 10.

Table 10: Results of Efficacy Analyses¹

	Protocol Defined ITT Population	
	Doxorubicin Hydrochloride Liposome Injection (n=239)	Topotecan (n=235)
TTP (Protocol Specified Primary Endpoint)		
Median (Months) ²	4.1	4.2
p-value ³		0.62
Hazard Ratio ⁴		0.96
95% CI for Hazard Ratio		(0.76, 1.20)
Overall Survival		
Median (Months) ²	14.4	13.7
p-value ⁵		0.05
Hazard Ratio ⁴		0.82
95% CI for Hazard Ratio		(0.68, 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) ²	6.9	5.9

¹ Analysis based on investigators' strata for protocol defined ITT population.

² Kaplan-Meier estimates.

³ p-value is based on the stratified log-rank test.

⁴Hazard 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.

⁵p-value not adjusted for multiple comparisons.

14.2 AIDS-Related Kaposi’s Sarcoma

Doxorubicin hydrochloride liposome injection was studied in an open-label, single-arm, multicenter study at a dose of 20 mg/m² every 3 weeks, until disease progression or unacceptable toxicity (Trial 5).

Data is described for a cohort of 77 patients retrospectively identified as having disease progression on prior systemic combination chemotherapy (at least two cycles of a regimen containing at least two of three treatments: bleomycin, vincristine or vinblastine, or doxorubicin) or as being intolerant to such therapy. Forty-nine of the 77 (64%) patients had received prior doxorubicin HCl.

The median time on study was 5.1 months (range 1 day to 15 months). The median cumulative dose of doxorubicin hydrochloride liposome injection was 154 mg/m² (range 20 to 620 mg/m²). Among the 77 patients, mean age was 38 years (range 24 to 54); 87% were Caucasian, 5% Hispanic, 4% Black, and 4% Asian/Other/Unknown; median CD4 count was 10 cells/mm³; ACTG staging criteria were 78% poor risk for tumor burden, 96% poor risk for immune system, and 58% poor risk for systemic illness at baseline; and mean Karnofsky status score was 74%. All patients had cutaneous or subcutaneous lesions, 40% also had oral lesions, 26% pulmonary lesions, and 14% had lesions of the stomach/intestine.

Two analyses of tumor response were used: one based on investigator assessment of changes in lesions based on modified ACTG criteria (partial response defined as no new lesions, sites of disease, or worsening edema; flattening of ≥50% of previously raised lesions or area of indicator lesions decreasing by ≥50%; and response lasting at least 21 days with no prior progression), and one based on changes in up to five prospectively indentified representative indicator lesions (partial response defined as flattening of ≥50% of previously raised indicator lesions, or >50% decrease in the area of indicator lesions and lasting at least 21 days with no prior progression). Of the 77 patients, 34 were evaluable for investigator assessment and 42 were evaluable for indicator lesion assessment; analyses of tumor responses are shown in Table 11.

Table 11: Response in Patients with Refractory¹ AIDS-Related Kaposi’s Sarcoma

Investigator Assessment	All Evaluable Patients (n=34)	Evaluable Patients Who Received Prior Doxorubicin (n=20)
Response ²		
Partial (PR)	27%	30%
Stable	29%	40%
Progression	44%	30%
Duration of PR (Days)		
Median	73	89
Range	42+ to 210+	42+ to 210+
Time to PR (Days)		

Median Range	43 15 to 133	53 15 to 109
Indicator Lesion Assessment	All Evaluable Patients (n=42)	Evaluable Patients Who Received Prior Doxorubicin (n=23)
Response ² Partial (PR) Stable Progression	48% 26% 26%	52% 30% 17%
Duration of PR (Days) Median Range	71 22+ to 210+	79 35 to 210+
Time to PR (Days) Median Range	22 15 to 109	48 15 to 109

¹ Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.

² There were no complete responses in this population.

Retrospective efficacy analyses were performed in two trials that had subsets of patients who received single-agent doxorubicin hydrochloride liposome injection and who were on stable antiretroviral therapy for at least 60 days prior to enrollment and until a response was demonstrated. In one trial, 7 of 17 (40%) patients had a durable response (median duration not reached but was longer than 11.6 months). In the second trial, 4 of 11 patients (40%) on a stable antiretroviral therapy demonstrated durable responses.

14.3 Multiple Myeloma

The efficacy of doxorubicin hydrochloride liposome injection in combination with bortezomib was evaluated in Trial 6, a randomized, open-label, international, multicenter study in 646 patients who had not previously received bortezomib and whose disease progressed during or after at least one prior therapy. Patients were randomized (1:1) to receive either doxorubicin hydrochloride liposome injection (30 mg/m²) administered IV on day 4 following bortezomib (1.3 mg/m² IV on days 1, 4, 8 and 11) or bortezomib alone every 3 weeks for up to 8 cycles or until disease progression or unacceptable toxicity. Patients who maintained a response were allowed to receive further treatment. The median number of cycles in each treatment arm was 5 (range 1 to 18).

The baseline demographics and clinical characteristics of the patients with multiple myeloma were similar between treatment arms (Table 12).

Table 12: Summary of Baseline Patient and Disease Characteristics

Patient Characteristics	Doxorubicin Hydrochloride Liposome Injection+bortezomib n=324	bortezomib n=322
Median age in years (range)	61 (28, 85)	62 (34, 88)
% Male/female	58 / 42	54 / 46
% Caucasian/Black/other	90 / 6 / 4	94 / 4 / 2
Disease Characteristics		
% with IgG/IgA/Light chain	57 / 27 / 12	62 / 24 / 11
% β 2 -microglobulin group		
\leq 2.5 mg/L	14	14
$>$ 2.5 mg/L and \leq 5.5 mg/L	56	55
$>$ 5.5 mg/L	30	31
Serum M-protein (g/dL): Median (Range)	2.5 (0 to10)	2.7 (0 to 10)
Urine M-protein (mg/24 hours): Median (Range)	107 (0 to 24883)	66 (0 to 39657)
Median Months Since Diagnosis	35.2	37.5
% Prior Therapy		
One	34	34
More than one	66	66
Prior Systemic Therapies for Multiple Myeloma		
Corticosteroid (%)	99	$>$ 99
Anthracyclines	68	67
Alkylating agent (%)	92	90
Thalidomide/lenalidomide (%)	40	43
Stem cell transplantation (%)	57	54

The primary outcome measure was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease or death due to progressive disease. The combination arm demonstrated significant improvement in TTP. As the prespecified primary objective was achieved at the interim analysis, patients in the bortezomib monotherapy group were then allowed to receive the doxorubicin hydrochloride liposome injection + bortezomib combination. Efficacy results are as shown in Table 13 and Figure 1.

Table 13: Efficacy of Doxorubicin Hydrochloride Liposome Injection in Combination With Bortezomib in the Treatment of Patients With Multiple Myeloma

Endpoint	Doxorubicin Hydrochloride Liposome Injection + bortezomib n=324	Bortezomib n=322
Time to Progression¹		
Progression or death due to progression (n)	99	150
Censored (n)	225	172
Median in days (months)	282 (9.3)	197 (6.5)
95% CI	250;338	170;217
Hazard ratio ² (95% CI)		0.55 (0.43, 0.71)
p-value ³		<0.001
Response (n)⁴	303	310
% Complete Response (CR)	5	3
% Partial Response (PR)	43	40
% CR + PR	48	43
p-value ⁵		0.25
Median Duration of Response (months) (95% CI)	10.2 (10.2; 12.9)	7 (5.9; 8.3)

¹ Kaplan Meier estimate.

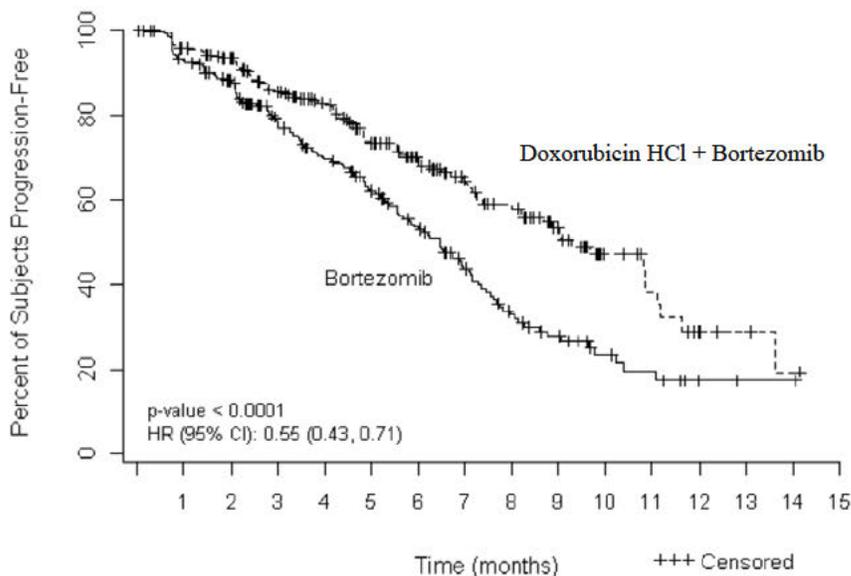
² Hazard ratio based on stratified Cox proportional hazards regression. A hazard ratio < 1 indicates an advantage for doxorubicin hydrochloride liposome injection+bortezomib.

³ Stratified log-rank test.

⁴ RR as per EBMT criteria.

⁵ Cochran-Mantel-Haenszel test adjusted for the stratification factors.

Figure 1-Time to Progression Kaplan-Meier Curve



Number of Subjects at Risk	
Doxorubicin HCl + Bortezomib	324 301 269 201 170 127 97 70 56 38 19 13 6 4 2 0
Bortezomib	322 290 253 189 150 112 84 56 35 25 14 9 2 1 1 0

At the final analysis of survival, 78% of subjects in the doxorubicin hydrochloride liposome injection and bortezomib combination therapy group and 80% of subjects in the bortezomib monotherapy group had died after a median follow up of 8.6 years. The median survival was 33 months in the doxorubicin hydrochloride liposome injection and bortezomib combination therapy group and 31 months in the bortezomib monotherapy group. There was no difference observed in overall survival at the final analysis [HR for doxorubicin hydrochloride liposome injection + bortezomib vs. bortezomib= 0.96 (95% CI 0.80, 1.14)].

Seventy-eight percent of subjects in the doxorubicin hydrochloride liposome injection and bortezomib combination therapy group and 80% of subjects in the bortezomib monotherapy group had received subsequent therapy.

15 REFERENCES

1. "Hazardous Drugs", *OSHA*, <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

Doxorubicin hydrochloride liposome injection is a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single-dose 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.

The following individually cartoned vials are available:

Table 14

mg in vial	fill volume	vial size	NDC #s
20 mg vial	10-mL	10-mL	43598-283-35
50 mg vial	25-mL	30-mL	43598-541-25

Refrigerate unopened vials of doxorubicin hydrochloride liposome injection at 2°-8°C (36°-46°F). Do not freeze.

Doxorubicin hydrochloride liposome injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Cardiomyopathy

Advise patients to contact their healthcare provider if they develop symptoms of heart failure [see *Warnings and Precautions (5.1)*].

Infusion-Related Reactions

Advise patients about the symptoms of infusion related reactions and to seek immediate medical attention if they develop any of these symptoms [see *Warnings and Precautions (5.2)*].

Myelosuppression

Advise patients to contact their healthcare provider for a new onset fever or symptoms of infection.

Hand-Foot Syndrome

Advise patients to notify their healthcare provider if they experience tingling or burning, redness, flaking, bothersome swelling, small blisters, or small sores on the palms of their hands or soles of their feet (symptoms of Hand-Foot Syndrome) [see *Warnings and Precautions (5.3)*].

Stomatitis

Advise patients to notify their healthcare provider if they develop painful redness, swelling, or sores in the mouth (symptoms of stomatitis).

Embryofetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider with a known or suspected pregnancy [see *Warnings and Precautions (5.5) and Use in Specific Populations (8.1)*].

Advise females and males of reproductive potential to use effective contraception during and for 6 months following treatment with doxorubicin hydrochloride liposome injection [see *Use in Specific Populations (8.3)*].

Lactation

Advise females not to breastfeed during treatment with doxorubicin hydrochloride liposome injection [see *Use in Specific Populations* (8.2)].

Infertility

Advise females and males of reproductive potential that doxorubicin hydrochloride liposome injection may cause temporary or permanent infertility [see *Use in Specific Populations* (8.3)].

Discoloration of Urine and Body Fluids

Inform patients that following doxorubicin hydrochloride liposome injection administration, a reddish-orange color to the urine and other body fluids may be observed. This nontoxic reaction is due to the color of the product and will dissipate as the drug is eliminated from the body.

Rx Only

Distributor:
Dr. Reddy's Laboratories Inc.,
Princeton NJ 08540

Made in India

Issued: 0416



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208657

LABELING REVIEWS

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	10/3/2016
ANDA Number(s)	208657
Review Number	2
Applicant Name	Dr. Reddy's Laboratories Limited
Established Name & Strength(s)	Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL) Single-dose Vials
Proposed Proprietary Name	None
Submission Received Date	4/4/2016
Labeling Reviewer	Younsook Kim
Labeling Team Leader	H. Ashley Jung
<p>Review Conclusion</p> <p><input checked="" type="checkbox"/> ACCEPTABLE – No Comments.</p> <p><input type="checkbox"/> ACCEPTABLE – Include Post Approval Comments</p> <p><input type="checkbox"/> Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.</p> <p><small>*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.</small></p> <p><input type="checkbox"/> On Policy Alert List</p>	

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) dated (add date):

None

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with Choose an item. all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated April 4, 2016.

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

None

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

The following comments are from the labeling review C2 based on the submission dated 10/8/2015.

1. GENERAL COMMENTS

- a. We strongly encourage you to assign different numbers for the Product Code, the middle digits of the NDC number to differentiate the 20 mg and 50 mg containers and ensure that the container and carton labels and package insert are updated to reflect the new numbers. When injectable products contain the same product concentration but a different total amount of drug, each of these injectable products should have a different product code assigned to help healthcare practitioners distinguish the difference in total drug content.
- b. Please revise the package type term (b) (4) to "Single-dose" throughout your labeling pieces. We refer you to Guidance for Industry "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use", which is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>.

Firm's Response and Assessment: The middle NDC numbers (Product Code) have been revised: -283- for the 20 mg and -541- for the 50 mg. (b) (4) has been replaced with "Single dose" throughout the labeling. Satisfactory.

2. CONTAINER LABEL

- a. Relocate the company logo to the bottom of the label.
- b. We recommend increasing the prominence of the active moiety name "DOXOrubicin Hydrochloride".
- c. Relocate "Cytotoxic Agent/ Must be diluted" to appear on the top of the side panel.
- d. Include "Single-Dose Vial. Discard unused portion" right below the strength statement.
- e. Revise to read "LIPOSOMAL FORMULATION-DO NOT SUBSTITUTE FOR DOXORUBICIN HCL".
- f. Revise the storage statement to read "Refrigerate, 2° - 8°C (36° - 46°F). Do not Freeze." and relocate to appear above the usual dosage statement on the side panel.
- g. (b) (4)

3. CARTON LABELING

- a. Relocate the company logo to the bottom of the label.
- b. Relocate "Sterile/ Cytotoxic Agent/ MUST BE DILUTED PRIOR TO ADMINISTRATION" to appear below the usual dosage statement on the side panel.
- c. Include "Single-Dose Vial. Discard unused portion" right below the strength statement.
- d. Revise to read "LIPOSOMAL FORMULATION-DO NOT SUBSTITUTE FOR DOXORUBICIN HCL".
- e. Revise the storage statement to read "Refrigerate, 2° - 8°C (36° - 46°F). Do not Freeze." and relocate to appear right below "FOR INTRAVENOUS INFUSION ONLY" on the principal display panel.
- f. (b) (4)
- g. Revise the listing of the ingredients by grouping them into an active ingredient, liposomal carriers and the rest of the ingredients to improve its clarity and readability (*i.e.*, Each mL contains doxorubicin HCl, 2 mg. PEGYLATED 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, approximately 2 mg; sucrose; histidine; and hydrochloric acid and/or sodium hydroxide).

Firm's Response and Assessment: The revised container and carton labels are satisfactory.

4. PRESCRIBING INFORMATION

- a. HIGHLIGHTS, Limitation statement: Revise the presentation of the established name to appear in upper case letters as such: "These highlights do not include all the information needed to use DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION safely and effectively. See full prescribing information for DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION."
- b. 12.3 Pharmacokinetics, Table 8, third column: Revise (b) (4) to read "0.004".

Firm's Response and Assessment: The revised labeling is satisfactory.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?

NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? NO

If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

**Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)**

MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): N50718/S-048

Supplement Approval Date: 4/16/2015

Proprietary Name: DOXIL

Established Name: Doxorubicin Hydrochloride Liposome Injection

Description of Supplement:

This "Prior Approval" supplemental new drug application provides updates to the CLINICAL STUDIES section of the United States Prescribing Information based on the final study report for DOXIL Study MMY-3001 entitled "A Randomized Controlled Study of DOXIL/CAELYX (doxorubicin HCL liposome injection) and VELCADE (bortezomib) or VELCADE Monotherapy for the Treatment of Relapsed Multiple Myeloma." In addition, the DOSAGE AND ADMINISTRATION and HOW SUPPLIED sections of the label revised to reflect the current language for handling cytotoxic agents.

FYI:

The CMC Supplements S-049 to 052 approved after S-048 did not require new labeling.

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): [Click here to enter text.](#)

Supplement Approval Date: [Click here to enter text.](#)

Proprietary Name: [Click here to enter text.](#)

Established Name: [Click here to enter text.](#)

Description of Supplement:

TEMPLATE (e.g., BPCA, PREA, Carve-out): [Click here to enter text.](#)

OTHER (Describe): [Click here to enter text.](#)

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

Satisfactory.

Labeling note for the declaration of the ammonium sulfate amount:

The RLD declares the amount of ammonium sulfate as 1 mg in each mL on the carton and 2 mg in each mL in the insert labeling whereas the ANDA declares as 2 mg in each mL both in the carton and insert labeling.

(b) (4)

^{(b) (4)} Therefore, the 2 mg/mL of ammonium sulfate on the carton of the pending ANDA should be acceptable.

Taken from Module 3.2.P.1 of NDA 050718:

(b) (4)

Taken from the BE review of the pending ANDA dated 6/24/2016:

Reviewer's Comments

Per the control correspondence #11-0539¹², the proposed formulation of Doxorubicin Hydrochloride Liposome Injection submitted by Dr. Reddy's Laboratories Limited was determined to be Q1 and Q2 the same as that of Doxil[®] (NDA052728), the RLD product at the time of submission of the control.

Per the comparative composition table above, Dr. Reddy's test product formulation is qualitatively (Q1) but not quantitatively (Q2) the same as that of Sun Pharma Global's product, the current RLD (ANDA203263). The amount of the histidine in the test product is within ±5% (b) (4) of the corresponding excipient in the reference product, but the sucrose concentration (b) (4) exceeds the allowable ±5% difference.]

However, during the review of ANDA203263 (Sun Pharma Global's Doxorubicin Hydrochloride Liposome Injection), the Division of Bioequivalence (DB) determined the formulation of the test product to be acceptable¹⁴, even though the test product formulation was not quantitatively (Q2) the same as that of Doxil[®]¹⁵. Please refer to Section 4.2 Formulation Data of the ANDA203263 DB review¹⁴ for details.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: Supplement-50, 01/27/2016]

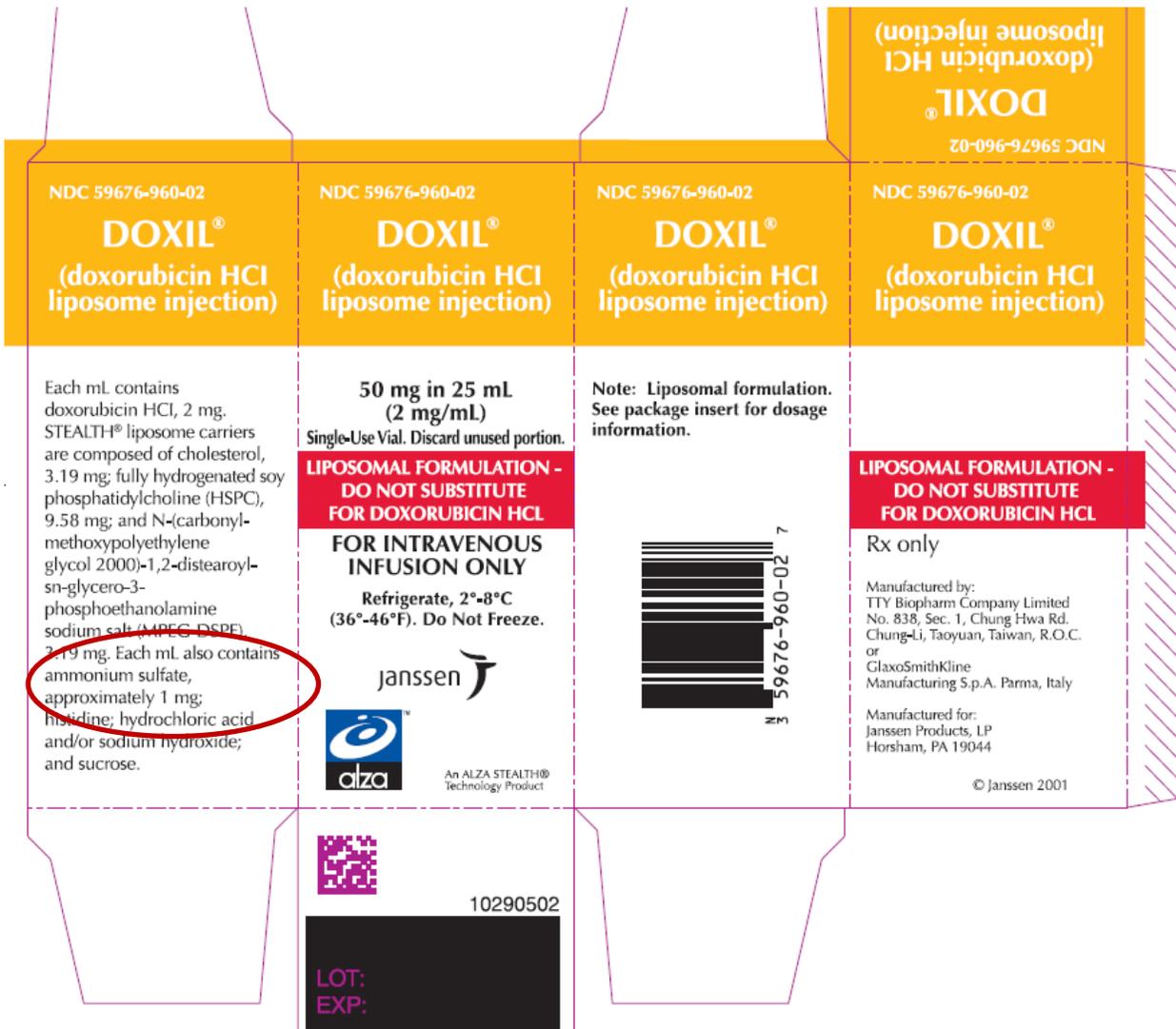
(FYI: S-050 was for addition of a new manufacturing site)

Vials:



Containers:

<p>NDC 59676-960-01 DOXIL® (doxorubicin HCl liposome injection)</p>	<p>NDC 59676-960-01 DOXIL® (doxorubicin HCl liposome injection)</p>	<p>NDC 59676-960-01 DOXIL® (doxorubicin HCl liposome injection)</p>	<p>NDC 59676-960-01 DOXIL® (doxorubicin HCl liposome injection)</p>
<p>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, approximately 1 mg; histidine; hydrochloric acid and/or sodium hydroxide; and sucrose.</p>	<p>20 mg in 10 mL (2 mg/mL) Single-Use Vial. Discard unused portion.</p> <p>LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL</p> <p>FOR INTRAVENOUS INFUSION ONLY</p> <p>Refrigerate, 2°-8°C (36°-46°F). Do Not Freeze.</p> <p>Janssen</p> <p>ALZA An ALZA STEALTH® Technology Product</p>	<p>Note: Liposomal formulation. See package insert for dosage information.</p> <p>59676-960-01 0</p> <p>© Janssen 2001</p>	<p>LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL</p> <p>Rx only</p> <p>Manufactured by: TTY Biopharm Company Limited No. 838, Sec. 1, Chung Hwa Rd. Chung-Li, Taoyuan, Taiwan, R.O.C. or GlaxoSmithKline Manufacturing S.p.A. Parma, Italy</p> <p>Manufactured for: Janssen Products, LP Horsham, PA 19044</p> <p>© Janssen 2001</p>
<p>LOT: EXP:</p>	<p>10290402</p>		



3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results

	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
<u>US</u> <u>P</u>	10/3/2016	NO	NA	NA
<u>PF</u>	10/3/2016	NO	NA	NA

Reviewer Comments:

This product does not have a USP monograph. The liposomal formulation is different from Doxorubicin Hydrochloride Injection and not interchangeable.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 10/3/2016.

Table 3 provides Orange Book patents for the Model Labeling N050718 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
NA						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter "Carve-out" or "None")
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

None

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**

Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**

Are there changes to the manufacturer/distributor/packer statements? **NO**

If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
The PEGYLATED liposome carriers are composed of cholesterol, 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and N-(carbonyl-methoxypolyethylene 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.	The PEGYLATED liposome carriers are composed of cholesterol, 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and N-(carbonyl-methoxypolyethylene 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.	No change noted.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment																								
<p>16 HOW SUPPLIED/STORAGE AND HANDLING Doxorubicin hydrochloride liposome injection is a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, (b) (4) 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. The following individually cartoned vials are available:</p> <table border="1"> <thead> <tr> <th>Table 14 mg in vial NDC #s</th> <th>fill volume</th> <th>vial size</th> <th></th> </tr> </thead> <tbody> <tr> <td>20 mg vial 283-35</td> <td>10-mL</td> <td>10-mL</td> <td>43598-</td> </tr> <tr> <td>50 mg vial (b) (4)</td> <td>25-mL</td> <td>30-mL</td> <td>43598-</td> </tr> </tbody> </table> <p>Refrigerate unopened vials of doxorubicin hydrochloride liposome injection at 2°-8°C (36°-46°F). Do not freeze. Doxorubicin hydrochloride liposome injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹</p>	Table 14 mg in vial NDC #s	fill volume	vial size		20 mg vial 283-35	10-mL	10-mL	43598-	50 mg vial (b) (4)	25-mL	30-mL	43598-	<p>16 HOW SUPPLIED/STORAGE AND HANDLING Doxorubicin hydrochloride liposome injection is a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single-dose 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. The following individually cartoned vials are available:</p> <table border="1"> <thead> <tr> <th>Table 14 mg in vial NDC #s</th> <th>fill volume</th> <th>vial size</th> <th></th> </tr> </thead> <tbody> <tr> <td>20 mg vial 283-35</td> <td>10-mL</td> <td>10-mL</td> <td>43598-</td> </tr> <tr> <td>50 mg vial 541-25</td> <td>25-mL</td> <td>30-mL</td> <td>43598-</td> </tr> </tbody> </table> <p>Refrigerate unopened vials of doxorubicin hydrochloride liposome injection at 2°-8°C (36°-46°F). Do not freeze. Doxorubicin hydrochloride liposome injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹</p>	Table 14 mg in vial NDC #s	fill volume	vial size		20 mg vial 283-35	10-mL	10-mL	43598-	50 mg vial 541-25	25-mL	30-mL	43598-	Package type and NDC numbers are revised. Satisfactory.
Table 14 mg in vial NDC #s	fill volume	vial size																								
20 mg vial 283-35	10-mL	10-mL	43598-																							
50 mg vial (b) (4)	25-mL	30-mL	43598-																							
Table 14 mg in vial NDC #s	fill volume	vial size																								
20 mg vial 283-35	10-mL	10-mL	43598-																							
50 mg vial 541-25	25-mL	30-mL	43598-																							

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
<p>Distributor: Dr. Reddy's Laboratories Inc., Princeton NJ 08540</p> <p>Made in India</p>	<p>Distributor: Dr. Reddy's Laboratories Inc., Princeton NJ 08540</p> <p>Made in India</p>	No change noted.

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

The chemistry review completed on 7/18/2016 states that the CMC-related labeling is adequate.

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? Yes No
If "No," explain.

Is the drug product subject of a USP monograph? Yes No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

HOW SUPPLIED section

i) Is the information accurate? Yes No

If "No," explain.

ii) Are the storage conditions acceptable? Yes No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for *injectables*, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? Yes No N/A

If "No," explain.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	20 mg/10 mL and 50 mg/25 mL Single-dose Vials	4/4/2016	Satisfactory
Blister	NA	--	--	--
Carton	Final	1 vial in 1 carton	4/4/2016	Satisfactory

(Other – specify)	NA	--	--	--
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	April 2016	4/4/2016	Satisfactory
Medication Guide	NA	--	--	--
Patient Information	NA	--	--	--
SPL Data Elements		9/2015	4/4/2016	Satisfactory



Huijeong
Jung

Digitally signed by Huijeong Jung
Date: 10/13/2016 04:18:42PM
GUID: 508da702000287c1e12e719fda6a6d14



Younsook
Kim

Digitally signed by Younsook Kim
Date: 10/04/2016 02:26 54PM
GUID: 552fd6e800b05b97e682c93faba494fe

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	02/22/2016
ANDA Number(s)	208657
Review Number	1
Applicant Name	Dr. Reddy's Laboratories Limited
Established Name & Strength(s)	Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL) Single-dose Vials
Proposed Proprietary Name	None
Submission Received Date	10/08/2015
Labeling Reviewer	Younsook Kim
Labeling Team Leader	H. Ashley Jung
Review Conclusion	
<input type="checkbox"/> ACCEPTABLE – No Comments	
<input type="checkbox"/> ACCEPTABLE – Include Post Approval Comments	
<input checked="" type="checkbox"/> Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant.	
*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.	
<input type="checkbox"/> On Policy Alert List	

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1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on February 22, 2016 based on your submission dated October 8, 2015:

1. GENERAL COMMENTS

- a. We strongly encourage you to assign different numbers for the Product Code, the middle digits of the NDC number to differentiate the 20 mg and 50 mg containers and ensure that the container and carton labels and package insert are updated to reflect the new numbers. When injectable products contain the same product concentration but a different total amount of drug, each of these injectable products should have a different product code assigned to help healthcare practitioners distinguish the difference in total drug content.
- b. Please revise the package type term “(b) (4)” to “Single-dose” throughout your labeling pieces. We refer you to Guidance for Industry “Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use”, which is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>.

2. CONTAINER LABEL

- a. Relocate the company logo to the bottom of the label.
- b. We recommend increasing the prominence of the active moiety name “DOXOrubicin Hydrochloride”.
- c. Relocate “Cytotoxic Agent/ Must be diluted” to appear on the top of the side panel.
- d. Include “Single-Dose Vial. Discard unused portion” right below the strength statement.
- e. Revise to read “LIPOSOMAL FORMULATION-DO NOT SUBSTITUTE FOR DOXORUBICIN HCL”.
- f. Revise the storage statement to read “Refrigerate, 2° - 8°C (36° - 46°F). Do not Freeze.” and relocate to appear above the usual dosage statement on the side panel.
- g. (b) (4)

3. CARTON LABELING

- a. Relocate the company logo to the bottom of the label.
- b. Relocate “Sterile/ Cytotoxic Agent/ MUST BE DILUTED PRIOR TO ADMINISTRATION” to appear below the usual dosage statement on the side panel.
- c. Include “Single-Dose Vial. Discard unused portion” right below the strength statement.
- d. Revise to read “LIPOSOMAL FORMULATION-DO NOT SUBSTITUTE FOR DOXORUBICIN HCL”.
- e. Revise the storage statement to read “Refrigerate, 2° - 8°C (36° - 46°F). Do not Freeze.” and relocate to appear right below “FOR INTRAVENOUS INFUSION ONLY” on the principal display panel.
- f. (b) (4)
- g. Revise the listing of the ingredients by grouping them into an active ingredient, liposomal carriers and the rest of the ingredients to improve its clarity and readability (*i.e.*, Each mL contains doxorubicin HCl, 2 mg. PEGYLATED 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, approximately 2 mg; sucrose; histidine; and hydrochloric acid and/or sodium hydroxide).

4. PRESCRIBING INFORMATION

- a. HIGHLIGHTS, Limitation statement: Revise the presentation of the established name to appear in upper case letters as such: **“These highlights do not include all the information needed to use DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION safely and effectively. See full prescribing information for DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION.”**
- b. 12.3 Pharmacokinetics, Table 8, third column: Revise (b) (4)” to read “0.004”.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) dated (add date). NA

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

None

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Has the ANDA been accepted for filing? YES

Are there any pending issues in DLR's SharePoint Drug Facts? NO

If Yes, please explain.

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO

If Yes, please explain.

Labeling Note:

S/E Determination for Doxorubicin for Injection (Powder form) NDA 050467:

S/E Determination	Initial	Doxorubicin HCL	doxorubicin HCL, injectable; injection, 10mg/10ml, 20mg/vial, 50mg/vial, and 150mg/vial	(b) (4)	050467	No Approval Actions (TAAR) can be taken prior to FRN	All disciplines can send communications (IR/EC/CC)	Shannon Baxole	12/28/2015
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The ANDA product is solution in liposomal formulation.

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

**Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)**

<input checked="" type="checkbox"/> MOST RECENTLY APPROVED <u>NDA</u> MODEL LABELING <i>(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)</i> NDA#/Supplement# (S-000 if original): N50718/S-048 Supplement Approval Date: 04/16/2015 Proprietary Name: DOXIL Established Name: Doxorubicin Hydrochloride Liposome Injection Description of Supplement: This "Prior Approval" supplemental new drug application provides updates to the CLINICAL STUDIES section of the United States Prescribing Information based on the final study report for DOXIL Study MMY-3001 entitled "A Randomized Controlled Study of DOXIL/CAELYX (doxorubicin HCL liposome injection) and VELCADE (bortezomib) or VELCADE Monotherapy for the Treatment of Relapsed Multiple Myeloma." In addition, the DOSAGE AND ADMINISTRATION and HOW SUPPLIED sections of the label revised to reflect the current language for handling cytotoxic agents. Labeling Note: S-049 approved on 10/09/2015 (b) (4) No new labeling was required. S-050 approved on 12/28/2015 provides for the addition of GlaxoSmithKline as a manufacturing site for DOXIL®. Final labeling including vials and cartons was submitted for DOXIL® product manufactured by GSK. Clinical information in the labeling remain the same.
<input type="checkbox"/> MOST RECENTLY APPROVED <u>ANDA</u> RLD LABELING ANDA#/Supplement# (S-000 if original): Click here to enter text. Supplement Approval Date: Click here to enter text. Proprietary Name: Click here to enter text. Established Name: Click here to enter text. Description of Supplement: Click here to enter text.
<input type="checkbox"/> TEMPLATE (e.g., BPCA, PREA, Carve-out): Click here to enter text.
<input type="checkbox"/> OTHER (Describe): Click here to enter text.

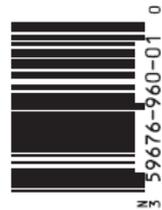
2.2.2 MODEL CONTAINER LABELS

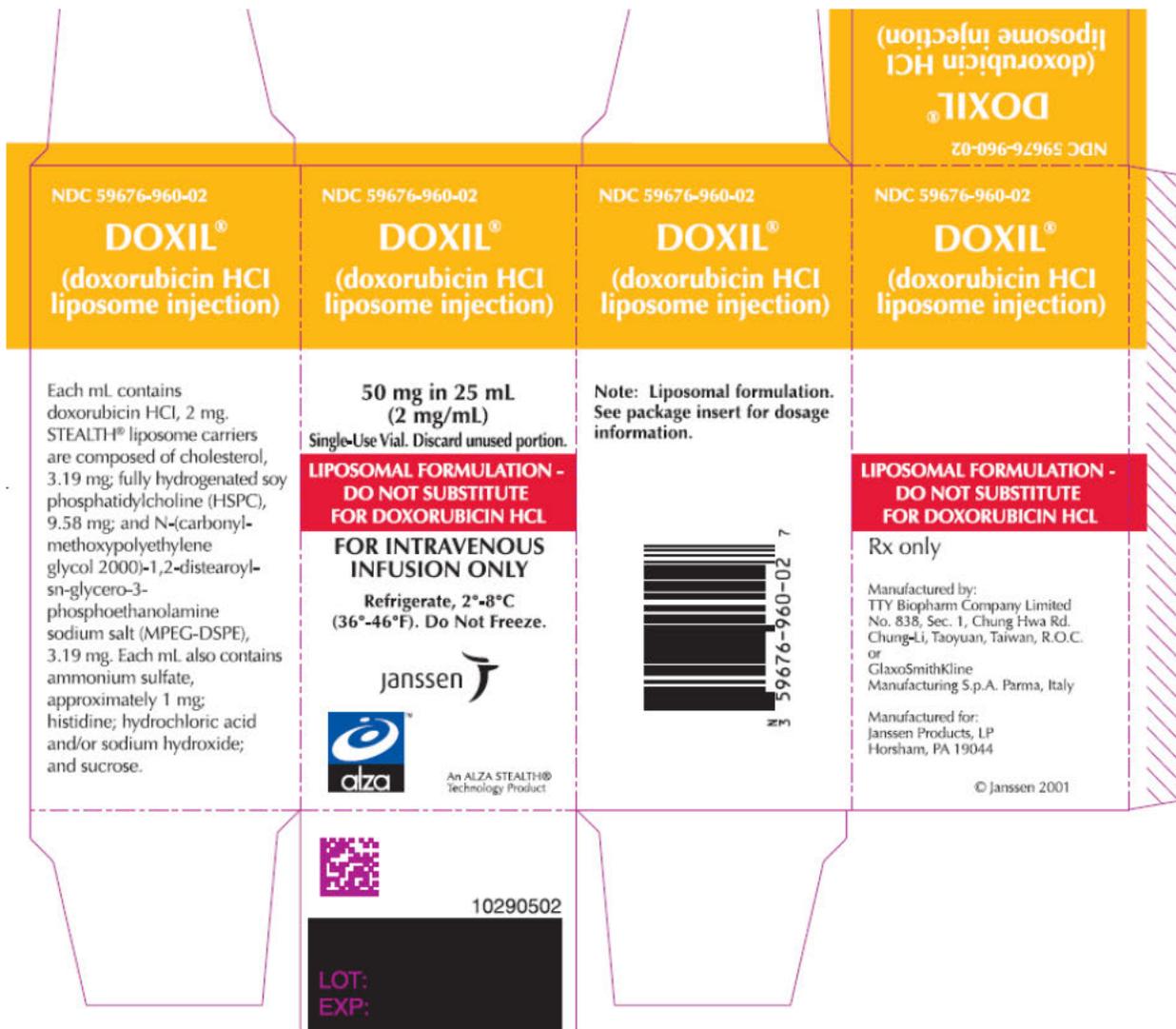
Model container/carton/blister labels (Source: Supplement-50, 01/27/2016)

Vials:

<p>NDC 59676-960-01</p> <p>DOXIL[®] (doxorubicin HCl liposome injection)</p> <p>20 mg in 10 mL (2 mg/mL)</p> <p>Single-Use Vial. Discard unused portion.</p> <p>LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL</p> <p>© Janssen 2001 10290201 Rx ONLY</p>	<p>FOR INTRAVENOUS INFUSION ONLY</p> <p>Refrigerate, 2°-8°C (36°-46°F). Do Not Freeze.</p> <p>See package insert for dosage information.</p> <p>Janssen Products, LP Horsham, PA 19044</p> <p>janssen</p> <p>alza An ALZA STEALTH[®] TECHNOLOGY PRODUCT</p>	 <p>0100359676960010</p> <p>LOT: EXP:</p>	<p>NDC 59676-960-02</p> <p>DOXIL[®] (doxorubicin HCl liposome injection)</p> <p>50 mg in 25 mL (2 mg/mL)</p> <p>Single-Use Vial. Discard unused portion.</p> <p>LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL</p> <p>© Janssen 2001</p> <p>janssen</p> <p>© Janssen 2001</p> <p>Janssen Products, LP Horsham, PA 19044</p> <p>alza An ALZA STEALTH[®] TECHNOLOGY PRODUCT</p>	<p>FOR INTRAVENOUS INFUSION ONLY</p> <p>Refrigerate, 2°-8°C (36°-46°F). Do Not Freeze.</p> <p>See package insert for dosage information.</p> <p>Rx ONLY</p>  <p>0100359676960027</p> <p>LOT: EXP:</p>
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Containers:

<p>NDC 59676-960-01</p> <p>DOXIL[®] (doxorubicin HCl liposome injection)</p> <p>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, approximately 1 mg; histidine; hydrochloric acid and/or sodium hydroxide; and sucrose.</p>	<p>NDC 59676-960-01</p> <p>DOXIL[®] (doxorubicin HCl liposome injection)</p> <p>20 mg in 10 mL (2 mg/mL)</p> <p>Single-Use Vial. Discard unused portion.</p> <p>LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL</p> <p>FOR INTRAVENOUS INFUSION ONLY</p> <p>Refrigerate, 2°-8°C (36°-46°F). Do Not Freeze.</p> <p>janssen</p> <p>alza An ALZA STEALTH[®] Technology Product</p>	<p>NDC 59676-960-01</p> <p>DOXIL[®] (doxorubicin HCl liposome injection)</p> <p>Note: Liposomal formulation. See package insert for dosage information.</p>  <p>59676-960-01 0</p>	<p>NDC 59676-960-01</p> <p>DOXIL[®] (doxorubicin HCl liposome injection)</p> <p>LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL</p> <p>Rx only</p> <p>Manufactured by: TTY Biopharm Company Limited No. 838, Sec. 1, Chung Hwa Rd. Chung-Li, Taoyuan, Taiwan, R.O.C. or GlaxoSmithKline Manufacturing S.p.A. Parma, Italy</p> <p>Manufactured for: Janssen Products, LP Horsham, PA 19044</p> <p>© Janssen 2001</p>
 <p>10290402</p> <p>LOT: EXP:</p>			



2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	2/22/2016	NO	NA	NA
PF	2/22/2016	NO	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The [Orange Book](#) was searched on 2/22/2016.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
NA						

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of Facility ANDA Manufactured (Cite Source)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
Source: 3.2.P.3: (b) (4)	<p><u>Vials:</u></p> <p>J15 Distributor: Dr. Reddy's Laboratories Inc., Princeton, NJ 08540 Made in India</p> <p><u>Cartons:</u></p> <p>Distributor: Dr. Reddy's Laboratories Inc., Princeton, NJ 08540 Made in India</p>	<p>Prescribing Information: Distributor: Dr. Reddy's Laboratories Inc., Princeton NJ 08540</p> <p>Made in India</p>

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

- Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
 OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **NA**

Is **the established name** for this ANDA acceptable? **YES**

Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**

Are the required USP recommendations reflected in the labeling? **NA**

Is the applicant's "patent carve out" acceptable? **NA**

Is the applicant's "exclusivity carve out" acceptable? **NA**

Is the Manufacturer statement acceptable? **NA**

Reviewer Comments:

1. The package labeling is in draft.
2. The established name for this ANDA product is Doxorubicin Hydrochloride Liposome Injection, which is different and not interchangeable with Doxorubicin Hydrochloride Injection according to Palliv Nithyanandan from the agency.
3. No monograph is present for the liposomal formulation*.
4. The prescribing information is same as the model labeling NDA 50718/S-048 approved on 04/16/2015.
5. Minor editorial revision:
 - a. HIGHLIGHTS, Limitation statement: Revise the presentation of the established name to appear in upper case letters as such: **“These highlights do not include all the information needed to use DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION safely and effectively. See full prescribing information for DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION.”**
 - b. 12.3 Pharmacokinetics, Table 8, third column: Revise (b)(4) to read “0.004”.

*Labeling Note: There is one ANDA approved for this product, ANDA 203263. The established name is declared as “Doxorubicin Hydrochloride Liposome Injection” and there is no USP monograph according to the labeling supplement review S-005 dated 08/25/2015.

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
<ul style="list-style-type: none"> • Cholesterol • Fully hydrogenated soy phosphatidylcholine (HSPC) • N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero3-phosphoethanolamine sodium salt (MPEG-DSPE) • Ammonium sulfate • Histidine • Hydrochloric acid • Sodium hydroxide • sucrose 	<ul style="list-style-type: none"> • Cholesterol • Fully hydrogenated soy phosphatidylcholine (HSPC) • N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero3-phosphoethanolamine sodium salt (MPEG-DSPE) • Ammonium sulfate • Histidine • Hydrochloric acid • Sodium hydroxide • sucrose

Reviewer Assessment:

Does the chemistry review follow the [Chemistry/Labeling Memorandum of Understanding \(MOU\)](#)?

YES, chemistry review pending

(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Are the inactive ingredients information consistent with “Components and Composition” information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review.) **PENDING CHEMISTRY REVIEW**

For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **YES**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

If the labeling includes a “Does not contain...” statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:

The chemistry review has not been assigned.

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling																	
Model Labeling	<p>DOXIL is 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. The following individually cartoned vials are available:</p> <table border="1"> <thead> <tr> <th colspan="4">Table 14</th> </tr> <tr> <th>mg in vial</th> <th>fill volume</th> <th>vial size</th> <th>NDC #s</th> </tr> </thead> <tbody> <tr> <td>20 mg vial</td> <td>10-mL</td> <td>10-mL</td> <td>59676-960-01</td> </tr> <tr> <td>50 mg vial</td> <td>25-mL</td> <td>30-mL</td> <td>59676-960-02</td> </tr> </tbody> </table> <p>Refrigerate unopened vials of DOXIL at 2°-8°C (36°-46°F). Do not freeze.</p> <p>DOXIL is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹</p>	Table 14				mg in vial	fill volume	vial size	NDC #s	20 mg vial	10-mL	10-mL	59676-960-01	50 mg vial	25-mL	30-mL	59676-960-02
Table 14																	
mg in vial	fill volume	vial size	NDC #s														
20 mg vial	10-mL	10-mL	59676-960-01														
50 mg vial	25-mL	30-mL	59676-960-02														
ANDA Labeling	<p>Doxorubicin hydrochloride liposome injection is a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, (b) (4) vials.</p> <p>Each 10-mL vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/mL.</p> <p>Each 30-mL vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/mL.</p> <p>The following individually cartoned vials are available:</p> <table border="1"> <thead> <tr> <th colspan="4">Table 14</th> </tr> <tr> <th>mg in vial</th> <th>fill volume</th> <th>vial size</th> <th>NDC #s</th> </tr> </thead> <tbody> <tr> <td>20 mg vial</td> <td>10-mL</td> <td>10-mL</td> <td>43598-283-35</td> </tr> <tr> <td>50 mg vial</td> <td>25-mL</td> <td>30-mL</td> <td>43598- (b) (4)</td> </tr> </tbody> </table> <p>Refrigerate unopened vials of doxorubicin hydrochloride liposome injection at 2°-8°C (36°-46°F). Do not freeze.</p> <p>Doxorubicin hydrochloride liposome injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹</p>	Table 14				mg in vial	fill volume	vial size	NDC #s	20 mg vial	10-mL	10-mL	43598-283-35	50 mg vial	25-mL	30-mL	43598- (b) (4)
Table 14																	
mg in vial	fill volume	vial size	NDC #s														
20 mg vial	10-mL	10-mL	43598-283-35														
50 mg vial	25-mL	30-mL	43598- (b) (4)														

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **YES, chemistry review pending**

If the chemistry review does NOT follow the MOU, is the description (scoring, color and imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **NA**

Does the ANDA require the same color coding as the Model Labeling? **NA**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**

Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**

Is the storage or dispensing statement acceptable as compared to the USP? **NA**

Reviewer Comments:

The chemistry review has not been assigned.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **CLICK HERE**

Is the Medication Guide same as the model labeling, except for allowable differences? **CLICK HERE**

Does the Medication Guide meet the requirements of [21 CFR 208.20](#)? **CLICK HERE**

Has the Applicant committed to provide a sufficient number of medication guides? **CLICK HERE**

Is the phonetic spelling of the proprietary or established name present? **CLICK HERE**

Is FDA 1-800-FDA-1088 phone number included? **CLICK HERE**

Reviewer Comments:

NA

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **CLICK HERE**

Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:

NA

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**

(For BLISTER labels go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**

Is title case used in expressing the established name? **YES**

Does labeling comply with Tall Man lettering recommendations found on [FDA webpage](#)? **YES**

Is container label too small to contain all required information? **NO** If yes, does the container meet the “too small” exemption found in [21 CFR 201.10\(i\)](#)? **NA**

Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **NO**

Is the following information properly displayed?

Net quantity statement: **YES**

Route(s) of administration (other than oral): **YES**

Warnings (if any) or cautionary statements (if any): **NO**

Medication Guide Pharmacist instructions per [21 CFR 208.24\(d\)](#): **NA**

[Controlled substance symbol](#): **NA**

Usual Dosage statement: **YES**

Product strength equivalency statement: **NA**

NDC: **NO**

Bar code per [21 CFR 201.25\(c\)\(2\)](#): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**

For foreign manufacturers, does the labeling have the country of origin? **YES**

Are the required USP recommendations reflected on the label(s)? **NA**

Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

Are multiple strengths differentiated by use of different color or other acceptable means? **YES**

Are the labels of related products differentiated to avoid selection errors? **NA**

Does the ANDA require the same color coding as the Model Labeling? **NO**

Are the requirements of [21 CFR 201.15](#) met for all required label statements? **YES**

Are the requirements of [21 CFR 201.100](#) met for all required label statements? **YES**

Reviewer Comments:

1. The declaration of the established name complies with the Tall Man lettering recommendations: DOXOrubicin.
2. Firm used the same product code for two different containers, 10 mL and 25 mL. See GENERAL COMMENTS.
3. Package type term: See GENERAL COMMENTS.
4. Please move the company logo to the bottom of the label.
5. We recommend increasing the prominence of the active moiety name “DOXOrubicin Hydrochloride”.
6. Relocate “Cytotoxic Agent/ Must be diluted” to appear on the top of the side panel.
7. Include “Single-dose vial. Discard unused portion” right below the strength statement.
8. Revise to read “LIPOSOMAL FORMULATION-DO NOT SUBSTITUTE FOR DOXORUBICIN HCL”.
9. Revise the storage statement to read “Refrigerate, 2° - 8°C (36° - 46°F). Do not Freeze.” and relocate to appear above the usual dosage statement on the side panel.
10. (b) (4)

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **YES**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **YES**

If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **NO**

Reviewer Comments:

The inactive ingredients are listed on the carton labeling and the vial has the statement of Retain in carton until time of use. Acceptable.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**

Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **CLICK HERE**

Reviewer Comments:

NA

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is there a prominent, boxed declaration reading “Pharmacy Bulk Package – Not for Direct Infusion” on the principal display panel following the expression of strength? **CLICK HERE**

Does the container label include graduation marks? **CLICK HERE**

Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **CLICK HERE**

Is the quantity or proportion of all inactive ingredients listed on label as required under [21 CFR 201.100\(b\)\(5\)\(iii\)](#)? **CLICK HERE**

Reviewer Comments:

NA

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **CLICK HERE**

Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **CLICK HERE**

Reviewer Comments:

NA

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**

If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **YES** If no, please explain the differences in the Reviewer Comments section.

If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **YES**

If country of origin is not on Container, does it appear on outer packaging labeling? **YES**

Reviewer Comments:

1. The declaration of the established name complies with the Tall Man lettering recommendations: DOXOrubicin.
2. Firm used the same product code for two different containers, 10 mL and 25 mL. See GENERAL COMMENTS.
3. Package type term: See GENERAL COMMENTS.
4. Please move the company logo to the bottom of the label.
5. Relocate “Sterile/ Cytotoxic Agent/ MUST BE DILUTED PRIOR TO ADMINISTRATION” to appear

- below the usual dosage statement on the side panel.
6. Include “Single-Dose Vial. Discard unused portion” right below the strength statement.
 7. Revise to read “LIPOSOMAL FORMULATION-DO NOT SUBSTITUTE FOR DOXORUBICIN HCL”.
 8. Revise the storage statement to read “Refrigerate, 2° - 8°C (36° - 46°F). Do not Freeze.” and relocate to appear right below “FOR INTRAVENOUS INFUSION ONLY” on the principal display panel.
 9. (b) (4)
 10. Revise the listing of the ingredients by grouping them into an active ingredient, liposomal carriers and the rest of the ingredients to improve its clarity and readability (*i.e.*, Each mL contains doxorubicin HCl, 2 mg. PEGYLATED 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, approximately 2 mg; sucrose; histidine; and hydrochloric acid and/or sodium hydroxide).

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

- Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**
- Is Drug Facts Labeling format acceptable per [21 CFR 201.66](#)? **CLICK HERE**
- Does “Questions?” have a toll-free number no less than 6 pt. font size [per 21 CFR 201.66\(c\)\(9\)](#) or “1-800-FDA-1088” per [21 CFR 201.66 \(c\)\(5\)\(vii\)](#)? **CLICK HERE**
- Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
- Is the applicant’s “patent carve out” acceptable? **CLICK HERE**
- Is the applicant’s “exclusivity carve out” acceptable? **CLICK HERE**
- Is the established name for this ANDA acceptable? **CLICK HERE**
- Is title case used in expressing the established name? **CLICK HERE**
- Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **CLICK HERE**
- Is the following information properly displayed?
- Pharmacological category: **CLICK HERE**
 - Net quantity statement: **CLICK HERE**
 - Route(s) of administration (other than oral): **CLICK HERE**
 - Warnings (if any) or cautionary statements (if any): **CLICK HERE**
 - NDC: **CLICK HERE**
 - Bar code per [21 CFR 201.25\(c\)\(2\)](#): **CLICK HERE**
- Is the Manufacturer/Distributor/Packager statement acceptable? **CLICK HERE**
- For foreign manufacturers, does the labeling have the country of origin? **CLICK HERE**
- Are the required USP recommendations reflected in the labeling? **CLICK HERE**
- Is the storage statement acceptable? **CLICK HERE**
- Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
- Are multiple strengths differentiated by use of different color or other acceptable means? **CLICK HERE**
- Are the labels of related products differentiated to avoid selection errors? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients Click here to enter text.	ANDA Inactive Ingredients Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients information consistent with “Components and Composition” information as provided in Module 3.2.P.1? **CLICK HERE**

Are the inactive ingredients listed in alphabetical order? **CLICK HERE**

For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **CLICK HERE**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**

If the labeling includes a “Does not contain...” statement, is it acceptable/allowed? **CLICK HERE** Has the statement been verified by chemistry? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	Click here to enter text.
ANDA (enter source of information of product description on the right hand column; e.g., chemistry Review & date, Module 3.2.P.5.1)	Click here to enter text.

Reviewer Assessment:

Is the description ([scoring](#), color and [imprint](#)) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**

Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**

Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**

If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.2.2 OTC: OTHER PATIENT LABELING

Are other patient labeling required? **CLICK HERE**

If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was other patient labeling submitted? **CLICK HERE**

Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.3 CONTAINER/CLOSURE

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.

Does the container require a child-resistant closure (CRC) as described in the [Poison Prevention Act and regulations](#)? **NA**

Are the tamper evident requirements met for [OTC](#) and [Controlled Substances](#)? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence.) **NA**

For ophthalmic products:

Does this ophthalmic product cap color match [the American Academy of Ophthalmology \(AAO\) packaging color-coding](#) scheme? **NA**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **CLICK HERE**

If YES, does text comply with the recommendations in USP General Chapter <1>? **CLICK HERE**

What is the cap and ferrule color? **Grey**

NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

(b) (4)

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**

If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	Stated Content	Location of the Information
Click here to enter text.	Click here to enter text.	Click here to enter text.

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **CLICK HERE**

Are the stated contents in the table above acceptable? **CLICK HERE**

Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per [21 CFR 201.323](#).

Did the chemistry reviewer verify the aluminum content? **CLICK HERE**

Are the labeling requirements met per [21 CFR 201.323](#)? **CLICK HERE**

Reviewer Comments:

NA

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the [SPL data elements](#) to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	ANDA Tablet/Capsule Size (mm) and imprint code from SPL	ANDA Tablet/Capsule Size (mm) and imprint code (Cite source of information such as the chemistry review that follows the MOU, Product Specification in 3.2.P.5.1, Commercial Batch Record in 3.2.P.3.3. etc.)
NA	NA	NA

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **NA**

Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments:

Satisfactory

4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

None

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline reviewer(s):

Reviewer Comments:

None

6. SPECIAL CONSIDERATIONS

None

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each labeling piece analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Draft	20 mg/10 mL and 50 mg/25 mL Single-dose Vials	10/08/2015	Revise
Blister	NA	--	--	--
Carton	Draft	1 vial in 1 carton	10/08/2015	Revise
(Other – specify)	NA	--	--	--

Table 13 Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	09/2015	10/08/2015	Revise
Medication Guide	NA	--	--	--
Patient Information	NA	--	--	--
SPL Data Elements		09/2015	10/08/2015	Revise

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208657

CHEMISTRY REVIEWS

Recommendation: Adequate

A/NDA 208657

Review 2

Drug Name/Dosage Form	Doxorubicin Hydrochloride Liposome Injection, 20 mg/10mL and 50 mg/25mL
Strength	2mg/mL
Route of Administration	Intravenous (Infusion)
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories Limited
US agent, if applicable	Srinivasa Rao 107, College Road East, Princeton, New Jersey 08540 Tel: (b) (6) Email: srao@drreddys.com

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	10/08/2015	DS DP, Process, Microbiology, Biopharmaceuticals
Quality / Response to Information Request	11/17/2015	DS DP, Process, Biopharmaceuticals
Quality/Response to Information Request	09/15/2016	DS DP, Process, Microbiology, Biopharmaceuticals
Quality/Response to Information Request	11/17/2016	DS DP, Process,
Multiple categories/subcategories	02/16/2017	DS DP, Process Biopharmaceuticals
Multiple categories/subcategories	03/22/2017	DS DP, Process, Facility, Biopharmaceuticals
Quality / Response to Information Request	05/11/2017	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	NA	NA
Drug Product	Hailing Zhang	Gil Jong Kang
Process	Yuesheng Ye	Chidambaram Nallaperumal
Microbiology	Tiwari Samata	Bhattacharya Nandini
Facility	Car Lee	Juandria Williams
Biopharmaceutics	Jing Li	Okponanabofa Eradiri
Regulatory Business Process Manager	Christina Pleas	NA
Application Technical Lead	Hailing Zhang	NA
Laboratory (OTR)	NA	NA
ORA Lead	NA	NA
Environmental	Hailing Zhang	Gil Jong Kang

Quality Review Data Sheet

[IQA Review Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	12/23/2016	NAI by David Skanchy
	Type II			Adequate		
	Type IV			Adequate		
	Type IV			Adequate		
	Type III			Adequate		
	Type III			Adequate		

(b) (4)	Type V	(b) (4)	Adequate	
---------	--------	---------	----------	--

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC Review	(b) (4)	Bio-IND for BE study
CMC Review		RLD

2. CONSULTS

NA

Executive Summary

[IQA Review Guide Reference](#)

I. Recommendations and Conclusion on Approvability

ANDA 208657 is submitted by Dr. Reddy's Laboratories Limited for Doxorubicin Hydrochloride Liposome Injection, 20 mg/10mL and 50 mg/25mL.

ANDA 208657 is recommended for approval, as the quality reviews of drug substance DMF, drug product, manufacturing, process and control, facility, microbiology, and biopharmaceutics all deem this ANDA adequate.

II. Summary of Quality Assessments

A. Product Overview

ANDA 208657 is submitted by Dr. Reddy's Laboratories Limited for Doxorubicin Hydrochloride Liposome Injection, 20 mg/10mL and 50 mg/25mL. Current Orange Book currently lists ANDA 203263 (Sun Pharma, approved on 02/04/2013) as the Reference Standards (RS). Doxil® approved under N050718 and owned by Janssen Res and Dev is the RLD and the regulatory basis for the submission of this ANDA. The ANDA sponsor Dr. Reddy's Laboratories Limited submitted (b) (4) for a bioequivalence study in the support of submission of ANDA 208567.

Doxorubicin hydrochloride liposome injection is 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 PEGYLATED liposome carriers are composed of cholesterol, 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and N-(carbonyl-methoxypolyethylene 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.

The proposed ANDA drug product is Q1/Q2 to RS product. The manufacturing process (b) (4)

Doxorubicin hydrochloride liposome injection is indicated for the treatment of ovarian cancer: 50 mg/m² intravenously over 60 minutes every 4 weeks for 4 courses minimum, and AIDS related Kaposi's Sarcoma: 20 mg/m² intravenously over 60 minutes every 3 weeks; multiple myeloma: 30 mg/m² intravenously over 60 minutes on day 4 of each 21-day cycle for eight cycles.

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. (b) (4)

Diluted doxorubicin hydrochloride liposome injection should be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours

0	←	Total Number of Comparability Protocols (ANDA only)
---	---	--

Proposed Indication(s) including Intended Patient Population	<p>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.</p> <p>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</p>
---	---

	<p>chemotherapy or intolerance to such therapy.</p> <p>Multiple Myeloma Doxorubicin hydrochloride liposome injection, in combination with bortezomib, is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib.</p>
Duration of Treatment	<p>Ovarian Cancer The recommended dose of doxorubicin hydrochloride liposome injection is 50 mg/m² intravenously over 60 minutes every 28 days until disease progression or unacceptable toxicity.</p> <p>AIDS-Related Kaposi’s Sarcoma The recommended dose of doxorubicin hydrochloride liposome injection is 20 mg/m² intravenously over 60 minutes every 21 days until disease progression or unacceptable toxicity.</p> <p>Multiple Myeloma The recommended dose of doxorubicin hydrochloride liposome injection is 30 mg/m² intravenously over 60 minutes on day 4 of each 21-day cycle for eight cycles or until disease progression or unacceptable toxicity. Administer doxorubicin hydrochloride liposome injection after bortezomib on day 4 of each cycle.</p>
Maximum Daily Dose	50 mg/m ² (total 90 mg for a 70 kg adult)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug substance: Doxorubicin Hydrochloride is official in the current USP. The API is supplied by (b) (4). DMF (b) (4) is referenced for the drug substance, and is adequate per the review (NAI) by David J Skanchy on 12/23/2016.

Drug product: The proposed ANDA drug product is Q1/Q2 to the RS. The pharmaceutical development utilized risk based and Quality by design approaches. Adequate data are provided to support that the ANDA product is pharmaceutically equivalent to the RS. The firm provided the following stability data:

(b) (4)

(b) (4)

All testing results are within the proposed stability specification. The sponsor proposed 18 months expiration dating period for Doxorubicin Hydrochloride Liposome Injection 20 mg/10mL and 50 mg/25mL based on the satisfactory results from 18 months stability data at long-term storage conditions.

Manufacturing, Process and Control:

(b) (4)

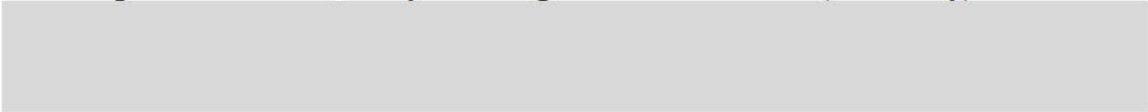
The manufacturing process is considered as adequate.

Facility: There appears to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's and their previous inspection results, history, and relevant experience. The facilities are determined acceptable in their identified functions and responsibilities to support approval of ANDA 208657 for manufacturing Doxorubicin Hydrochloride Liposome Injection.

Biopharmaceutics: The proposed dissolution method is adequate for quality control of the drug product. The proposed dissolution acceptance criteria are permissive and FDA recommended new acceptance criteria based on the data provided. The Applicant acknowledged the FDA recommended acceptance criteria. The FDA approved in vitro release method and the acceptance criteria agreed to with the Applicant are as follows:

In vitro release method	Apparatus	Culture tube, incubation in water bath
	Agitation	No
	Medium	pH 6.5 buffer (2M Ammonium Chloride and 0.2M L-Histidine)
	Temperature	47°C
Acceptance criteria	2 hr	(b) (4) %
	4 hr	(b) (4) %
	8 hr	NLT (b) (4) %

Microbiology: the submission is recommended for approval on the basis of sterility assurance.

C. Special Product Quality Labeling Recommendations (NDA only)**D. Final Risk Assessment (see Attachment)**

Final risk assessment is not applicable for this ANDA, (b) (4)
(b) (4) Rise based assessment has be utilized to review this ANDA.



Hailing
Zhang

Digitally signed by Hailing Zhang
Date: 5/13/2017 07:53:54AM
GUID: 52fbecbc00297c6adb1041acad9f4eb



DRUG SUBSTANCE

Product Background: ANDA 208657 is submitted by Dr. Reddy's Laboratories Limited for Doxorubicin Hydrochloride Liposome Injection, 20 mg/10mL and 50 mg/25mL. Orange Book currently lists ANDA 203263 (Sun Pharma, approved on 02/04/2013) as the Reference Listed Drug. Doxil® approved under N050718 and owned by Janssen Res and Dev is the regulatory basis for the submission of this ANDA.

Drug substance doxorubicin hydrochloride is a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. *caesis*. (b) (4)

It is red-orange crystalline powder, soluble in water.

Maximum daily dose (MDD) for this product is 50 mg/m² (total 90 mg for a 70 kg adult). Per ICH guidance (Q3A and Q3B, the following thresholds are identified for a drug substance and drug product:

	IT	QT
Drug substance	0.1%	0.15%
Drug Product		(b) (4)

However, since this is a fermentation product, the limits may vary from the ICH guidance.

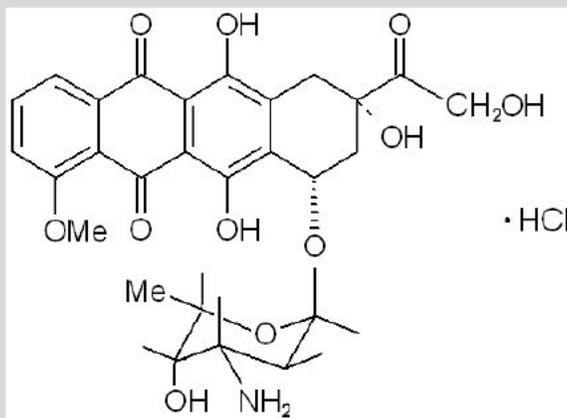
ANDA: 208657 (Review # 1A)

Chemical Name and Structure:

Chemical Name:

Doxorubicin Hydrochloride (5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-, hydrochloride (8S-cis)-.)

Chemical Structure:



Molecular formula: $C_{27}H_{29}NO_{11} \cdot HCl$

Molecular weight: 579.99 g/mol

CAS#: [25316-40-9]

DMF # (if applicable): (b) (4)

Applicant Name/DMF Holder: (b) (4)

(b) (4)

Post-Approval Stability Protocol and Commitment

NA

Reviewer's Assessment:

NA

R Regional Information

Comparability Protocols

NA

Reviewer's Assessment:

NA

Post-Approval Commitments

NA

Reviewer's Assessment:

NA

Lifecycle Management Considerations

NA

NA

List of Deficiencies:

None

Primary Drug Substance Reviewer Name and Date: Hailing Zhang, 07/06/2016, 11/21/2016, 05/08/2017 (Review #2)

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Pahala Simamora, 7/15/2016, 11/22/2016 (response to IR#1)

DRUG PRODUCT

Product Background:

NDA 050718 was approved for Doxorubicin Hydrochloride Liposome Injection, 2mg/mL (Doxil®) on 11/17/1997 and is owned by Jassen Res and Dev. it was listed as RLD for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL. ANDA 203263 was approved for generic Doxorubicin Hydrochloride Liposome Injection, 2mg/mL on 02/04/2013 and is owned by Sun Pharma Global. It is currently listed as RLD for Doxorubicin Hydrochloride Liposome Injection, 2 mg/mL in Orange Book.

The ANDA sponsor Dr. Reddy's Laboratories Limited submitted [REDACTED] (b) (4) for a bioequivalence study in the support of submission of ANDA 208567.

Doxorubicin hydrochloride liposome injection is 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 PEGYLATED liposome carriers are composed of cholesterol, 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and N-(carbonyl-methoxypolyethylene 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.

Doxorubicin hydrochloride liposome injection is indicated for the treatment of ovarian cancer: 50 mg/m² intravenously over 60 minutes every 4 weeks for 4 courses minimum, and AIDS related Kaposi's Sarcoma: 20 mg/m² intravenously over 60 minutes every 3 weeks; multiple myeloma: 30 mg/m² intravenously over 60 minutes on day 4 of each 21-day cycle for eight cycles.

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. [REDACTED] (b) (4)

[REDACTED] Diluted doxorubicin hydrochloride liposome injection should be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours.

ANDA: 208567 (Review #2)

Drug Product Name / Strength: 2 mg/mL supplied in 20 mg/10 mL or 50 mg/25 mL of single dosage vial

Route of Administration: I.V. infusion



Applicant Name: Dr. Reddy's Laboratories Limited

(b) (4)

(b) (4)

Reviewer's Assessment: Adequate

The firm provided satisfactory post-approval protocol and commitment.

R Regional Information

Environmental Analysis

Reviewer's Assessment: Adequate

The firm stated this application qualifies for categorical exclusion as per 21 CFR § 25.31 (a).

Methods Verification Package: Refer to S.4 and P.4**Reviewer's Assessment:**

Method validation is submitted. Please Refer to S.4 and P.4. for comments and deficiencies.

Comparability Protocols: NA**Reviewer's Assessment: NA**

Post-Approval Commitments: Refer to P.7

Reviewer's Assessment:

Post-approval commitment is satisfactory.

Lifecycle Management Considerations: NA

Reviewer's Assessment:

NA

List of Deficiencies (Review #2)

None

***Primary Drug Product Reviewer Name and Date: Hailing Zhang, 07/06/2016,
11/21/2018(Review #1A), 05/05/2017 (Review #2)***

***Secondary Reviewer Name and Date (and Secondary Summary, as needed): Pahala
Simamora, 7/18/2016, 11/22/2016 (for review of IR#1 response)***

LABELING

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? Yes No

If "No," explain.

Is the drug product subject of a USP monograph? Yes No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? Yes No

If "No," explain.

ii) Are the storage conditions acceptable? Yes No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? Yes No N/A

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? Yes No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: NA

NA

List of Deficiencies: None

**Primary Drug Product Reviewer Name and Date: Hailing Zhang, 07/06/2016, 05/08/2017
(Review #2)**

Secondary Drug Product Reviewer Name and Date: [Pahala Simamora](#), 7/18/2016



Gil Jong
Kang

Digitally signed by Gil Jong Kang
Date: 5/08/2017 01:46:46PM
GUID: 508da7040002895abefd4134899d8a56



Hailing
Zhang

Digitally signed by Hailing Zhang
Date: 5/08/2017 01:47:03PM
GUID: 52fbecbc000297c6adb1041acad9f4eb

ANDA 208657- Doxorubicin Hydrochloride Injection
ATTACHMENT II: List of Deficiencies for Complete Response

A. Drug Substance Deficiencies
None

B. Drug Product Deficiencies

1.

2.

3.

4.

(b) (4)

5.

(b) (4)

C. Environmental Analysis Deficiencies

None

D. Labeling Deficiencies

None

E. Process Deficiencies

1.

(b) (4)

2.

3.

4.

5.

F. Facilities Deficiencies

None

G. Biopharmaceutics Deficiencies

1. We acknowledge that you submitted f_2 values for the in vitro leakage tests conducted in 50% human plasma and under low frequency ultrasound. Provide the similarity factor f_2 values for the profile comparisons using 12 units of test and reference products for each of the in vitro leakage tests. Equivalent in vitro leakage under multiple conditions supports a lack of uncontrolled leakage under a range of physiological conditions and equivalent drug delivery to the tumor cells.
2. Justify the selection of the concentrations of ammonium chloride and L-histidine in the medium used for the proposed in vitro release method.
3. We acknowledge the stability data up to 18 months at the 2-hr and 8-hr time points and the batch release data you provided in section 3.2.P.8.3. It is noted that the 2-hr in vitro release data at the initial stability time point is higher than the 2-hr data at batch release. Please clarify the initial time point of the stability program relative to batch release. It is also noted that both 2-hr and 8-hr data show a trend as a function of storage time, with 12-month and 18-month data going up and 3-month and 15-month data going down (the difference between the 15-month and 18-month data are more than 20%). Investigate the root cause for the trend observed. In addition, demonstrate the robustness and reproducibility of the in vitro release testing methodology.
4. Provide complete in vitro release data for the stability batches by including all the time points. It is noted that the complete data may not be available prior to 18 months. Provide the complete in vitro release data at the current stability time point for the stability batches or the release/ stability data of any new batch manufactured using the same composition and process.
5. Due to lack of the complete in vitro release data for evaluation and the observed trend of the stability data, the adequacy of the proposed in vitro release method cannot be determined, and evaluation of the acceptance criteria is pending.

H. Microbiology Deficiencies

N/A

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date: Pahala Simamora, 12/23/2016

FACILITIES

Product Background:

Doxorubicin Hydrochloride Liposome Injectable is an anthracycline cytostatic antibiotic, liposomal drug product packaged in a sterile, (b) (4) vial, and diluted with 5% Dextrose Injection, USP prior to administration. This is a drug shortage product.

Indications for use:

- Ovarian cancer, after failure of platinum-based chemotherapy;
- AIDS-related Kaposi’s Sarcoma, after failure of prior systemic chemotherapy or intolerance to such therapy;
- Multiple Myeloma, in combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.

The reference listed drug (RLD) is Doxil®, NDA 050718 approved 17 November 1997.

ANDA: 208657

Drug Product Name / Strength:

Doxorubicin Hydrochloride Liposome Injection 20mg/10mL and 50mg/25mL

Route of Administration: IV (Infusion)

Applicant Name: Dr. Reddy's Laboratories Limited

Review Summary: Doxorubicin Hydrochloride Liposome Injection is produced (b) (4)
 (b) (4) The proposed facilities are found to be acceptable because they have adequate quality systems and capabilities to perform the proposed functions in commercial manufacturing.

List Submissions being reviewed (table):

Submission	Submission date
Original submission	10/8/2015

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

(b) (4)

Comparability Protocols**Reviewer's Assessment:** N/A***Post-Approval Commitments*****Reviewer's Assessment:** N/A***Lifecycle Management Considerations***

(b) (4)

List of Deficiencies: None***Primary Facilities Reviewer Name and Date:*** Carl Lee, Drafted 10/27/16
Revised 11/28/16***Secondary Reviewer Name and Date (and Secondary Summary, as needed):******Juandria Williams, PhD; DIA/B3; November 28, 2016***



Juandria
Williams

Digitally signed by Juandria Williams
Date: 12/21/2016 08:39 34PM
GUID: 513b65ab0005b7cb48614cd3d341d717



Carl
Lee

Digitally signed by Carl Lee
Date: 12/07/2016 01:49:16PM
GUID: 573cc062013a2d0cc4bcf842b08368e7



PROCESS

Product Background: This is a liposomal drug product for injection filled in glass vials.

NDA/ANDA: ANDA 208657

Drug Product Name / Strength: Doxorubicin Hydrochloride Liposome Injection /
20 mg/10 mL and 50 mg/25 mL

Route of Administration: IV (Infusion)

Applicant Name: Dr. Reddy's Laboratories Limited

Review Summary:

(b) (4)

List Submissions being reviewed (table):

Document Reviewed	Description
10/08/2015	Original submission
11/17/2015	Quality information
02/08/2016	Quality information
09/15/2016	Quality information

Highlight Key Outstanding Issues from Last Cycle:

(b) (4)

Primary Process Reviewer Name and Date:

Yuesheng Ye, drafted on 6/13/2016, and revised on 6/22/2016, 7/14/2016 and 7/18/2016

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

Minor comments/questions are noted.

N. Chidambaram, Ph.D., 06/20/2016

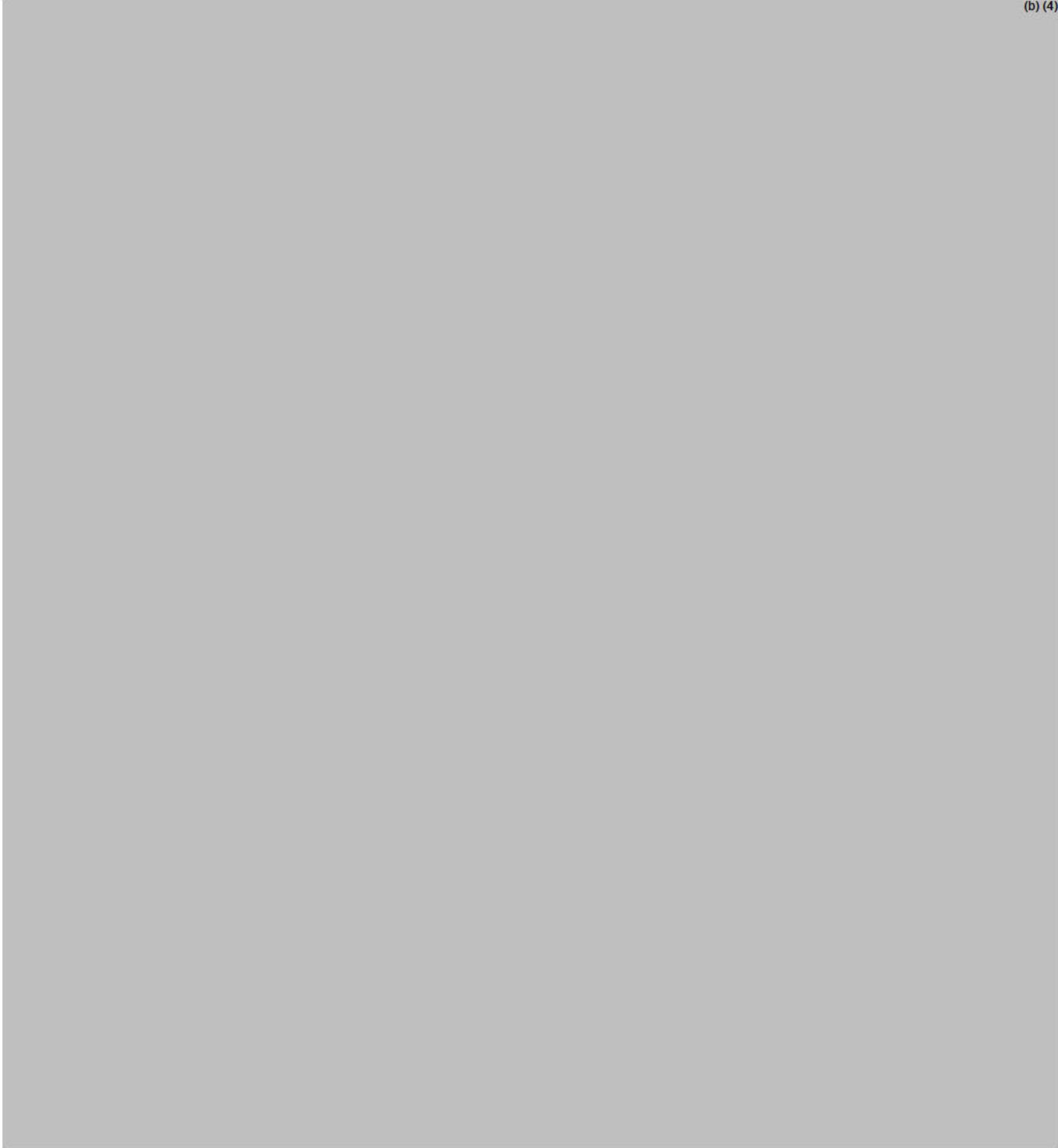
I concur

N. Chidambaram, Ph.D., 06/22/2016, 07/18/2016

Review for the First IR Response

The 1st IR was issued on August 1, 2016, and the response was received on September 15, 2016

(b) (4)



Primary Process Reviewer Name and Date:

Yuesheng Ye, drafted on 10/28/2016, revised on 11/02/2016.

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

Minor revisions are noted.

N. Chidambaram, Ph.D., 11/01/2016.

I concur

N. Chidambaram, Ph.D., 11/02/2016.



PROCESS

Product Background: This is a liposomal drug product for injection filled in glass vials.

NDA/ANDA: ANDA 208657

Drug Product Name / Strength: Doxorubicin Hydrochloride Liposome Injection /
20 mg/10 mL and 50 mg/25 mL

Route of Administration: IV (Infusion)

Applicant Name: Dr. Reddy's Laboratories Limited

Review Summary:

(b) (4)

List Submissions being reviewed (table):

Document Reviewed	Description
10/08/2015	Original submission
11/17/2015	Quality information
02/08/2016	Quality information

Highlight Key Outstanding Issues from Last Cycle:

N/A

Concise Description Outstanding Issues Remaining:

(b) (4)



QUALITY ASSESSMENT



Primary Process Reviewer Name and Date:

Yuesheng Ye, drafted on 6/13/2016, and revised on 6/22/2016, 7/14/2016 and 7/18/2016

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

Minor comments/questions are noted.

N. Chidambaram, Ph.D., 06/20/2016

I concur

N. Chidambaram, Ph.D., 06/22/2016, 07/18/2016

MICROBIOLOGY

Product Background:

Doxorubicin Hydrochloride Liposome Injection is indicated for the treatment of patients with ovarian cancer after failure of platinum-based chemotherapy.

NDA/ANDA: 208657

Drug Product Name/Strength: Doxorubicin Hydrochloride Liposome Injection, IV (Infusion), 20mg/10mL and 50mg/25mL, packaged in a single dose.

Route of Administration: Sterile liposome Injection for IV Infusion

Applicant Name: Dr. Reddy's Laboratories Limited

Manufacturing Site:

(b) (4)

Method of Sterilization:

(b) (4)

Review Summary:

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

List Submissions being reviewed (table):

Submit	Received	Review Request	Assigned to Reviewer
10/08/2015	10/08/2015	N/A	03/03/2016
09/15/2016	09/15/2016	N/A	N/A

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining:

A Microbiology Information Request was issued to the applicant on September 01, 2016, and the applicant provided adequate response in their amendment dated 9/15/16 which is being reviewed here.

SUPPORTING/RELATED DOCUMENTS:

(b) (4)

ANDA 204561 and associated microbiology review 204561.doc (not recommended overall but acceptable for the referenced section) dated 5/4/16 reviewed by Wendy Tan

(b) (4)

**REMARKS:**

This is an electronic submission.

No CP was included in the application.

The TAD is 01/17/2017. The Q2 'complete by' date is 06/27/2016.

The applicant has requested expedited review for the submission.

A Microbiology Information Request was issued to the applicant on September 01, 2016, and the applicant forwarded responses on September 15, 2016.

P.1 Description of the Composition of the Drug Product**Reviewer's Assessment:**

(Section 3.2.P.1).

The drug product is supplied as a sterile injectable, single-dose, translucent red liposomal dispersion in 10 mL or 30 mL glass, (b) (4) vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL.

- **Drug product composition –**

S. No.	Components	Quantity (mg/mL)	Quantity (mg/vial)		Pharmaceutical Function (b) (4)
			20 mg/10mL	50 mg/25mL	
1.	Doxorubicin Hydrochloride USP	2 mg/mL	20 mg	50 mg	
2.	Cholesterol NF	3.19 mg/mL	31.9 mg	79.75 mg	
3.	Fully hydrogenated soy phosphatidylcholine (HSPC)	9.58 mg/mL	95.8 mg	239.5 mg	
4.	N-(carboxyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE)	3.19 mg/mL	31.9 mg	79.75 mg	
5.	Ammonium Sulfate NF	Approximately 2 mg/mL	Approximately 20 mg	Approximately 50 mg	
6.	Histidine USP	(b) (4)			
7.	Sucrose NF				
8.	Sodium Hydroxide NF				
9.	Hydrochloric acid NF				
10.	(b) (4)				
11.					
12.					

(b) (4)

Acceptable

P.2 Pharmaceutical Development

Reviewer's Assessment:

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

P.2.5 Microbiological Attributes

Reviewer's Assessment:

(b) (4)

Acceptable

Reviewer's Assessment:

The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling

Acceptable

List of Deficiencies:

None Identified.

Primary Microbiology Reviewer Name and Date:

Samata Tiwari 11/02/2016

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

Nandini Bhattacharya 11/03/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208657

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE **ADDENDUM REVIEW**

ANDA No.	208657
Drug Product Name	Doxorubicin Hydrochloride Liposome Injection
Strength(s)	20 mg/10 mL and 50 mg/25 mL
Applicant Name	Dr. Reddy's Laboratories Limited
Applicant Address	Integrated Product Development Organization Innovation Plaza, Survey Nos. 42, 45, 46 & 54, Bachupally, Quthubullapur Mandal, Hyderabad, Telangana, 500090 INDIA
Applicant's Point of Contact	Srinivasa Rao, Senior Director & Head Regulatory Affairs - North America Dr. Reddy's Laboratories, Inc 107 College Road East, Princeton, New Jersey, 08540
Contact's Telephone Number	(b) (6) Email: srao@drreddys.com
Contact's Fax Number	908-450-1476
Original Submission Date(s)	October 8, 2015
Submission Date(s) of Amendment(s) Under Review	February 16, 2017 (Amendment #10) ¹
Primary Reviewer	Yoriko Harigaya, Pharm.D.
Secondary Reviewer	Parthapratim Chandaroy, Ph.D.
Tertiary Reviewer	N/A
Study Number(s)	591-13
Study Type(s)	Fasting
Strength(s)	50 mg/25 mL
Clinical Site A	Dr. V. Satya Suresh Attili, M.B.B.S., M.D., DM, PDCR.
Clinical Site A Address	BIBI General Hospital & Cancer Centre, 16-3-991/1/C, Govt. Printing Press Road, Malakpet, Hyderabad - 500 024, Telangana, India.
Clinical Site B	Dr. K. S. Kirushna Kumar, M.B.B.S., M.D.
Clinical Site B Address	Meenakshi Mission Hospital & Research Centre, Lake Area, Melur Road, Madurai - 625 107, Tamil Nadu, India.
Clinical Site C	Dr. Gopichand Mamillapalli, M.B.B.S., M.S., DNB, M. Ch.
Clinical Site C Address	City Cancer Center, # 33-25-33, Ch. Venkata Krishnayya Street Suryaraopet, Vijayawada – 520 002, Andhra Pradesh, India.
Clinical Site D	Dr. Jayanti G Patel, M.B.B.S., M.D.
Clinical Site D Address	Nirmal Hospital® Pvt. Ltd., Ring Road, Civil Street, Near Kadiwala School, Surat - 395 002, Gujarat, India.
Clinical Site E	Dr. Sudha Somappa, M.B.B.S., D.M.R.T.
Clinical Site E Address	Srinivasam Cancer Care Hospitals India Pvt. Ltd., No. 236/1, Vijayashree Layout, Arekere, Bannerghatta Main Road, Bangalore - 560 076, Karnataka, India.

¹ This amendment is only referenced as it is the currently open project in GDRP and is not reviewed here

Clinical Site F	Dr. Rajnish Vasant Nagarkar, M.B.B.S., M.S., BSS., DNB., MRCSEd., MNAMS.		
Clinical Site F Address	Curie Manavata Cancer Centre, Opp. Mahamarg Bus Stand, Mumbai Naka, Nashik 422 004, Maharashtra, India.		
(Clinical Site G*)	Dr. Kattuputtur Narayanan Srinivasan, M.B.B.S., DMRT., DRM., Dr. G. Vishwanathan Speciality Hospitals,		
(Clinical Site G Address)	27, Babu Road, Trichy - 620 008, Tamil Nadu, India.		
Clinical Site H	Prof. Dr. SurendraNath Senapati, M.D.		
Clinical Site H Address	Acharya Harihar Regional Cancer Centre, Department of Radiation Oncology, Medical Road, Mangalabag, Cuttack - 753 007, Odisha, India.		
Clinical Site I	Prof. Dr. SurendraNath Senapati, M.D.		
Clinical Site I Address	MNJ Institute of Oncology and Regional Cancer Centre, Red Hills, Hyderabad - 500 004, Telangana, India.		
Clinical Site J	Dr. K. Velavan, M.D., R.T.		
Clinical Site J Address	Erode Cancer Centre, Velavan Nagar (Near Chintamani Petrol Bunk), Perundurai Road, Thindal, Erode - 638 012, Tamil Nadu, India.		
Clinical Site K	Dr. Smita Gupte, M.B.B.S., M.D.		
Clinical Site K Address	Cancer Clinic & Nursing Home, Block No. 4-B, Hyatt Medicare, Plot No. 12 / 2, Dr. N. B. Khare Marg, Dhantoli, Nagpur – 440 012, Maharashtra, India.		
Analytical Site	(b) (4)		
Analytical Site Address	(b) (4)		
OSIS status	<u>Backlog, Year 1 and Year 2 ANDAs</u>		<u>Post October 1, 2014 ANDAs</u>
	<input type="checkbox"/> Pending		<input type="checkbox"/> To Be Determined by OSIS
	<input type="checkbox"/> Complete		<input type="checkbox"/> Pending For Cause Inspection
	<input type="checkbox"/> N/A (Waiver)		<input checked="" type="checkbox"/> Complete
Waiver	<input type="checkbox"/> Granted <input type="checkbox"/> Tentatively granted <input type="checkbox"/> Not granted <input checked="" type="checkbox"/> N/A		
QC Dissolution	<input type="checkbox"/> Pending <input checked="" type="checkbox"/> Adequate* <input type="checkbox"/> Inadequate		
Formulation	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate		
Will Response to CR Result in a Reformulation?	<input type="checkbox"/> Possibly <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A		
Overall Review Result	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate		
Revised/New Draft Guidance Generated as Part of Current Review	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO		
DEFICIENCY CLASSIFICATION	<input type="checkbox"/> Major (Deficiencies to be communicated by CR)		
	<input type="checkbox"/> Minor		
	<input checked="" type="checkbox"/> Not Applicable (Review is Adequate)		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1, 2	Fasting Study	50 mg/m ² (2 mg/mL)	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate

1, 2, 3	Liposome Size Distribution	2 mg/mL	<input checked="" type="checkbox"/> Adequate <input type="checkbox"/> Inadequate
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*GDRP, ANDA-208657-ORIG-1-AMDND-10, Biopharmaceutics Quality Review, A208657-IQA-BIOPHARMACEUTICS (completed, but not archived yet)

1 EXECUTIVE SUMMARY

This is an addendum to the original bioequivalence (BE) review of ANDA 208657 on Doxorubicin Hydrochloride Liposome Injection² and the firm's amendment dated February 16, 2017³. The objective of the addendum is to evaluate the impact of the Office of Study Integrity and Surveillance (OSIS) inspection of the clinical site A (i.e., BIBI General Hospital & Cancer Centre) on the fasting BE study #591-13 of the current application.

The original application contains the results of a fasting BE study (#591-13) comparing the test product, Dr. Reddy's Laboratories Limited's Doxorubicin Hydrochloride Liposome Injection, 50 mg/m² (2 mg/mL) to the corresponding Reference Standard (RS), Sun Pharma Global FZE's⁴ Doxorubicin Hydrochloride Liposome Injection, 50 mg/m² (2 mg/mL) (ANDA 203263; approved on February 4, 2013). In addition to the PK endpoint BE study, the firm conducted *in vitro* liposome size distribution study per the product specific BE guidance⁵.

The firm's *in vivo* fasting BE study #591-13 was previously found adequate, and the Office of Study Integrity and Surveillance (OSIS) status for only the clinical site A was pending in the original BE review².

The OSIS inspected the clinical site A from March 28 - April 1 and April 4 - 7, 2016 for the BE Study #591-13 under the current ANDA 208657 (b) (4)

(b) (4) The current OSIS outcome for the clinical site A is "Official Action Indicated (OAI)"⁶. Based on the evaluation, the OSIS findings will have **no impact** on the *in vivo* BE study #591-13. The application remains **adequate** from a Division of Bioequivalence perspective.

The current application's OSIS status is **complete**. **There is no additional comment to be sent to the firm.**

² GDRP, ANDA-208657-ORIG-1, Bioequivalence Primary Review, dated 06/24/2016

³ GS review, ANDA208657, SDN10, Module 1.2. dated 2/16/2017

⁴ The firm used Doxil (NDA #050718, current holder Janssen Research & Development LLC), the current reference listed drug (RLD), as its basis of ANDA submission, which was found acceptable by the Division of Filing Review prior to submission of the current ANDA (GDRP ANDA 208657 Filing Primary Review 18 Nov 2015 [A208657N000DFR_BE_CHK.docx; page 5 of 19](#))

⁵ Bioequivalence Recommendations for Specific Drug Products for Doxorubicin HCl Liposomal Injection posted at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf> (Recommended Feb 2010; Revised Nov 2013, Dec 2014)

⁶ GDRP, ANDA-208657-ORIG-1, Site: BIBI GENERAL HOSPITALS AND CANCER CENTRE, EIR Review Memo for Bibi Clinical Research Department Hyderabad India.pdf, dated Aug. 2, 2016

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3 SUBMISSION SUMMARY

As per the original review⁷, there are 10 clinical sites utilized in the BE study #591-13. The OSIS status for the clinical site A (BIBI General Hospital & Cancer Centre, Telangana, India) was pending in the original BE review.

The OSIS arranged inspections for the BE Study #591-13 conducted at clinical site A. The current classifications of clinical and analytical site inspections for Study #591-13 are listed in the tables below.

ID	Clinical Site	OSIS Final Classification
A	BIBI General Hospital & Cancer Centre, Telangana, India ⁸	OAI
B	Meenakshi Mission Hospital & Research Center Tamil Nadu, India ¹³	NAI
C	City Cancer Centre, Vijayawada, India ⁹	NAI
D	Nirmal Hospital Pvt Ltd, Surat; Gujarat, India ¹⁰	NAI
E	Srinivasam Cancer Care Hospitals India Pvt. Ltd., Bangaluru, India ¹¹	VAI (no impact: see original review ⁷)
F	Curie Manavata Cancer Centre, Nashik, India ¹²	NAI
H	Acharya Harihar Regional Cancer Center Department of Radiation Oncology, Odisha India ¹³	NAI
I	MNJ Institute of Medical Oncology and Regional Cancer Center, Hyderabad, India ¹⁴	NAI
J	Erode Cancer Centre Pvt. Ltd., Erode, India ¹⁴	NAI
K	Cancer Clinic & Nursing Home, Maharashtra, India ¹³	NAI

⁷ GDRP, ANDA-208657-ORIG-1, Bioequivalence Primary Review, dated 06/24/2016

⁸ GDRP, ANDA-208657-ORIG-1, Site: BIBI GENERAL HOSPITALS AND CANCER CENTRE, EIR Review Memo for Bibi Clinical Research Department Hyderabad India.pdf, dated Aug. 2, 2016

⁹ GDRP, ANDA-208657-ORIG-1, Site: CITY CANCER CENTRE, EIR Review_ANDA (b) (4) 208657 Final-all signed.pdf, dated 04/27/2016

¹⁰ GDRP, ANDA-208657-ORIG-1, Site: NIRMAL HOSPITAL PRIVATE LTD, EIR Review- ANDA208657-Nirmal- (b) (4).pdf, dated 04/18/2016

¹¹ GDRP, ANDA-208657-ORIG-1, Site: SRINIVASAM CANCER CARE HOSPITALS INDIA PRIVATE LIMITED, EIR Review Memo for Srinivasam Bangaluru India_Final.pdf, dated 06/04/2016

¹² GDRP, ANDA-208657-ORIG-1, Site: CURIE MANAVATA CANCER CENTRE, Final EIR Review ANDA 208657 at Curie.pdf, dated 06/10/2016

¹³ GDRP, ANDA-208657-ORIG-1, Site: ACHARYA HARIHAR REGIONAL CANCER CENTRE, DEPARTMENT OF RADIATION ONCOLOGY, EIR Review ANDA208657.pdf, dated 04/14/2016

¹⁴ GDRP, ANDA-208657-ORIG-1, Site: MNJ INSTITUTE OF MEDICAL ONCOLOGY AND REGIONAL CANCER CENTER, Final EIR Review ANDA 208657 at Erode MNJ (2).pdf, dated 05/31/2016

Analytical Site	OSIS Final Classification
(b) (4)	VAI (no impact: see original review ⁷)

OAI: Official Action Indicated
VAI: Voluntary Action Indicated
NAI: No Action Indicated

For the clinical site A, Form FDA 483 was issued to the firm. The Establishment Inspection Report (EIR) review is provided under Section 3.1 below.

3.1 OSIS Findings



¹⁵ GDRP, ANDA-208657-ORIG-1, Site: (b) (4)
EIR review-Analytical with attachments.pdf, dated (b) (4)

Completed Assignment for 208657 ID: 30999

Reviewer: Harigaya, Yoriko

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Doxorubicin Hydrochloride Liposome Injection , 0.5%

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
30999	10/8/2015	BIO	OSIS Inspection Report Review [1]	1	1
30999	10/8/2015	Parallel	OSIS Inspection Report: Review of Systemic Observations Identified by the Parent Reviewer [0.25]	0.25	0.25
				Total:	1.25

BIOPHARMACEUTICS

Product Background:

ANDA: 208657-ORIG-1-AMEND-10

**Drug Product Name / Strength: Doxorubicin Hydrochloride Liposome Injection
20 mg/ 10 mL and 50 mg/ 25 mL**

Route of Administration: Injectable; IV (Infusion)

Applicant Name: Dr. Reddy's Laboratories Limited

EXECUTIVE SUMMARY:

Background:

ANDA 208657, submitted by Dr Reddy's, is seeking approval of Doxorubicin hydrochloride liposome injection, 20mg/10mL and 50mg/ 25mL, for the treatment of ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma, under the 505(j) path. Although the innovator drug product is DOXIL (approved under NDA 050718), the current RLD designated in the Orange Book is Doxorubicin hydrochloride liposome injection 20mg/ 10mL and 50mg/ 25mL (Sun Pharma), approved under ANDA 203623.

The Applicant conducted a fasting bioequivalence (BE) study comparing the test product to the RLD, Sun Pharma Global's Doxorubicin Hydrochloride Liposome Injection, 50 mg/m² (2 mg/mL). In addition to the BE study, the firm conducted an *in vitro* liposome size distribution study per the BE guidance. Both studies have been evaluated by OGD and found adequate.¹

Submission:

The original submission received a Complete Response letter on Dec 27, 2016 due to Pharmaceutical Quality deficiencies. The resubmission in response to the CR letter was received on Feb 16, 2017.

Review's Objective:

This Biopharmaceutics review is focused on evaluating the following:

- The *in vitro* leakage test
- The proposed *in vitro* release method
- The proposed *in vitro* release acceptance criteria

¹ Yoriko Harigaya, ANDA 208657 Bioequivalence review, 6/24/2016.

Reviewer’s Assessment:

The proposed dissolution method is adequate for quality control of the drug product. The proposed dissolution acceptance criteria are permissive and FDA recommended new acceptance criteria based on the data provided. The Applicant acknowledged the FDA recommended acceptance criteria. The FDA approved in vitro release method and the acceptance criteria agreed to with the Applicant are as follows:

In vitro release method	Apparatus	Culture tube, incubation in water bath
	Agitation	No
	Medium	pH 6.5 buffer (2M Ammonium Chloride and 0.2M L-Histidine)
	Temperature	47°C
Acceptance criteria	2 hr	(b) (4) %
	4 hr	%
	8 hr	NLT (b) (4) %

Conclusion and Recommendation:

From a Biopharmaceutics perspective, ANDA 208657 for Doxorubicin Hydrochloride Liposome Injection 20 mg/ 10 mL and 50 mg/ 25 mL is recommended for **APPROVAL**.

List of Submissions being reviewed:

eCTD Sequence #	Submission Date	Submission
0000	10/08/2015	New ANDA
0001	11/17/2015	Quality/Response to Information Request
0006	09/15/2016	Quality/Response to Information Request
0009	02/16/2017	Quality/Response to Information Request
0010	03/22/2017	Quality/Response to Information Request

Highlight Key Outstanding Issues from Last Cycle:

None. First review cycle.

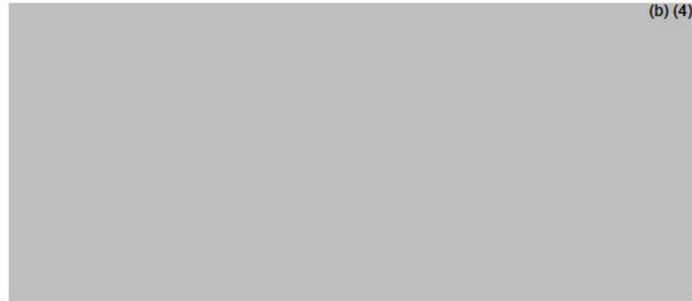
Concise Description of Outstanding Issues: None.

BCS Designation

Reviewer’s Assessment:

BCS classification is not applicable as the proposed drug product is not an oral dosage form.

(b) (4)



Permeability: No information is provided.

Dissolution: See the following sections.

Dissolution Method and Acceptance Criteria

1. Is the formulation of the proposed drug product qualitatively and quantitatively the same as the RLD product?

JANSSEN’s DOXIL® (Doxorubicin HCl liposome injection) is the designated listed drug for Doxorubicin HCl liposome injection and was also listed as the RLD in the Orange Book. However, due to the unavailability / limited supply of this product, Doxorubicin Hydrochloride liposome injection from Sun Pharma Global approved under ANDA 203263 was selected as the Reference Standard (RS) in the current Orange Book.

The composition of the proposed drug product is compared to that of the previous and current RLD products, as shown in Table 2. The proposed drug product is qualitatively and quantitatively the same as the RS and the RLD.

Table 2. Composition of The Proposed Drug Product

Qualitative and Quantitative Composition			
Ingredients	Current RS	Original Innovator product	Proposed Generic Product
	Doxorubicin Hydrochloride Liposome Injection 20mg/10mL and 50mg/25mL (2mg/mL) (Sun Pharma Global)	Doxil® [Doxorubicin Hydrochloride Liposome Injection 20mg/10mL and 50mg/25mL (2mg/mL)] (Janssen)	Doxorubicin Hydrochloride Liposome Injection 20mg/10mL and 50mg/25mL (2mg/mL) (Dr. Reddy’s)
Doxorubicin Hydrochloride USP	2 mg/mL	2 mg/mL	2 mg/mL
Cholesterol NF	3.19 mg/mL	3.19 mg/mL	3.19 mg/mL
Fully hydrogenated soy phosphatidylcholine (HSPC)	9.58 mg/mL	9.58 mg/mL	9.58 mg/mL

N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE)	3.19 mg/mL	3.19 mg/mL	3.19 mg/mL
Ammonium Sulfate NF	Approximately 2mg/mL	Approximately 2mg/mL	Approximately 2mg/mL
Histidine USP	(b) (4)		
Sucrose NF			
(b) (4)			
Sodium Hydroxide NF	(b) (4) adjust pH to 6.5	(b) (4) adjust pH to 6.5	(b) (4) adjust pH to 6.5
Hydrochloric acid NF	adjust pH to 6.5	adjust pH to 6.5	adjust pH to 6.5
	(b) (4)		

The manufacturing process and the physicochemical characteristics of the liposomes are evaluated by the Chemistry review team.

2. What is the in vivo release mechanism of the proposed drug product?

(b) (4)

Reviewer's Comments:

(b) (4)

The in vitro release studies under different pHs mimic the in vivo release in various tissues. The similarity in in vitro release under various conditions between the proposed and the reference products can partly support the similarity in in vivo release.

3. Did the firm conduct the in vitro leakage studies to demonstrate that there is no uncontrolled drug leakage?

² ML Immordino, F Dosio and L Cattell, Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. Int J Nanomedicine, 2006 Sep 1(3): 297-315.

Following FDA “Draft guidance on Doxorubicin Hydrochloride (Recommended Feb 2010; Revised Nov 2013, Dec 2014)” the in vitro leakage studies from Doxorubicin Liposome were conducted. The test conditions for the in vitro leakage studies are summarized in Table 3.

Table 3. In vitro leakage conditions for doxorubicin liposomes

In Vitro Drug Leakage Condition	Purpose	Rationale
At 37°C in 50% human plasma for 24 hours	Evaluate liposome stability in blood circulation	Plasma mostly mimics blood conditions.
At 37°C with pH values 5.5, 6.5, and 7.5 for 24 hours in buffer	Mimic drug release in normal tissues, around cancer cells, or inside cancer cells	Normal tissues: pH 7.3 Cancer tissues: pH 6.6 Insider cancer cells (endosomes and lysosomes): pH 5-6 (Endosome and lysosomes of cancer cells may be involved in liposome uptake and induce drug release).
At a range of temperatures (43°C, 47°C, 52°C, 57°C) in pH 6.5 buffer for up to 12 hours or until complete release	Evaluate the lipid bilayer integrity	The phase transition temperature (T _m) of lipids is determined by lipid bilayer properties such as rigidity, stiffness and chemical composition. Differences in release as a function of temperature (below or above T _m) will reflect small differences in lipid properties
At 37°C under low-frequency (20 kHz) ultrasound for 2 hours or until complete release.	Evaluate the state of encapsulated drug in the liposome.	Low-frequency ultrasound (20 kHz) disrupts the lipid bilayer via a transient introduction of pore-like defects and will render the release of doxorubicin controlled by the dissolution of the gel inside the liposome.

4. Did the firm provide the complete dissolution data for the leakage studies? Was the similarity (f2) in leakage (or non-leakage) demonstrated between the proposed drug product and the RLD product under various conditions?

1) In vitro drug release at 37 °C in 50% human plasma

The drug release profile of the reference products (Sun Pharma’s product, Doxil® and Caelyx³ injection) at 37°C in 50% human plasma was provided, which showed negligible drug release. In the IR response dated 09/15/2016, the Firm provided the release data with 12 units of test and RLD product. Since the exhibit batches have expired, a new batch of test product (batch # 500237) was used. The new batch was manufactured using the same components (raw material

³ Caelyx (pegylated liposomal doxorubicin) injection is another liposome injection of doxorubicin which was manufactured by the same manufacturer as Doxil. However Caelyx is NOT the reference product of this ANDA, and it is NOT the same drug as Doxil. (b) (4)

Caelyx is marketed in Europe and Doxil is marketed in US.

and packaging material) with same composition and the manufacturing process. The comparative in vitro release profiles are shown in Figure 1, and the similarity factor f_2 is 88.8, indicating similarity.

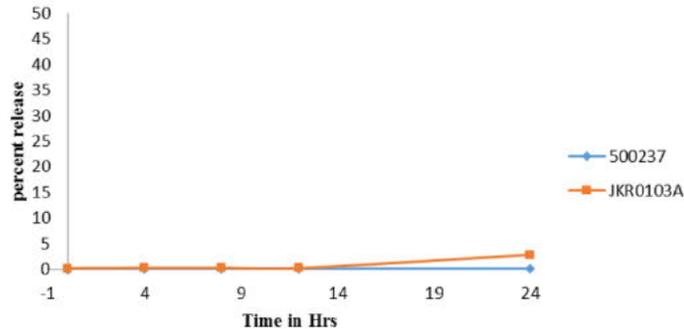


Figure 1. in vitro leakage at 37°C in 50% human plasma

2) In vitro drug release at 37 °C with pH values 5.5, 6.5, and 7.5 for 24 hours in buffer

Table 4. In vitro leakage at 37 °C at pH 5.5

% Drug Release						
Time in Hours	Test Formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
1						
3						
6						
12						
24						

Table 5. In vitro leakage at 37 °C at pH 6.5

% Drug Release						
Time in Hours	Test Formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
1						
2						
3						
6						
12						
24						

Table 6. In vitro leakage at 37 °C at pH 7.5

% Drug Release						
Time in Hours	Test Formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
1	(b) (4)					
2						
3						
6						
12						
24						

The Applicant noted that the in-vitro release in pH 5.5 was less than (b) (4)%. The in-vitro drug release was observed to be more discriminating in pH 6.5 when compared to pH 7.5.

3) In vitro drug release at a range of temperatures (43°C, 47°C, 52°C, 57°C) in pH 6.5

As per the draft BE guidance, the in vitro drug release study was performed at a range of temperatures 43°C, 47°C, 52°C and 57°C in pH 6.5 buffer (having 2M Ammonium chloride & 0.2M Histidine buffer) for complete release to evaluate the lipid bilayer integrity. The Applicant selected 2M Ammonium chloride & 0.2M Histidine buffer as the dissolution medium based on information from the Summary Basis of Approval for Doxil®.

Table 7. In vitro leakage at 43 °C at pH 6.5

% Drug Release						
Time in Hours	Test Formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
0.5	(b) (4)					
1						
2						
4						
12						
24						
36						
48						

Table 8. In vitro leakage at 47 °C at pH 6.5

% Drug Release						
Time in Hours	Test formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
0.5						
1						
2						
4						
12						
24						
36						
48						

Table 9. In vitro leakage at 52 °C at pH 6.5

% Drug Release						
Time in Hours	Test formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B.No: 202837 (20mg/10mL)	B.No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
0.5						
1						
2						
4						
12						
24						
36						
48						

Table 10. In vitro leakage at 57 °C at pH 6.5

% Drug Release						
Time in Hours	In-House formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B.No: 202837 (20mg/10mL)	B.No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
0.5						
1						
2						
4						
12						
24						
36						
48						

The Applicant noted that the *in vitro* drug release test using the pH 6.5 buffer (2M Ammonium Chloride-0.2M Histidine) at 47°C shows potential as being an appropriate *in vitro* drug release method for batch release quality control.

4) In vitro drug release under low-frequency ultrasound

In the IR response dated 09/15/2016, the firm provided the comparative *in vitro* leakage test under ultrasound conducted using the RLD product and a new batch of the test product (Batch # 500237). The comparative profiles are shown in Figure 2. The f_2 value was calculated to be 96.4, indicating similarity.

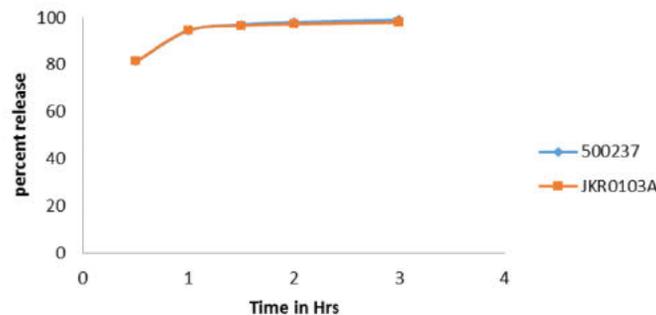


Figure 2. *in vitro* leakage under low-frequency (20 kHz) ultrasound

Reviewer's Comments:

The proposed drug product is qualitatively and quantitatively the same as the reference product,

*(b) (4) (to be evaluated by the chemistry review team). Therefore, the proposed drug product is expected to have comparable *in vitro* release as the reference product.*

*The comparative *in vitro* leakage test is recommended in the BE guidance, in order to ensure that the stability of the liposomes, the release in various tissues, and the integrity of the membrane bilayer of the proposed drug product are comparable to the RLD product. Therefore f_2 calculation is required for the *in vitro* leakage test.*

The Applicant performed the *in vitro* leakage studies for the reference products (Sun Pharma's product, Doxil® and Caelyx injection) to understand the characteristics of the RLD. However, for the proposed drug product, the Applicant did not perform all the recommended leakage tests. In particular, the test in 50% plasma and the test under low-frequency ultrasound were not initially performed.

For the tests conducted, the Applicant provided data for 3 batches of the proposed drug product and 3 batches of the RLD (Doxil) product. However, only one value was provided for each batch at each time point. In addition, the similarity factor (f_2) was not calculated between the test and reference product. The Applicant will be asked to provide the complete data and the f_2 values.

The following IR comments were conveyed to the Applicant on August 1, 2016.

1. *We acknowledge that you submitted the in vitro leakage studies in section 3.2.P.2. However it is noted that you did not conduct the test in 50% human plasma and under low frequency ultrasound for the proposed drug product. In addition, you did not provide information regarding sample sizes, the variability in each test, the complete data and the similarity factor f2 values. Submit the following information:*
- *The comparative in vitro leakage test conducted using the proposed drug product and the reference product at 37 °C in 50% human plasma to evaluate the liposome stability in blood.*
 - *The comparative in vitro leakage test conducted using the proposed drug product and the reference product under low-frequency (20 kHz) ultrasound to evaluate the state of encapsulated drug in the liposome.*
 - *The sample sizes and individual data with the variability (standard deviation and/or CV%) for each lot used in each of the drug leakage tests.*
 - *The similarity factor f2 values for the profile comparisons using 12 units of test and reference products per test of in vitro leakage and dissolution for batch release.*

In the IR response dated 9/15/2016, the Applicant provided the in vitro leakage data collected in 50% human plasma and under low frequency ultrasound, and calculated f2 values which indicated similarity. However the Applicant did not provide f2 calculation for the rest of the in vitro leakage tests. The response is not satisfactory, and f2 value for each in vitro leakage test will be requested.

The Applicant also provided f2 values for batch release dissolution test, which will be included in later section.

The following IR comment was conveyed to the Applicant on December 27, 2016:

We acknowledge that you submitted f2 values for the in vitro leakage tests conducted in 50% human plasma and under low frequency ultrasound. Provide the similarity factor f2 values for the profile comparisons using 12 units of test and reference products for each of the in vitro leakage tests. Equivalent in vitro leakage under multiple conditions support a lack of uncontrolled leakage under a range of physiological conditions and equivalent drug delivery to the tumor cells.

In the response received on 02/16/2017, the Applicant provided the f2 values for the profile comparisons between the test and reference products, the results are shown in Table 11, and supported similarity. The response is acceptable.

Table 11 Similarity factor (f2 value) for Test vs RLD under in vitro leakage conditions

In Vitro Drug Leakage - Test Conditions	Test Batch	RLD batch	Similarity factor (f2 value)
At 37°C with pH value 5.5	500237	JKR0489A	63.22
At 37°C with pH value 6.5	500237	JKR0103A	58.55
At 37°C with pH value 7.5	500237	JKR0103A	63.01
At 43°C in pH 6.5 buffer	500237	JKR0103A	56.89

At 47°C in pH 6.5 buffer	500082	JKM7084A	50.41
At 52°C in pH 6.5 buffer	500237	JKP5089A	78.37
At 57°C in pH 6.5 buffer	500237	JKP5089A	73.80

5. If the proposed dissolution method is not a USP method or listed on the FDA website:

a) What data are submitted to support the discriminating ability of the Applicant's proposed method?

In the original submission, the Applicant proposed two in vitro release methods for QC testing.

1st Method:

Apparatus	Culture tube, incubation in water bath
Agitation	No
Medium	pH 6.5 buffer (2M Ammonium Chloride and 0.2M L-Histidine)
Temperature	47°C

According to the analytical procedure described in 3.2.P.5.2, the dissolution medium was prepared

[Redacted] (b) (4)

2nd Method:

Apparatus	[Redacted] (b) (4)
Agitation	[Redacted]
Medium	[Redacted]
Temperature	[Redacted]

[Redacted] (b) (4)

(b) (4)

However, in the original ANDA, no data were provided to demonstrate the discriminating ability of either of the proposed methods. The following IR comments were sent to the Applicant on August 1, 2016.

- 2. It is noted that you proposed two dissolution methods for the QC test at batch release. However, neither of the methods has been demonstrated to be discriminating. Provide data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the target product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables*

(b) (4)

The FDA recommends that one of the two methods should be selected based on results of the investigation of their discriminating power.

In the IR response received on 09/15/2016, The Applicant tested the discriminating nature of the proposed dissolution methods

(b) (4)

(b) (4)

(b) (4)

Therefore, the Applicant selected the 1st Method using pH 6.5 histidine buffer as the dissolution media for testing the drug product at release and stability testing.

b) Is the proposed dissolution method acceptable? If not what are the deficiencies?

Yes. The proposed dissolution method (1st Method using pH 6.5 buffer (2M Ammonium Chloride-0.2M Histidine) at 47°C) is shown to be discriminating with respect to drug product composition, and the method has been fully validated (the method validation report is provided in section 3.2.P.5.3). The proposed method showed high inter-batch variability, especially in the stability studies, but the Applicant was able to find the root cause of the variability and proposed a series of precautions to take when conducting the test. The proposed method is adequate for quality control of the drug product. The details are discussed in the section of Acceptance Criteria under Question #12.

Reviewer's Comments:

As shown below, FDA recommended the generic Applicants to develop a method starting at pH 6.00±0.05 and at 47°C±0.5°C, but did not provide recommendation on apparatus/ equipment.

Doxorubicin Hydrochloride	Injectable (Liposomal)	Develop a method to characterize in vitro release, starting at pH 6.00 ± 0.05 and at 47°C ± 0.5°C. Replicate for 12 dosage vials.			9/10/2012	0, 0.5, 1, 2, 3, 4, 5 hours
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The Applicant initially proposed two in vitro release methods for doxorubicin hydrochloride liposomes. Both methods employed pH 6.5 buffer and both were conducted at 47 °C. (b) (4)

In response to FDA’s request, the Applicant demonstrated that both methods are discriminating with respect to changes in drug product composition. Method 1 using pH 6.5 histidine buffer was selected as the final QC method. The method was fully validated. The Applicant did not provide justification for selection of the concentration of the Ammonium Chloride and L-Histidine though.

As will be discussed in a later section, high inter-batch variability and huge differences between the batch release data and the stability data at initial time points were observed. The Applicant was requested to investigate whether these were caused by inadequacy of the in vitro release method.

The following IR comment was conveyed to the Applicant on December 27, 2016.

Justify the selection of the concentrations of ammonium chloride and L-histidine in the medium used for the proposed in vitro release method.

In the response received on 02/16/2017, the Applicant stated that the selections of 2 M ammonium chloride and 0.2 M L-histidine are based on the “summary basis of approval for the RLD, Doxil”. In addition, the robustness of the selected buffer concentration was examined (b) (4) of the concentrations of ammonium chloride and L-histidine. As shown in Table 13, the variation did not appear to significantly impact the in vitro release of the drug product and the method was demonstrated to be robust. The response is acceptable.

Table 13 Impact of changes in buffer concentrations on in vitro release of the drug product

Time point	% drug release (Batch No. 203830, Batch Size: 12L)	
	(b) (4)	(b) (4)
2 hr	(b) (4)	(b) (4)
4 hr	(b) (4)	(b) (4)
8 hr	(b) (4)	(b) (4)
12 hr	(b) (4)	(b) (4)

The investigation on the root cause for the difference between the batch release data and the stability data at initial time point will be discussed in later section.

6. Did the firm provide 12 units (non-pooled) of both test and reference product in applicable dissolution/release testing?

Yes.

7. Was the dissolution testing conducted on the bio-batch?

Yes. The Bio-batch # 500082 was tested.

8. What was the age of the test product at the time of dissolution testing?

The 20mg/ 10mL test product was about 6 months old at the time of testing. The 50mg/ 25mL test product was 21-23 months old, which is beyond the currently proposed expiration date of 18 months. The Applicant was asked to provide data to support the use of the 50mg/ 25mL batches.

Table 14. Age of the test product

Strength	Batch #	Manufacture Date	Testing Date	Age (months)
20mg/ 10mL	500080	Nov 2013	14 Apr 2014	5-6
	500082	Nov 2013	14 Apr 2014	5-6
	500083	Nov 2013	14 Apr 2014	5-6
50mg/ 25mL	500084	Nov 2013	29 Sep 2015	22-23
	500085	Nov 2013	28 Sep 2015	22-23
	500086	Dec 2013	29 Sep 2015	21-22

The following IR comments were conveyed to the Applicant on August 1, 2016.

3. The batches of the proposed drug product 50 mg/ 25mL are beyond the proposed expiration date of 18 months at the time of dissolution testing. Provide data to demonstrate that there is no change in the product quality for these batches.

In the response received on 9/15/2016, The Applicant noted that all the three batches of 50mg/25mL presentation were tested and found to meet the shelf life specification at the time when the dissolution testing was conducted (when the drug product was about 20 months old). The 20 months stability data are provided in Annexure-23 of the cover letter dated 9/15/2016. The data suggest that the initial time point was 17/01/2014 for the 50mg/25mL batches, when the batches were 1-2 months old. The data also appear to suggest that there is an increase in in-vitro release rate from the initial time point to the 20-month time point. The Applicant has data of 6 units for the initial time point, and the 12-unit data are only available at the 20-month time point.

It is noted that the 50mg/25mL are not the bio-batches, and setting of acceptance criterion can be based on the data of the bio-batch, which was tested within the expiry date. The response is acceptable.

9. Was the dissolution/release testing conducted on unexpired reference product?

Yes. The reference product was unexpired.

Table 15. Age of the reference product

Strength	Batch #	Expiration Date	Testing Date
20mg/ 10mL	JKM7084A	May 2015	4 Jun 2014

50mg/ 25mL	JKP2573A	Nov 2016	21 Sep 2015
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10. Did the firm provide complete dissolution data (i.e. all raw data, mean, range, %CV, dates of testing) to support the proposed acceptance criteria(on)? Were the data submitted for all proposed strengths of the drug product?

The Applicant provided the complete dissolution data for the exhibit batches obtained using both dissolution methods, as summarized in the APPENDIX 1.

11. Was the similarity (*f*₂) in in-vitro release using the application in vitro release method demonstrated between the Test and Reference product at batch release

The similarity factor (*f*₂) for batch release dissolution for the test and reference products is provided in the IR response received on 09/15/2016. Both the Applicant's and this reviewer's calculation are summarized below. As the Applicant has chosen method 1 as the final QC method. The *f*₂ values are only provided for the QC method.

Table 16. Similarity factor (*f*₂) for test and reference products at batch release using the proposed QC in vitro release method

Test Batch	Reference Listed Drug	Applicant Submitted <i>f</i> ₂ Values	Reviewer Calculated <i>f</i> ₂ Values
500080	JKM7084A	50	46.7
500082	JKM7084A	53	50.1
500083	JKM7084A	50	47.4
500084	JKM7084A	64	61.3
500085	JKM7084A	74	68.9
500086	JKM7084A	64	59.4

Reviewer's Comments:

*It is noted that there are two batches (batch # 500080 and 500083) that did not demonstrate similarity to the RLD batch (SUN product) according to the reviewer's calculation. As the bio-batch (#500082) showed similar in vitro release profile as the RLD batch (*f*₂=50.1), the small differences observed in release profiles of the test and reference products are acceptable.*

12. Is the proposed dissolution acceptance criteria acceptable? If not, what is the recommendation with justification?

The initially proposed acceptance criteria are as follows:

Method 1 (pH 6.5 buffer at 47 °C): NLT (b) (4) % at 2 hrs.
 (Final QC method) NLT (b) (4) % at 8 hrs

Method 2 (b) (4) NLT (b) (4)

The Applicant proposed to conduct dissolution testing of the inverted vials only for the stability studies. This is acceptable, as the inverted orientation represents a more stressed condition than

the upright orientation. As requested by the Agency, the complete stability dissolution data for the exhibit /primary registration batches are provided in section 3.2.P.8.3.

The initially proposed acceptance criteria are not acceptable, and the following IR comments are provided in the IR letter dated August 1, 2016:

4. *The proposed dissolution acceptance criteria are permissive and not acceptable. For the setting of the dissolution acceptance criteria of the proposed drug product, the following points should be considered:*
- *The dissolution profile data from the pivotal clinical batches and primary stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).*
 - *Provide the complete stability dissolution data (individual, mean, range, CV%) for the exhibit/ primary stability batches in “.xpt” format or in excel spreadsheet. Include data at all the sampling time points in addition to the proposed specification time points.*
 - *The acceptance criteria should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).*
 - *Given the slow release of the drug product, a minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be where at least 80% of drug is released. If the maximum amount released is less than 80%, the last time point should be when the plateau of the release profile has been reached.*
 - *In general, the selection of the dissolution acceptance criteria ranges is based on mean target value $\pm 10\%$ and $>80\%$ for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model.*
 - *A detailed discussion of the justification of the proposed dissolution acceptance criterion should be included in your submission.*

In the IR response dated 09/15/2016, the Applicant proposed the following revised acceptance criteria for the final QC method (Method 1, in pH6.5 Histidine buffer at 47°C):

2 hr	NLT (b) (4) 0%
4 hr	(b) (4) 0%
8 hr	NLT (b) (4) 0%
	(b) (4)

The revised acceptance criteria remain unacceptable, due to the wide ranges proposed without justification. The batch release data provided in APPENDIX 1 are plotted in the Figure below.



(b) (4)

Reviewer's Comments:

The batch release data support the following acceptance criteria:

	(b) (4)
2 hr	(b) (4) %
4 hr	%
8 hr	NLT (b) (4) %

The Applicant also provided the “.xpt” file for the stability data at 2hr and 8hr time points in section 3.2.P.8. The data are plotted by this Reviewer and the figures are shown below.



(b) (4)

Reviewer's Comments:

The following concerns arise when comparing the stability data to the batch release data:

- The stability data at the 2hr time point were significantly higher than the batch release data presented above, which indicates the proposed in vitro release method may not be robust.*
- The 8-hr time point was not included in the batch release test, so no comparison can be made.*
- The bio-batch (500082) appears to be among the slow batches at release, but appears to be the fastest release batch during stability.*
- A trend was observed for the stability data at both the 2hr and 8hr time points as a function of storage time, with 12-month and 18-month data going up and 3-month and 15-month data going down (the difference between the 15-month and 18-month data are more than 20%).*
- More importantly, all batches (including the biobatch) placed on stability did not conform to the acceptance criteria supported by the batch release data. These observations indicate that the drug product quality may not be satisfactory and the proposed expiry dating of 18 months may not be supported.*

Due to the noticeable differences between the batch release and stability data, the Applicant was asked to investigate the root cause for the observed discrepancies, and improve the in vitro release method if needed.

The Applicant is also requested to provide the complete in vitro release data for the stability batches by including all the time points. It is noted that the complete data may not be available prior to 18 months; the Applicant is being asked to provide data including all time points at the current stability time point or the release/ stability data of any new batches manufactured using the same composition and process.

The following IR comments were conveyed to the Applicant on December 27, 2016:

We acknowledge the stability data up to 18 months at the 2-hr and 8-hr time points and the batch release data you provided in section 3.2.P.8.3. It is noted that the 2-hr in vitro release data at the initial stability time point is higher than the 2-hr data at batch release. Please clarify the initial time point of the stability program relative to batch release. It is also noted that both 2-hr and 8-hr data show a trend as a function of storage time, with 12-month and 18-month data going up and 3-month and 15-month data going down (the difference between the 15-month and 18-month data are more than 20%). Investigate the root cause for the trend observed. In addition, demonstrate the robustness and reproducibility of the release testing methodology.

Provide complete in vitro release data for the stability batches by including all the time points. It is noted that the complete data may not be available prior to 18 months. Provide the complete in vitro release data at the current stability time point for the stability batches or the release/ stability data of any new batch manufactured using the same composition and process.

Due to lack of the complete in vitro release data for evaluation and the observed trend of the stability data, the adequacy of the proposed in vitro release method cannot be determined, and evaluation of the acceptance criteria is pending.

In the response received on 02/16/2017, the Applicant explained that the 2-hr data for batch release were generated on 12 dosage units, while the 2-hr stability data were generated on 6 dosage units on a different date, which may have caused the data variation.

The Applicant further investigated the root cause for the observed stability trend and data variation. The complete investigation report is provided in Annexure-8 of the cover letter dated 02/16/2017 (<\\cdsesub1\evsprod\anda208657\0009\m1\us\12-cover-letters\cover-letter-0009-20170216.pdf>).

Various variations in dissolution method parameters were evaluated to understand their impact on drug release. The parameters that have significant impact include the following:



(b) (4)

Reviewer's Comments:

Based on the Applicant's investigation, the dissolution method is very sensitive to variations in dissolution testing conditions, especially the pH of the dissolution medium and the temperature of the water bath. The Applicant proposed precautions to take in future dissolution testing, which appeared to generate good reproducibility. The method has been demonstrated to be discriminating. Therefore the proposed dissolution method with taking extra precautions is acceptable for quality control of the drug product.

However, the investigation results may have invalidated the data obtained before such precautions were taken, especially the stability data which showed huge variability and fluctuation due to lack of tight control. Therefore setting of the acceptance criteria cannot be based on the stability data, including the data from the Bio-batch, though the biobatch was aged when the BE study was conducted. Re-testing the biobatch with the updated testing procedure may not be useful as the biobatch has expired.

The Applicant provided the in vitro release data for a commercial scale batch (#500237) manufactured by using the same composition and process. The in vitro release data (n=12) at the current stability time point (15-month) obtained using the QC dissolution method (pH 6.5 buffer at 47 °C) are summarized in the Table below.

Table 17 in vitro release data at 15 months long term storage condition for batch #500237

	2 hr	4 hr	8 hr	12 hr
Average	43.2	63.2	86.9	91.1
Min	(b) (4)			
Max	(b) (4)			
SD	1.3	1.3	1.6	0.2
%CV	2.9	2.1	1.9	0.2

The 17-month stability in vitro release data are provided for the same batch of #500237 in Annexure-8 and summarized below.

Table 18 in vitro release data at 17 months long term storage condition for batch #500237

	2 hr	4 hr	8 hr	12 hr
Average	48.3	69.0	90.1	92.4
Min	(b) (4)			
Max	(b) (4)			
SD	0.4	0.5	0.2	0.0
%CV	0.9	0.8	0.2	0.0

Based on the data provided, the Applicant proposed the following acceptance criteria for the in vitro release test:

2 hr	(b) (4) %
4 hr	(b) (4) %
8 hr	NLT (b) (4) %
(b) (4)	

Reviewer’s Comments:

The proposed acceptance criteria are not acceptable, as the ranges for the 2-hr and 4-hr are as wide as (b) (4) % without justification.

The setting of the acceptance criteria could be based on the batch release data and the stability data of the biobatch (the age of the biobatch (500082) ranged from 8 to 16 months during the period of the bioequivalence study). However the lack of tight control on the dissolution method caused variation in the stability dissolution data. Therefore the acceptance criteria were set based on the batch release data (obtained on samples of 5-6 months old and 22-23 months old) and the newly provided dissolution data for commercial scale batch #500237 (15 and 17-month old). The following acceptance criteria are recommended:

2 hr	(b) (4) %
4 hr	(b) (4) %
8 hr	NLT (b) (4) %

The following Information Request was conveyed to the Applicant on March 21, 2017.

The proposed in vitro release acceptance criteria are permissive and not acceptable. Based on your batch release data and the new in vitro release data provided for batch #500237, we recommend that you implement the following acceptance criteria for your proposed drug product, and provide the revised specification table with the updated acceptance criteria for the in vitro release test.

<i>Time</i>	<i>% released</i>
<i>2 hr</i>	(b) (4) %
<i>4 hr</i>	%
<i>8 hr</i>	NLT (b) (4) %

The Applicant responded on March 22, 2017, and accepted the FDA’s recommendation. The in-vitro release acceptance criteria for the proposed drug product has been revised accordingly. The response is acceptable.

Biowaiver Request

Reviewer’s Assessment:

The Applicant requested a biowaiver for Doxorubicin hydrochloride liposome injection 50mg/ 25mL strength, and it will be reviewed by OGD.

Information Request: None.

Conclusion and Recommendation:

From a Biopharmaceutics perspective, ANDA 208657 for Doxorubicin Hydrochloride Liposome Injection 20 mg/ 10 mL and 50 mg/ 25 mL is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

Jing Li, Ph.D. 3/27/2017

Biopharmaceutics Reviewer

Division of Biopharmaceutics

Office of New Drug Products

Office of Pharmaceutical Quality

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



Okpo Eradiri, Ph.D. 3/28/2017
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality



APPENDIX 1. IN VITRO DISSOLUTION DATA FOR DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION



(b) (4)

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Table 20. Summary of in Vitro Dissolution Studies in pH 6.5 Histidine Buffer (Final QC method)

Dissolution Conditions		Apparatus:	Culture tube & incubation in water bath											
		Speed of Rotation:	Not applicable											
		Medium:	pH 6.5 Buffer (Ammonium Chloride and L- Histidine) - Dissolution in QC release media											
		Volume:	4mL Dissolution Medium & 4mL sample (1:1)											
		Temperature:	47°C											
Firms' Proposed Specifications		Not less than ^(b) / ₍₄₎ % at 2 hours and Not less than ^(b) / ₍₄₎ % at 8 hours of drug is released from Liposomes												
Dissolution Testing Site (Name, Address)		^(b) / ₍₄₎												
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)								Study Report Location
						0.5	1	2	4	6	12	24	48	
Study Report #: U5/FP/018/13	26 Dec 2013	Test: Doxorubicin hydrochloride liposome injection 20mg/10mL (Dr. Reddy's) Batch No.: 500080 Manufacture Date: November, 2013	20mg/10mL Liposomal injection	12 units	Mean	24	28.1	42.7	65.1	79.8	96.9	98.4	100	Module 2.7.1.2 and Module 5.3.1.3
					Range	^(b) / ₍₄₎								
					%CV	3.8	3.7	2.5	4.1	1.7	0.1	0.1	0.1	
Study Report #: U5/FP/022/13	28 Dec 2013	Test: Doxorubicin hydrochloride liposome injection 20mg/10mL (Dr. Reddy's) Batch No.: 500082 Manufacture Date: November, 2013	20mg/10mL Liposomal injection	12 units	Mean	22.8	33.2	46.0	65.7	82.4	97.1	99.0	100.1	Module 2.7.1.2 and Module 5.3.1.3
					Range	^(b) / ₍₄₎								
					%CV	11.6	3.7	1.3	1.1	0.4	0.1	0.2	0.1	
Study Report #: U5/FP/023/13	27 Dec 2013	Test: Doxorubicin hydrochloride liposome injection 20mg/10mL (Dr. Reddy's) Batch No.: 500083 Manufacture Date: November, 2013	20mg/10mL Liposomal injection	12 units	Mean	22.5	30.4	43.9	63.7	79.6	94.0	95.8	97.0	Module 2.7.1.2 and Module 5.3.1.3
					Range	^(b) / ₍₄₎								
					%CV	9.6	4.3	2.5	2.6	1.6	0.2	0.2	0.1	

Study Report #: U5/MS/634/14	02 June 2014	Reference: Doxorubicin hydrochloride liposome injection 20mg/10mL (Sun Pharma) Lot No.: JKM7084A Expiration Date: May, 2015	20mg/10mL Liposomal injection	12 units	Mean	37.9	47.1	55.1	72.1	86.5	94.3	95.2	96.6
					Range	(b) (4)							
					%CV	1.7	4.0	0.8	0.9	0.6	0.1	0.1	0.1
Study Report #: AR/2852/09/2015	30 Sep 2015	Test: Doxorubicin hydrochloride liposome injection 50mg/25mL (Dr. Reddy's) Batch No.: 500084 Manufacture Date: November, 2013	50mg/25mL Liposomal injection	12 units	Mean	28.2	37.2	51.7	71.9	85.0	94.7	95.1	96.5
					Range	(b) (4)							
					%CV	1.3	2.3	0.3	1.2	0.6	0.2	0.1	0.1
Study Report #: AR/2678/09/2015	27 Sep 2015	Test: Doxorubicin hydrochloride liposome injection 50mg/25mL (Dr. Reddy's) Batch No.: 500085 Manufacture Date: November, 2013	50mg/25mL Liposomal injection	12 units	Mean	33.0	42.6	55.7	77.2	90.0	94.9	96.6	98.1
					Range	(b) (4)							
					%CV	4.0	1.0	1.1	1.4	0.7	0.2	0.1	0.1
Study Report #: AR/2853/09/2015	30 Sep 2015	Test: Doxorubicin hydrochloride liposome injection 50mg/25mL (Dr. Reddy's) Batch No.: 500086 Manufacture Date: December, 2013	50mg/25mL Liposomal injection	12 units	Mean	28.3	36.9	52.1	72.7	85.7	94.2	94.4	95.8
					Range	(b) (4)							
					%CV	2.7	1.2	2.6	2.1	1.4	0.3	0.1	0.1
Study Report #: U5/MS/1235/15	21 Sep 2015	Reference: Doxorubicin hydrochloride liposome injection 50mg/25mL Lot No.: JKP2573A Expiration Date: November, 2016	50mg/25mL Liposomal injection	12 units	Mean	34.9	40.9	56.3	78.6	91.8	94.9	95.3	97.9
					Range	(b) (4)							
					%CV	1.1	0.8	1.8	0.8	0.3	0.1	0.1	0.6



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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: ANDA 208657

**Drug Product Name / Strength: Doxorubicin Hydrochloride Liposome Injection
20 mg/ 10 mL and 50 mg/ 25 mL**

Route of Administration: Injectable; IV (Infusion)

Applicant Name: Dr. Reddy's Laboratories Limited

Introduction:

ANDA 208657, submitted by Dr Reddy's, is seeking approval of Doxorubicin hydrochloride liposome injection, 20mg/10mL and 50mg/ 25mL, for the treatment of ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma, under the 505(j) path. Although the innovator drug product is DOXIL (approved under NDA 050718), the current RLD designated in the Orange Book is Doxorubicin hydrochloride liposome injection 20mg/ 10mL and 50mg/ 25mL (Sun Pharma), approved under ANDA 203623.

The Applicant conducted a fasting bioequivalence (BE) study comparing the test product to the RLD, Sun Pharma Global's Doxorubicin Hydrochloride Liposome Injection, 50 mg/m² (2 mg/mL). In addition to the BE study, the firm conducted an *in vitro* liposome size distribution study per the BE guidance. Both studies have been evaluated by OGD and found adequate.¹

List Submissions being reviewed (table):

eCTD Sequence #	Submission Date	Submission
0000	10/08/2015	New ANDA
0001	11/17/2015	Quality/Response to Information Request
0006	09/15/2016	Quality/Response to Information Request

Highlight Key Outstanding Issues from Last Cycle:

None. First review cycle.

Concise Description of Outstanding Issues:

¹ Yoriko Harigaya, ANDA 208657 Bioequivalence review, 6/24/2016.

- The Applicant's proposed in-house in vitro release method was shown to be discriminating, however high inter-batch variability and inconsistent in vitro release data at batch release and during stability were observed. The Applicant needs to demonstrate these were not caused by lack of robustness of the method.
- Recommendations on the acceptance criteria are not provided due to the inadequacy of the in vitro release method.
- The comparative in vitro leakage studies were conducted following the BE guidance for doxorubicin hydrochloride liposome injection. However, the f_2 values were not provided for all the tests and hence were requested.

Overall, the proposed dissolution method and acceptance criteria are inadequate, and the information request comments outlined at the end of this review need to be conveyed to the Applicant.

BCS Designation

Reviewer's Assessment:

BCS classification is not applicable as the proposed drug product is not an oral dosage form.

(b) (4)

Permeability: No information is provided.

Dissolution: See the following sections.

Dissolution Method and Acceptance Criteria

1. Is the formulation of the proposed drug product qualitatively and quantitatively the same as the RLD product?

JANSSEN's DOXIL® (Doxorubicin HCl liposome injection) is the designated listed drug for Doxorubicin HCl liposome injection and was also listed as the RLD in the Orange Book. However, due to the unavailability / limited supply of this product, Doxorubicin Hydrochloride liposome injection from Sun Pharma Global approved under ANDA 203263 was selected as the RLD in the current Orange Book.

The composition of the proposed drug product is compared to that of the previous and current RLD products, as shown in Table 2. The proposed drug product is qualitatively and quantitatively the same as the RLD products.

Table 2. Composition of The Proposed Drug Product

Qualitative and Quantitative Composition			
Ingredients	Current RLD	Original Innovator product	Proposed Generic Product
	Doxorubicin Hydrochloride Liposome Injection 20mg/10mL and 50mg/25mL (2mg/mL) (Sun Pharma Global)	Doxil® [Doxorubicin Hydrochloride Liposome Injection 20mg/10mL and 50mg/25mL (2mg/mL)] (Janssen)	Doxorubicin Hydrochloride Liposome Injection 20mg/10mL and 50mg/25mL (2mg/mL) (Dr. Reddy's)
Doxorubicin Hydrochloride USP	2 mg/mL	2 mg/mL	2 mg/mL
Cholesterol NF	3.19 mg/mL	3.19 mg/mL	3.19 mg/mL
Fully hydrogenated soy phosphatidylcholine (HSPC)	9.58 mg/mL	9.58 mg/mL	9.58 mg/mL
N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE)	3.19 mg/mL	3.19 mg/mL	3.19 mg/mL
Ammonium Sulfate NF	Approximately 2mg/mL	Approximately 2mg/mL	Approximately 2mg/mL
Histidine USP	(b) (4)		
Sucrose NF	(b) (4)		
(b) (4)	(b) (4)		
Sodium Hydroxide NF	(b) (4) adjust pH to 6.5	(b) (4) adjust pH to 6.5	(b) (4) adjust pH to 6.5
Hydrochloric acid NF	(b) (4) adjust pH to 6.5	(b) (4) adjust pH to 6.5	(b) (4) adjust pH to 6.5
	(b) (4)		

The manufacturing process and the physicochemical characteristics of the liposomes are evaluated by the Chemistry review team.

2. What is the in vivo release mechanism of the proposed drug product?

(b) (4)

² ML Immordino, F Dosio and L Cattel, Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. Int J Nanomedicine, 2006 Sep 1(3): 297-315.

(b) (4)

Reviewer's Comments:

(b) (4)

The in vitro release studies under different pHs mimic the in vivo release in various tissues. The similarity in in vitro release under various conditions between the proposed and the reference products can partly support the similarity in in vivo release.

3. Did the firm conduct the in vitro leakage studies to demonstrate that there is no uncontrolled drug leakage?

Following FDA “Draft guidance on Doxorubicin Hydrochloride (Recommended Feb 2010; Revised Nov 2013, Dec 2014)” the in vitro leakage studies from Doxorubicin Liposome were conducted. The test conditions for the in vitro leakage studies are summarized in Table 3.

Table 3. In vitro leakage conditions for doxorubicin liposomes

In Vitro Drug Leakage Condition	Purpose	Rationale
At 37°C in 50% human plasma for 24 hours	Evaluate liposome stability in blood circulation	Plasma mostly mimics blood conditions.
At 37°C with pH values 5.5, 6.5, and 7.5 for 24 hours in buffer	Mimic drug release in normal tissues, around cancer cells, or inside cancer cells	Normal tissues: pH 7.3 Cancer tissues: pH 6.6 Insider cancer cells (endosomes and lysosomes): pH 5-6 (Endosome and lysosomes of cancer cells may be involved in liposome uptake and induce drug release).
At a range of temperatures (43°C, 47°C, 52°C, 57°C) in pH 6.5 buffer for up to 12 hours or until complete release	Evaluate the lipid bilayer integrity	The phase transition temperature (T _m) of lipids is determined by lipid bilayer properties such as rigidity, stiffness and chemical composition. Differences in release as a function of temperature (below or above T _m) will reflect small differences in lipid properties

<p>At 37°C under low-frequency (20 kHz) ultrasound for 2 hours or until complete release.</p>	<p>Evaluate the state of encapsulated drug in the liposome.</p>	<p>Low-frequency ultrasound (20 kHz) disrupts the lipid bilayer via a transient introduction of pore-like defects and will render the release of doxorubicin controlled by the dissolution of the gel inside the liposome.</p>
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4. Did the firm provide the complete dissolution data for the leakage studies? Was the similarity (*f2*) in leakage (or non-leakage) demonstrated between the proposed drug product and the RLD product under various conditions?

1) In vitro drug release at 37 °C in 50% human plasma

The drug release profile of the reference products (Sun Pharma’s product, Doxil® and Caelyx³ injection) at 37°C in 50% human plasma was provided, which showed negligible drug release. In the IR response dated 09/15/2016, the Firm provided the release data with 12 units of test and RLD product. Since the exhibit batches have expired, a new batch of test product (batch # 500237) was used. The new batch was manufactured using the same components (raw material and packaging material) with same composition and the manufacturing process. The comparative in vitro release profiles are shown in Figure 1, and the similarity factor *f2* is 88.8, indicating similarity.

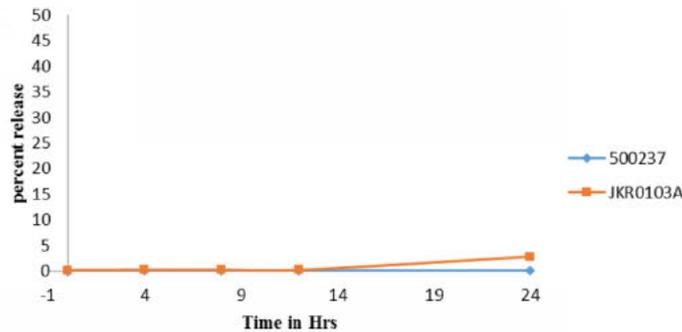


Figure 1. in vitro leakage at 37°C in 50% human plasma

2) In vitro drug release at 37 °C with pH values 5.5, 6.5, and 7.5 for 24 hours in buffer

Table 4. In vitro leakage at 37 °C at pH 5.5

³ Caelyx (pegylated liposomal doxorubicin) injection is another liposome injection of doxorubicin which was manufactured by the same manufacturer as Doxil. However Caelyx is NOT the reference product of this ANDA, and it is NOT the same drug as Doxil. (b) (4)

Caelyx is marketed in Europe and Doxil is marketed in US.

% Drug Release						
Time in Hours	Test Formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
1	(b) (4)					
3						
6						
12						
24						

Table 5. In vitro leakage at 37 °C at pH 6.5

% Drug Release						
Time in Hours	Test Formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
1	(b) (4)					
2						
3						
6						
12						
24						

Table 6. In vitro leakage at 37 °C at pH 7.5

% Drug Release						
Time in Hours	Test Formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
1	(b) (4)					
2						
3						
6						
12						
24						

The Applicant noted that the in-vitro release in pH 5.5 was found to be less than (b) (4)%. The in-vitro drug release was observed to be more discriminating in pH 6.5 when compared to pH 7.5.

3) In vitro drug release at a range of temperatures (43°C, 47°C, 52°C, 57°C) in pH 6.5

As per the draft BE guidance, the in vitro drug release study was performed at a range of temperatures 43°C, 47°C, 52°C and 57°C in pH 6.5 buffer (having 2M Ammonium chloride & 0.2M Histidine buffer) for complete release to evaluate the lipid bilayer integrity. The Applicant selected 2M Ammonium chloride & 0.2M Histidine buffer as the dissolution medium based on information from the Summary Basis of Approval for Doxil®.

Table 7. In vitro leakage at 43 °C at pH 6.5

% Drug Release						
Time in Hours	Test Formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
0.5						(b) (4)
1						
2						
4						
12						
24						
36						
48						

Table 8. In vitro leakage at 47 °C at pH 6.5

% Drug Release						
Time in Hours	Test formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B. No: 202837 (20mg/10mL)	B. No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
0.5						(b) (4)
1						
2						
4						
12						
24						
36						
48						

Table 9. In vitro leakage at 52 °C at pH 6.5

% Drug Release						
Time in Hours	Test formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B.No: 202837 (20mg/10mL)	B.No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
0.5						(b) (4)
1						
2						
4						
12						
24						
36						
48						

Table 10. In vitro leakage at 57 °C at pH 6.5

% Drug Release						
Time in Hours	In-House formulation			Doxil		
	B. No: 202830 (20mg/10mL)	B.No: 202837 (20mg/10mL)	B.No: 202838 (20mg/10mL)	Lot No.: 1009649 (20mg/10mL)	Lot No.: 1003283 (20mg/10mL)	Lot No.: 1010638 (20mg/10mL)
0.5	(b) (4)					
1						
2						
4						
12						
24						
36						
48						

The Applicant noted that the *in vitro* drug release test using the pH 6.5 buffer (2M Ammonium Chloride-0.2M Histidine) at 47°C shows potential as being an appropriate *in vitro* drug release method for batch release quality control.

4) *In vitro* drug release under low-frequency ultrasound

In the IR response dated 09/15/2016, the firm provided the comparative *in vitro* leakage test under ultrasound conducted using the RLD product and a new batch of the test product (Batch # 500237). The comparative profiles are shown in Figure 2. The *f2* value was calculated to be 96.4, indicating similarity.

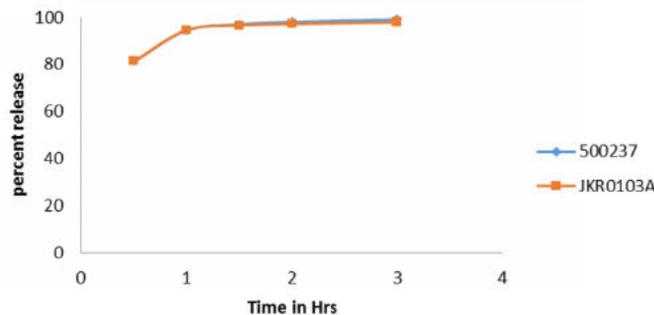


Figure 2. *in vitro* leakage under low-frequency (20 kHz) ultrasound

Reviewer’s Comments:

*The proposed drug product is qualitatively and quantitatively the same as the reference product, (b) (4) (to be evaluated by the chemistry review team). Therefore, the proposed drug product is expected to have comparable *in vitro* release as the reference product.*

*The comparative *in vitro* leakage test is recommended in the BE guidance, in order to ensure that the stability of the liposomes, the release in various tissues, and the integrity of the membrane bilayer of the proposed drug product are comparable to the RLD product. Therefore *f2* calculation is required for the *in vitro* leakage test.*

The Applicant performed the in vitro leakage studies for the reference products (Sun Pharma's product, Doxil® and Caelyx injection) to understand the characteristics of the RLD. However, for the proposed drug product, the Applicant did not perform all the recommended leakage tests. In particular, the test in 50% plasma and the test under low-frequency ultrasound were not initially performed.

For the tests conducted, the Applicant provided data for 3 batches of the proposed drug product and 3 batches of the RLD (Doxil) product. However, only one value was provided for each batch at each time point. In addition, the similarity factor (f_2) was not calculated between the test and reference product. The Applicant will be asked to provide the complete data and the f_2 values.

The following IR comments were conveyed to the Applicant on August 1, 2016.

- 1. We acknowledge that you submitted the in vitro leakage studies in section 3.2.P.2. However it is noted that you did not conduct the test in 50% human plasma and under low frequency ultrasound for the proposed drug product. In addition, you did not provide information regarding sample sizes, the variability in each test, the complete data and the similarity factor f_2 values. Submit the following information:***
 - The comparative in vitro leakage test conducted using the proposed drug product and the reference product at 37 °C in 50% human plasma to evaluate the liposome stability in blood.***
 - The comparative in vitro leakage test conducted using the proposed drug product and the reference product under low-frequency (20 kHz) ultrasound to evaluate the state of encapsulated drug in the liposome.***
 - The sample sizes and individual data with the variability (standard deviation and/or CV%) for each lot used in each of the drug leakage tests.***
 - The similarity factor f_2 values for the profile comparisons using 12 units of test and reference products per test of in vitro leakage and dissolution for batch release.***

In the IR response dated 9/15/2016, the Applicant provided the in vitro leakage data collected in 50% human plasma and under low frequency ultrasound, and calculated f_2 values which indicated similarity. However the Applicant did not provide f_2 calculation for the rest of the in vitro leakage tests. The response is not satisfactory, and f_2 value for each in vitro leakage test will be requested.

The Applicant also provided f_2 values for batch release dissolution test, which will be included in later section.

The following IR comment need to be conveyed to the Applicant:

We acknowledge that you submitted f_2 values for the in vitro leakage tests conducted in 50% human plasma and under low frequency ultrasound. Provide the similarity factor f_2 values for the profile comparisons using 12 units of test and reference products for each of the in vitro leakage tests. Equivalent in vitro leakage under multiple conditions support a lack of uncontrolled leakage under a range of physiological conditions and equivalent drug delivery to the tumor cells.

5. If the proposed dissolution method is not a USP method or listed on the FDA website:

a) What data are submitted to support the discriminating ability of the Applicant's proposed method?

In the original submission, the Applicant proposed two in vitro release methods for QC testing.

1st Method:

Apparatus	Culture tube, incubation in water bath
Agitation	No
Medium	pH 6.5 buffer (2M Ammonium Chloride and 0.2M L-Histidine)
Temperature	47°C

According to the analytical procedure described in 3.2.P.5.2, (b) (4)



2nd Method:

Apparatus	(b) (4)
Agitation	
Medium	
Temperature	



However, in the original ANDA, no data were provided to demonstrate the discriminating ability of either of the proposed methods. The following IR comments were sent to the Applicant on August 1, 2016.

- 2. It is noted that you proposed two dissolution methods for the QC test at batch release. However, neither of the methods has been demonstrated to be discriminating. Provide data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the target product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables* (b) (4)
. The FDA recommends that one of the two methods should be selected based on results of the investigation of their discriminating power.

In the IR response received on 09/15/2016, The Applicant tested the discriminating nature of the proposed dissolution methods (b) (4)
(b) (4)

(b) (4)

Therefore, the Applicant selected the 1st Method using pH 6.5 histidine buffer as the dissolution media for testing the drug product at release and stability testing.

b) Is the proposed dissolution method acceptable? If not what are the deficiencies?

No. Though the proposed dissolution method (1st Method using pH 6.5 buffer (2M Ammonium Chloride-0.2M Histidine) at 47°C) is shown to be discriminating with respect to drug product composition, and the method has been fully validated (the method validation report is provided in section 3.2.P.5.3), the proposed method has shown high inter-batch variability. In addition, huge differences were observed between the release data and the stability data at initial time points for all batches, which indicate either the method is not robust, or the drug product quality is not satisfactory. The details are discussed in the section of Acceptance Criteria under Question #12.

Reviewer's Comments:

As shown below, FDA recommended the generic Applicants to develop a method starting at pH 6.00±0.05 and at 47°C±0.5°C, but did not provide recommendation on apparatus/ equipment.

Doxorubicin Hydrochloride	Injectable (Liposomal)	Develop a method to characterize in vitro release, starting at pH 6.00 ± 0.05 and at 47°C ± 0.5°C. Replicate for 12 dosage vials.			9/10/2012	0, 0.5, 1, 2, 3, 4, 5 hours
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The Applicant initially proposed two in vitro release methods for doxorubicin hydrochloride liposomes. Both methods employed pH 6.5 buffer and both were conducted at 47 °C. However the composition of the buffers were different, with one composed of 2M Ammonium Chloride and 0.2M Histidine, (b) (4)

In response to FDA’s request, the Applicant demonstrated that both methods are discriminating with respect to changes in drug product composition. Method 1 using pH 6.5 histidine buffer was selected as the final QC method. The method was fully validated. The Applicant did not provide justification for selection of the concentration of the Ammonium Chloride and L-Histidine though.

As will be discussed in a later section, high inter-batch variability and huge differences between the batch release data and the stability data at initial time points were observed. The Applicant needs to investigate whether these were caused by inadequacy of the in vitro release method.

The following IR comment need to be conveyed to the Applicant.

Justify the selection of the concentrations of ammonium chloride and L-histidine in the medium used for the proposed in vitro release method.

6. Did the firm provide 12 units (non-pooled) of both test and reference product in applicable dissolution/release testing?

Yes.

7. Was the dissolution testing conducted on the bio-batch?

Yes. The Bio-batch # 500082 was tested.

8. What was the age of the test product at the time of dissolution testing?

The 20mg/ 10mL test product was about 6 months old at the time of testing. The 50mg/ 25mL test product was 21-23 months old, which is beyond the currently proposed expiration date of 18 months. The Applicant will be asked to provide data to support the use of the 50mg/ 25mL batches.

Table 12. Age of the test product

Strength	Batch #	Manufacture Date	Testing Date	Age (months)
20mg/ 10mL	500080	Nov 2013	14 Apr 2014	5-6
	500082	Nov 2013	14 Apr 2014	5-6
	500083	Nov 2013	14 Apr 2014	5-6
50mg/ 25mL	500084	Nov 2013	29 Sep 2015	22-23

	500085	Nov 2013	28 Sep 2015	22-23
	500086	Dec 2013	29 Sep 2015	21-22

The following IR comments were conveyed to the Applicant on August 1, 2016.

- 3. *The batches of the proposed drug product 50 mg/ 25mL are beyond the proposed expiration date of 18 months at the time of dissolution testing. Provide data to demonstrate that there is no change in the product quality for these batches.***

In the response received on 9/15/2016, The Applicant noted that all the three batches of 50mg/25mL presentation were tested and found to meet the shelf life specification at the time when the dissolution testing was conducted (when the drug product was about 20 months old). The 20 months stability data are provided in Annexure-23 of the cover letter dated 9/15/2016. The data suggest that the initial time point was 17/01/2014 for the 50mg/25mL batches, when the batches were 1-2 months old. The data also appear to suggest that there is an increase in in-vitro release rate from the initial time point to the 20-month time point. The Applicant has data of 6 units for the initial time point, and the 12-unit data are only available at the 20-month time point.

It is noted that the 50mg/25mL are not the bio-batches, and setting of acceptance criterion can be based on the data of the bio-batch, which was tested within the expiry date. The response is acceptable.

9. Was the dissolution/release testing conducted on unexpired reference product?

Yes. The reference product was unexpired.

Table 13. Age of the reference product

Strength	Batch #	Expiration Date	Testing Date
20mg/ 10mL	JKM7084A	May 2015	4 Jun 2014
50mg/ 25mL	JKP2573A	Nov 2016	21 Sep 2015

10. Did the firm provide complete dissolution data (i.e. all raw data, mean, range, %CV, dates of testing) to support the proposed acceptance criteria(on)? Were the data submitted for all proposed strengths of the drug product?

The Applicant provided the complete dissolution data for the exhibit batches obtained using both dissolution methods, as summarized in the APPENDIX.

11. Was the similarity (*f*₂) in in-vitro release using the application in vitro release method demonstrated between the Test and Reference product at batch release

The similarity factor (*f*₂) for batch release dissolution for the test and reference products is provided in the IR response received on 09/15/2016. Both the Applicant’s and this reviewer’s calculation are summarized below. As the Applicant has chosen method 1 as the final QC method. The *f*₂ values are only provided for the QC method.

Table 14. Similarity factor (f_2) for test and reference products at batch release using the proposed QC in vitro release method

Test Batch	Reference Listed Drug	Applicant Submitted f_2 Values	Reviewer Calculated f_2 Values
500080	JKM7084A	50	46.7
500082	JKM7084A	53	50.1
500083	JKM7084A	50	47.4
500084	JKM7084A	64	61.3
500085	JKM7084A	74	68.9
500086	JKM7084A	64	59.4

Reviewer's Comments:

It is noted that there are two batches (batch # 500080 and 500083) that did not demonstrate similarity to the RLD batch (SUN product) according to the reviewer's calculation. The bio-batch (#500082) showed similar in vitro release profile as the RLD batch ($f_2=50.1$). Because the proposed method is under accelerated condition and is not relevant to in vivo release conditions, the small differences observed in release profiles of the test and reference products are acceptable.

12. Is the proposed dissolution acceptance criteria acceptable? If not, what is the recommendation with justification?

The initially proposed acceptance criteria are as follows:

Method 1 (pH 6.5 buffer at 47 °C): NLT (b) (4) % at 2 hrs.
 (Final QC method) NLT (b) (4) % at 8 hrs

Method 2 (b) (4) (b) (4)

The Applicant proposed to conduct dissolution testing of the inverted vials only for the stability studies. This is acceptable, as the inverted orientation represents a more stressed condition than the upright orientation. As requested by the Agency, the complete stability dissolution data for the exhibit /primary registration batches are provided in section 3.2.P.8.3.

The initially proposed acceptance criteria are not acceptable, and the following IR comments are provided in the IR letter dated August 1, 2016:

4. The proposed dissolution acceptance criteria are permissive and not acceptable. For the setting of the dissolution acceptance criteria of the proposed drug product, the following points should be considered:

- The dissolution profile data from the pivotal clinical batches and primary stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).*

- *Provide the complete stability dissolution data (individual, mean, range, CV%) for the exhibit/ primary stability batches in “.xpt” format or in excel spreadsheet. Include data at all the sampling time points in addition to the proposed specification time points.*
- *The acceptance criteria should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).*
- *Given the slow release of the drug product, a minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be where at least 80% of drug is released. If the maximum amount released is less than 80%, the last time point should be when the plateau of the release profile has been reached.*
- *In general, the selection of the dissolution acceptance criteria ranges is based on mean target value $\pm 10\%$ and $>80\%$ for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model.*
- *A detailed discussion of the justification of the proposed dissolution acceptance criterion should be included in your submission.*

In the IR response dated 09/15/2016, the Applicant proposed the following revised acceptance criteria for the final QC method (Method 1, in pH6.5 Histidine buffer at 47°C):

2 hr	NLT	(b) (4) %
4 hr	(b) (4)	0%
8 hr	NLT	(b) (4) %

The revised acceptance criteria remains unacceptable, due to the wide ranges proposed without justification. The batch release data provided in the APPENDIX are plotted in the Figure below.



The batch release data appear to support the following acceptance criteria:

	(b) (4)
2 hr	(b) (4) 0%
4 hr	(b) (4) 0%
8 hr	NLT (b) (4) 0%

The Applicant also provided the “.xpt” file for the stability data and 2hr and 8hr time points in section 3.2.P.8. The data are plotted by this Reviewer and the figures are shown below.



However, the following concerns arise when comparing the stability data to the batch release data:

- The stability data at the 2hr time point were significantly higher than the batch release data presented above, which indicates the proposed in vitro release method may not be robust.
- The 8-hr time point was not included in the batch release test, so no comparison can be made.
- The bio-batch (500082) appears to be among the slow release batches at release, but appears to be the fastest release batch during stability.
- A trend was observed for the stability data at both the 2hr and 8hr time points as a function of storage time, with 12-month and 18-month data going up and 3-month and 15-month data going down (the difference between the 15-month and 18-month data are more than 20%).
- More importantly, all batches (including the biobatch) did not conform to the acceptance criteria supported by the batch release data. These observations indicate that the drug product quality may not be satisfactory and the proposed expiry dating of 18 months is not supported.

Reviewer's Comments:

It is noted that the age of the biobatch (500082) ranged from 8 to 16 months during the bioequivalence study, which was found adequate by OGD. Therefore the stability data of the biobatch should be taken into consideration when setting acceptance criteria. Due to the noticeable differences between the batch release data and the stability data, the recommendation for the acceptance criteria is pending. The Applicant has to investigate the root cause for the observed discrepancies, and improve the in vitro release method if needed.

The Applicant is also requested to provide the complete in vitro release data for the stability batches by including all the time points. It is noted that the complete data may not be available prior to 18 months; the Applicant is being asked to provide data including all time points at the current stability time point or the release/ stability data of any new batches manufactured using the same composition and process.

The following IR comments need to be conveyed to the Applicant:

We acknowledge the stability data up to 18 months at the 2-hr and 8-hr time points and the batch release data you provided in section 3.2.P.8.3. It is noted that the 2-hr in vitro release data at the initial stability time point is higher than the 2-hr data at batch release. Please clarify the initial time point of the stability program relative to batch release. It is also noted that both 2-hr and 8-hr data show a trend as a function of storage time, with 12-month and 18-month data going up and 3-month and 15-month data going down (the difference between the 15-month and 18-month data are more than 20%). Investigate the root cause for the trend observed. In addition, demonstrate the robustness and reproducibility of the release testing methodology.

Provide complete in vitro release data for the stability batches by including all the time points. It is noted that the complete data may not be available prior to 18 months. Provide the complete in vitro release data at the current stability time point for the stability batches or the release/ stability data of any new batch manufactured using the same composition and process.

Due to lack of the complete in vitro release data for evaluation and the observed trend of the stability data, the adequacy of the proposed in vitro release method cannot be determined, and evaluation of the acceptance criteria is pending.

Biowaiver Request**Reviewer's Assessment:**

The Applicant requested a biowaiver for Doxorubicin hydrochloride liposome injection 50mg/25mL strength, and it will be reviewed by OGD.

Information Request:

- 1. We acknowledge that you submitted f_2 values for the in vitro leakage tests conducted in 50% human plasma and under low frequency ultrasound. Provide the similarity factor*

- f2 values for the profile comparisons using 12 units of test and reference products for each of the in vitro leakage tests. Equivalent in vitro leakage under multiple conditions support a lack of uncontrolled leakage under a range of physiological conditions and equivalent drug delivery to the tumor cells.*
- 2. Justify the selection of the concentrations of ammonium chloride and L-histidine in the medium used for the proposed in vitro release method.*
 - 3. We acknowledge the stability data up to 18 months at the 2-hr and 8-hr time points and the batch release data you provided in section 3.2.P.8.3. It is noted that the 2-hr in vitro release data at the initial stability time point is higher than the 2-hr data at batch release. Please clarify the initial time point of the stability program relative to batch release. It is also noted that both 2-hr and 8-hr data show a trend as a function of storage time, with 12-month and 18-month data going up and 3-month and 15-month data going down (the difference between the 15-month and 18-month data are more than 20%). Investigate the root cause for the trend observed. In addition, demonstrate the robustness and reproducibility of the in vitro release testing methodology.*
 - 4. Provide complete in vitro release data for the stability batches by including all the time points. It is noted that the complete data may not be available prior to 18 months. Provide the complete in vitro release data at the current stability time point for the stability batches or the release/ stability data of any new batch manufactured using the same composition and process.*
 - 5. Due to lack of the complete in vitro release data for evaluation and the observed trend of the stability data, the adequacy of the proposed in vitro release method cannot be determined, and evaluation of the acceptance criteria is pending.*

Primary Biopharmaceutics Reviewer Name and Date:

Jing Li, Ph.D. 11/16/2016

Biopharmaceutics Reviewer

Division of Biopharmaceutics

Office of New Drug Products

Office of Pharmaceutical Quality

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

Okpo Eradiri, Ph.D. 11/28/2016

Acting Biopharmaceutics Lead

Division of Biopharmaceutics

Office of New Drug Products

Office of Pharmaceutical Quality

APPENDIX IN VITRO DISSOLUTION DATA FOR DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION

(b) (4)



Table 16. Summary of in Vitro Dissolution Studies in pH 6.5 Histidine Buffer (Final QC method)

Dissolution Conditions		Apparatus:	Culture tube & incubation in water bath											
		Speed of Rotation:	Not applicable											
		Medium:	pH 6.5 Buffer (Ammonium Chloride and L- Histidine) - Dissolution in QC release media											
		Volume:	4mL Dissolution Medium & 4mL sample (1:1)											
		Temperature:	47°C											
Firms' Proposed Specifications		Not less than ^(b) / ₍₄₎ % at 2 hours and Not less than ^(b) / ₍₄₎ % at 8 hours of drug is released from Liposomes												
Dissolution Testing Site (Name, Address)		^(b) / ₍₄₎												
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Manufacture Date) Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)								Study Report Location
						0.5	1	2	4	6	12	24	48	
Study Report #: U5/FP/018/13	26 Dec 2013	Test: Doxorubicin hydrochloride liposome injection 20mg/10mL (Dr. Reddy's) Batch No.: 500080 Manufacture Date: November, 2013	20mg/10mL Liposomal injection	12 units	Mean	24	28.1	42.7	65.1	79.8	96.9	98.4	100	Module 2.7.1.2 and Module 5.3.1.3
					Range	^(b) / ₍₄₎								
					%CV	3.8	3.7	2.5	4.1	1.7	0.1	0.1	0.1	
Study Report #: U5/FP/022/13	28 Dec 2013	Test: Doxorubicin hydrochloride liposome injection 20mg/10mL (Dr. Reddy's) Batch No.: 500082 Manufacture Date: November, 2013	20mg/10mL Liposomal injection	12 units	Mean	22.8	33.2	46.0	65.7	82.4	97.1	99.0	100.1	Module 2.7.1.2 and Module 5.3.1.3
					Range	^(b) / ₍₄₎								
					%CV	11.6	3.7	1.3	1.1	0.4	0.1	0.2	0.1	
Study Report #: U5/FP/023/13	27 Dec 2013	Test: Doxorubicin hydrochloride liposome injection 20mg/10mL (Dr. Reddy's) Batch No.: 500083 Manufacture Date: November, 2013	20mg/10mL Liposomal injection	12 units	Mean	22.5	30.4	43.9	63.7	79.6	94.0	95.8	97.0	Module 2.7.1.2 and Module 5.3.1.3
					Range	^(b) / ₍₄₎								
					%CV	9.6	4.3	2.5	2.6	1.6	0.2	0.2	0.1	

Study Report #: U5/MS/634/14	02 June 2014	Reference: Doxorubicin hydrochloride liposome injection 20mg/10mL (Sun Pharma) Lot No.: JKM7084A Expiration Date: May, 2015	20mg/10mL Liposomal injection	12 units	Mean	37.9	47.1	55.1	72.1	86.5	94.3	95.2	96.6
					Range	(b) (4)							
					%CV	1.7	4.0	0.8	0.9	0.6	0.1	0.1	0.1
Study Report #: AR/2852/09/2015	30 Sep 2015	Test: Doxorubicin hydrochloride liposome injection 50mg/25mL (Dr. Reddy's) Batch No.: 500084 Manufacture Date: November, 2013	50mg/25mL Liposomal injection	12 units	Mean	28.2	37.2	51.7	71.9	85.0	94.7	95.1	96.5
					Range	(b) (4)							
					%CV	1.3	2.3	0.3	1.2	0.6	0.2	0.1	0.1
Study Report #: AR/2678/09/2015	27 Sep 2015	Test: Doxorubicin hydrochloride liposome injection 50mg/25mL (Dr. Reddy's) Batch No.: 500085 Manufacture Date: November, 2013	50mg/25mL Liposomal injection	12 units	Mean	33.0	42.6	55.7	77.2	90.0	94.9	96.6	98.1
					Range	(b) (4)							
					%CV	4.0	1.0	1.1	1.4	0.7	0.2	0.1	0.1
Study Report #: AR/2853/09/2015	30 Sep 2015	Test: Doxorubicin hydrochloride liposome injection 50mg/25mL (Dr. Reddy's) Batch No.: 500086 Manufacture Date: December, 2013	50mg/25mL Liposomal injection	12 units	Mean	28.3	36.9	52.1	72.7	85.7	94.2	94.4	95.8
					Range	(b) (4)							
					%CV	2.7	1.2	2.6	2.1	1.4	0.3	0.1	0.1
Study Report #: U5/MS/1235/15	21 Sep 2015	Reference: Doxorubicin hydrochloride liposome injection 50mg/25mL Lot No.: JKP2573A Expiration Date: November, 2016	50mg/25mL Liposomal injection	12 units	Mean	34.9	40.9	56.3	78.6	91.8	94.9	95.3	97.9
					Range	(b) (4)							
					%CV	1.1	0.8	1.8	0.8	0.3	0.1	0.1	0.6

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	208657
Drug Product Name	Doxorubicin Hydrochloride Liposome Injection
Strengths	20 mg/10 mL and 50 mg/25 mL
Applicant Name	Dr. Reddy's Laboratories Limited
Address	Integrated Product Development Organization Innovation Plaza, Survey Nos. 42, 45, 46 & 54, Bachupally, Quthbullapur Mandal, Hyderabad, Telangana, 500090 INDIA
US Agent Name and the mailing address	Srinivasa Rao, Senior Director & Head Regulatory Affairs - North America Dr. Reddy's Laboratories, Inc 107 College Road East, Princeton, New Jersey, 08540
US agent's Telephone Number	609-375-9922
US Agent's Fax Number	908-450-1476
US Agent's Email Address	srao@drreddys.com
Original Submission Date	October 8, 2015
Submission Date of Amendment Under Review	N/A
Reviewer	Yoriko Harigaya, Pharm.D.
Study Number (s)	591-13
Study Type (s)	Fasting
Strength (s)	50 mg/25 mL
Clinical Site A	Dr. V. Satya Suresh Attili, M.B.B.S., M.D., DM, PDCR.
Clinical Site A Address	BIBI General Hospital & Cancer Centre, 16-3-991/1/C, Govt. Printing Press Road, Malakpet, Hyderabad - 500 024, Telangana, India.
Clinical Site B	Dr. K. S. Kirushna Kumar, M.B.B.S., M.D.
Clinical Site B Address	Meenakshi Mission Hospital & Research Centre, Lake Area, Melur Road, Madurai - 625 107, Tamil Nadu, India.
Clinical Site C	Dr. Gopichand Mamillapalli, M.B.B.S., M.S., DNB, M. Ch.
Clinical Site C Address	City Cancer Center, # 33-25-33, Ch. Venkata Krishnayya Street Suryaraopet, Vijayawada – 520 002, Andhra Pradesh, India.
Clinical Site D	Dr. Jayanti G Patel, M.B.B.S., M.D.
Clinical Site D Address	Nirmal Hospital® Pvt. Ltd., Ring Road, Civil Street, Near Kadiwala School, Surat - 395 002, Gujarat, India.
Clinical Site E	Dr. Sudha Somappa, M.B.B.S., D.M.R.T.
Clinical Site E Address	Srinivasam Cancer Care Hospitals India Pvt. Ltd., No. 236/1, Vijayashree Layout, Arekere, Bannerghatta Main Road, Bangalore - 560 076, Karnataka, India.
Clinical Site F	Dr. Rajnish Vasant Nagarkar, M.B.B.S., M.S., BSS., DNB., MRCSEd., MNAMS.
Clinical Site F Address	Curie Manavata Cancer Centre, Opp. Mahamarg Bus Stand, Mumbai Naka, Nashik 422 004, Maharashtra, India.

(Clinical Site G*)	Dr. Kattuputtur Narayanan Srinivasan, M.B.B.S., DMRT., DRM., Dr. G. Vishwanathan Speciality Hospitals,		
(Clinical Site G Address)	27, Babu Road, Trichy - 620 008, Tamil Nadu, India.		
Clinical Site H	Prof. Dr. SurendraNath Senapati, M.D.		
Clinical Site H Address	Acharya Harihar Regional Cancer Centre, Department of Radiation Oncology, Medical Road, Mangalabag, Cuttack - 753 007, Odisha, India.		
Clinical Site I	Prof. Dr. SurendraNath Senapati, M.D.		
Clinical Site I Address	MNJ Institute of Oncology and Regional Cancer Centre, Red Hills, Hyderabad - 500 004, Telangana, India.		
Clinical Site J	Dr. K. Velavan, M.D., R.T.		
Clinical Site J Address	Erode Cancer Centre, Velavan Nagar (Near Chintamani Petrol Bunk), Perundurai Road, Thindal, Erode - 638 012, Tamil Nadu, India.		
Clinical Site K	Dr. Smita Gupte, M.B.B.S., M.D.		
Clinical Site K Address	Cancer Clinic & Nursing Home, Block No. 4-B, Hyatt Medicare, Plot No. 12 / 2, Dr. N. B. Khare Marg, Dhantoli, Nagpur – 440 012, Maharashtra, India.		
Analytical Site	(b) (4)		
Analytical Site Address	(b) (4)		
Study Number (s)	Not Provided		
Study Type (s)	Liposome Size Distribution		
Strength (s)	2 mg/mL		
In Vitro Liposome Size Distribution Testing Site	(b) (4)		
In Vitro Liposome Size Distribution Testing Address	(b) (4)		
OSIS Status	<u>Backlog, Year 1 and Year 2 ANDAs</u> <input type="checkbox"/> Pending <input type="checkbox"/> Complete <input type="checkbox"/> Not Applicable The results of OSIS inspection will not alter the outcome of the study.		<u>Year 3 ANDAs</u> <input checked="" type="checkbox"/> To Be Determined by OSIS <input type="checkbox"/> Pending For Cause Inspection
OVERALL REVIEW RESULT	ADEQUATE		
REVISED/NEW DRAFT GUIDANCE INCLUDED	No		
COMMUNICATION	<input type="checkbox"/> ECD <input type="checkbox"/> IR <input checked="" type="checkbox"/> NOT APPLICABLE		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1, 2	Fasting Study	50 mg/m ² (2 mg/mL)	ADEQUATE
1, 2, 3	Liposome Size Distribution	2 mg/mL	ADEQUATE

* No patients were randomized in Site G.

1 EXECUTIVE SUMMARY

This application contains the results of fasting bioequivalence (BE) study comparing the test product, Dr. Reddy's Laboratories Limited's Doxorubicin Hydrochloride Liposome Injection, 50 mg/m² (2 mg/mL) to the corresponding reference product, Sun Pharma Global's¹ Doxorubicin Hydrochloride Liposome Injection, 50 mg/m² (2 mg/mL). In addition to the PK endpoint BE study, the firm conducted *in vitro* liposome size distribution study per BE guidance².

The fasting BE study was designed as a multi-center, randomized, open label, two-period, two-treatment, two-way crossover, single dose BE study in patients of ovarian cancer whose disease had progressed or recurred after platinum based chemotherapy and who were already receiving or scheduled to start therapy with the reference listed drug.

In the fasting BE study, AUC_{0-t}, AUC_∞ and C_{max} of the test and reference products were comparable for both free doxorubicin and encapsulated doxorubicin. In the *in vitro* liposomal size distribution, the results of Population BE (PBE) statistical analyses for both D50 and span meet the PBE criteria. For details, please refer to Section 4.1

Drug release test will be reviewed by Office of Pharmaceutical Quality (OPQ).

The application is **adequate** from the bioequivalence perspective.

¹ The firm used Doxil (NDA #050718 from Janssen Pharma, the innovator), instead of the current RLD, as its basis of ANDA submission, which was found acceptable by the Division of Filing Review prior to submission of the current ANDA (GDRP ANDA 208657 Filing Primary Review 18 Nov 2015 [A208657N000DFR_BE_CHK.docx: page 5 of 19](#))

² Bioequivalence Recommendations for Specific Drug Products for Doxorubicin HCl Liposomal Injection posted at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf> (Recommended Feb 2010; Revised Nov 2013, Dec 2014)

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL and 50 mg/25 mL
Reference Product³	Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL and 50 mg/25 mL are the RLDs
RLD Manufacturer	Sun Pharma Global
ANDA No.	203263
RLD Approval Date	February 4, 2013
Indication⁴	Doxorubicin hydrochloride is an anthracycline topoisomerase inhibitor indicated for: - Ovarian cancer after failure of platinum-based chemotherapy. - AIDS-related Kaposi's Sarcoma after failure of prior systemic chemotherapy or intolerance to such therapy.

3.2 PK/PD Information⁴

Bioavailability	<p>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 a 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 below:</p> <p>Pharmacokinetic Parameters of Doxorubicin Hydrochloride Liposome Injection in Patients With AIDS-Related Kaposi's Sarcoma</p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter (units)</th> <th colspan="2">Dose</th> </tr> <tr> <th>10 mg/m²</th> <th>20 mg/m²</th> </tr> </thead> <tbody> <tr> <td>Peak Plasma Concentration (mcg/mL)</td> <td>4.12 ± 0.215</td> <td>8.34 ± 0.49</td> </tr> <tr> <td>Plasma Clearance (L/h/m²)</td> <td>0.056 ± 0.01</td> <td>0.041 ± 0.004</td> </tr> <tr> <td>Steady State Volume of Distribution (L/m²)</td> <td>2.83 ± 0.145</td> <td>2.72 ± 0.12</td> </tr> <tr> <td>AUC (mcg/mL·h)</td> <td>277 ± 32.9</td> <td>590 ± 58.7</td> </tr> <tr> <td>First Phase (λ₁) Half-Life (h)</td> <td>4.7 ± 1.1</td> <td>5.2 ± 1.4</td> </tr> <tr> <td>Second Phase (λ₂) Half-Life (h)</td> <td>52.3 ± 5.6</td> <td>55 ± 4.8</td> </tr> </tbody> </table> <p>N = 23 Mean ± Standard Error</p> <p>Doxorubicin hydrochloride liposome injection displayed linear pharmacokinetics over the range of 10 to 20 mg/m².</p> <p>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</p>		Parameter (units)	Dose		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/mL·h)	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
	Parameter (units)	Dose																							
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/mL·h)	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																							

³ Electronic Orange Book

(http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=019962&TABLE1=OB_Rx), accessed on 08/5/2015

⁴ Label for Doxorubicin HCl Liposome Injection from drugs@fda.gov. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203263lbl.pdf Approved on 02/04/2013.

	proportional at a 50 mg/m ² 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/m ² , 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	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 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/m ² at a dose of 20 mg/m ² . This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24 to 35 L/h/m ² . 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.
Half-life	Disposition occurred in two phases after doxorubicin hydrochloride liposome injection 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 area under the curve (AUC). At 50 mg/m ² , the elimination half-life of doxorubicin hydrochloride liposome injection is expected to be longer and the clearance lower compared to a 20 mg/m ² dose.
Dosage and Administration	Administer doxorubicin hydrochloride liposome injection at an initial rate of 1 mg/m ² in 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. - Ovarian cancer: 50 mg/m ² IV every 4 weeks for 4 courses minimum - AIDS-related Kaposi's Sarcoma: 20 mg/m ² IV every 3 weeks
Maximum Daily Dose	50 mg/m ² IV every 4 weeks
Drug Specific Issues (if any)	<p>Black Box Warning</p> <p>WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION</p> <ol style="list-style-type: none"> 1. 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 2 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. 2. Acute infusion-related reactions including, but not limited to, flushing,

	<p>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 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.</p> <ol style="list-style-type: none"> 3. Severe myelosuppression may occur. 4. Dosage should be reduced in patients with impaired hepatic function. 5. 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.
--	---

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, Fasting and Liposome Size Distribution
---------------------------------------	---

1.	Type of study:	Fasting*
	Design:	Single-dose, two-way crossover in vivo
	Strength:	50 mg/vial or 20 mg/vial
	Dose	50 mg/m ²
	Subjects:	Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug (RLD) or the reference standard product.
	Additional Comments:	Refer to the Drug Specific BE Guidance

* 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
Bioequivalence based on (90% CI):	AUC and Cmax for free doxorubicin and liposome encapsulated doxorubicin Note: the pivotal bioequivalence study should be conducted using test product produced by the proposed commercial scale manufacturing process.

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% upper confidence bound)	D50 and SPAN [(i.e. D90- D10)/D50] or polydispersity index using the population bioequivalence approach.
Additional Comments:	N/A

Waiver request of in-vivo testing:	N/A	
Source of most recent recommendations:	Bioequivalence Recommendations for Specific Drug Products for Doxorubicin HCl Liposome Injection posted at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf (Recommended Feb 2010; Revised Nov 2013, Dec 2014)	
Control correspondence related to the posted BE guidance	CC#09-0398: \\cdsnas\OGDS6\CONTROLS\2009-docs\09-0398.pdf Note: <div style="background-color: #cccccc; height: 100px; width: 100%;"></div> (b) (4)	
Summary of OGD or DB History	Pending ANDAs (Not Yet Reviewed)	Yes
	Approved ANDAs	Yes
	Previously Reviewed ANDAs	Yes
	Protocols	Yes
	Controls	Yes
	Citizen Petitions	Yes (see Section 3.3.1)

3.3.1 Citizen Petition⁵

On April 8, 2014, Sun Pharma Global FZE submitted the citizen petition regarding FDA’s designation of the Petitioner’s doxorubicin hydrochloride liposomal injection product as the RLD. *The petition requests that FDA: Withdraw designation of ANDA #203263 as the RLD for doxorubicin (liposomal), and reject any application referring to the Sun product approved under ANDA #203263 as the RLD. Alternatively, if FDA continues to list Sun’s product as the RLD, the Petition requests that FDA: Require any drug application (pending or future) that references ANDA #203263 as the RLD to demonstrate bioequivalence with statistically enhanced confidence.*

This Petition was denied.

⁵ Citizen Petition Docket ID: FDA-2014-P-0417

3.4 Pre-Study Bioanalytical Method Validation

Bioanalytical Method Validation for Encapsulated Doxorubicin

Information Requested	Data			
Bioanalytical method validation report location	Module 5, section 5.3.1.4, Appendix 16.6, Page 01 to 288 of 971			
Analyte	Encapsulated doxorubicin			
Internal standard (IS)	(b) (4)			
Method description	(b) (4)			
Limit of quantitation (ng/mL)	150.039 ng / mL (Addendum-I)			
Average recovery of drug (%) LQC, MQC & HQC	74.1 %, 79.0 % and 67.9 % (Addendum-I)			
Average recovery of IS (%)	74.9 % (Addendum-I)			
Standard curve concentrations (ng/mL)	150.039 to 60069.591 ng / mL (Addendum-I)			
	Working standard QCs (Addendum-I & Errata)		Liposomal Formulation QCs (Addendum-I)	
QC concentrations (ng/mL)	LOQ QC	151.743 ng/mL	LQC (FOR)	446.712 ng/mL
	LQC	446.303 ng/mL	MQC (FOR)	27439.335 ng/mL
	MQC	28175.677 ng/mL	HQC (FOR)	45732.225 ng/mL
	HQC	45444.640 ng/mL	DIL QC (FOR)	179270.323 ng/mL

QC intraday precision range (%)	2.1 % to 4.4 % (Addendum-I)	4.7 % to 5.5 % (Addendum-I)
QC intraday accuracy range (%)	99.9 % to 106.0 % (Addendum-I)	104.9 % to 109.0 % (Addendum-I)
QC interday precision range (%)	2.1 % to 5.3 % (Addendum-I)	4.2 % to 5.5 % (Addendum-I)
QC interday accuracy range (%)	94.6 % to 107.1 % (Addendum-I)	101.7 % to 108.3 % (Addendum-I)
Bench-top stability (hrs)	8.0 hours (in ice-cold water bath) for both, working standard QCs and liposomal formulation QCs (Addendum-I)	
Stock stability (days)	10 days (within 2 to 8°C) (for stock solution of ISTD & spiking solutions of drug at higher & lower level) (Addendum-I)	
Processed stability (hrs)	66.0 hours (within 2 to 8°C) (Addendum-I) 2.0 hours (at room temperature) (Addendum-I)	
Freeze-thaw stability (cycles)	4 cycles (at -65 ± 10°C) for both, working standard QCs and liposomal formulation QCs (Addendum-I)	
Long-term storage stability (days)	268 days at -65 ± 10°C for both, working standard QCs and liposomal formulation QCs (Addendum-IV) and 167 days at -22 ± 5°C for both, working standard QCs and liposomal formulation QCs (Addendum-III)	
Dilution integrity	179270.323 ng / mL diluted 5 fold (Addendum-I) 99595.409 ng / mL diluted 5 & 10 fold	
Selectivity	No interfering peaks noted in human blank plasma samples (Addendum-I)	

Bioanalytical Method Validation for Free Doxorubicin

Information Requested	Data	
Bioanalytical method validation report location	Module 5, section 5.3.1.4, Appendix 16.6, Page 289 to 572 of 971	
Analyte	Free Doxorubicin	
Internal standard (IS)	(b) (4)	
Method description	(b) (4)	
Limit of quantitation (ng/mL)	5.015 ng / mL (Addendum-II)	
Average recovery of drug (%) LQC, MQC & HQC	77.4 %, 88.4 % and 94.6 % (Addendum-III)	
Average recovery of IS (%)	87.1 % (Addendum-III)	
Standard curve concentrations (ng/mL)	5.015 to 2007.827 ng /mL (Addendum-II)	
QC concentrations (ng/mL)	LOQ QC	5.245 ng/mL (Addendum-II)
	LQC	14.985 ng/mL (Addendum-II)
	MQC	1012.480 ng/mL (Addendum-II)
	HQC	1534.061 ng/mL (Addendum-II)
	DIL QC	6002.847 ng/mL (Addendum-II)
	Working standard QCs	Liposomal Formulation QCs
QC intraday precision range (%)	1.7 % to 4.1 % (Addendum-II)	5.5 % to 11.4 % (Addendum-II)
QC intraday accuracy range (%)	89.8 % to 106.3 % (Addendum-II)	Not Applicable
QC interday precision range (%)	5.1 % to 8.2 % (Addendum-II)	6.9 % to 8.4 % (Addendum-II)
QC interday accuracy range (%)	91.7 % to 107.2 % (Addendum-II)	Not Applicable
Bench-top stability (hrs)	10.0 hours (in ice-cold water bath) for both, working standard QCs and liposomal formulation QCs (Addendum-II)	
Stock stability (days)	08 days (within 2 to 8°C) (for stock solution of drug & ISTD and spiking solution of drug at lower level) (Addendum-II)	
Processed stability (hrs)	107.0 hours (within 2 to 8°C) (Addendum-II) 2.0 hours (at room temperature) (Addendum-II)	
Freeze-thaw stability (cycles)	4 cycles (at -65 ± 10°C) for both, working standard QCs and liposomal formulation QCs (Addendum-II)	
Long-term storage stability (days)	289 days at -65 ± 10°C for both, working standard QCs and liposomal formulation QCs (Addendum-V) and 186 days at -22 ± 5°C for both, working standard QCs and liposomal formulation QCs (Addendum-IV)	
Dilution integrity	6002.847 ng / mL diluted 5 fold (Addendum-II) 8048.355 ng / mL diluted 5 & 10 fold	
Selectivity	No interfering peaks noted in human blank plasma samples (Addendum-II)	

(b) (4)

Reviewer's Comments:

- Regarding Quality Control samples, the firm states that as the working standard to be used for the preparation of CC/QC samples is non-liposomal, the method validation will not mimic the study sample analysis requirement as the formulation to be dosed would be liposomal. Hence, to check the reproducibility and extraction efficiency of the method for quantification of encapsulated Doxorubicin, Quality Control samples were prepared from both working standard as well as from liposomal doxorubicin standard (Reference / Test Formulation). The firm's approach is acceptable.
- To generate long-term stability of analyte in human plasma, the LC-MS/MS method for the quantification of Encapsulated Doxorubicin and Free Doxorubicin in human plasma has been partially developed and validated for the following changes, as per Global SOP No. (b) (4)
 - Change in instrument (i.e. (b) (4))
 - Modification in extraction method
 - **Change in calibration curve range** (i.e. from 301.516 – 31998.525 ng /mL to 150.039 – 60069.591 ng /mL) for Encapsulated Doxorubicin and (i.e., from 10.045 - 2501.697 ng/mL to 5.015 - 2007.827 ng /mL) for Free Doxorubicin.

In addition, following experiment was also performed, which was not mentioned in Global SOP No. (b) (4)

- Mobile phase stability

Per Method Validation Report, the original calibration curves for encapsulated doxorubicin (i.e., 301.516 - 31998.525 ng /mL) and free doxorubicin (i.e., 10.045 - 2501.697 ng/mL) using former method and instrument are also acceptable.

- LC/MS/MS method with solid phase extraction was used to estimate Encapsulated Doxorubicin and Free Doxorubicin in human plasma containing K₂EDTA as anti-coagulant in both pre-study and in study.
- The firm submitted adequate Long Term Storage Stability (LTSS) data of encapsulated doxorubicin in K₂EDTA human plasma established for 167 days at -22°C ± 5°C and 268 days at -65°C ± 5°C which covers the study sample storage period of 142 days. For free doxorubicin, the LTSS data for 186 days at -22°C ± 5°C and 289 days at -65°C ± 5°C covers the study sample storage period of 175 days.
- The recovery % (%CV) of Encapsulated Doxorubicin at LQC, MQC and HQC were 74.1% (4.6), 79.0% (1.5) and 67.9% (1.8), respectively, and the recovery % (%CV) of ISTD was 74.9% (4.1). The mean of % recovery obtained at QC levels were consistent for Encapsulated Doxorubicin.

For Free Doxorubicin, the recovery % (%CV) of drug at LQC, MQC and HQC are 77.4% (2.6), 88.4% (3.7) and 94.6% (2.0), and the recovery % (%CV) of ISTD was 87.1% (9.4). The mean of % recovery obtained at QC levels were not consistent (the difference between QC samples is greater than 17%). However, this is acceptable, since $\%CV \leq 3.7$ (%CV of mean recovery of HQC, MQC and LQC is 10.0) is reasonably low. Such disparity between free and encapsulated doxorubicin recovery is also observed in (b) (4)

SOPs submitted	Yes
Does the duration of the each of the LTSS stability parameters support the sample preparation and assay dates?	Yes

The results of pre-study bioanalytical method validation are **adequate**.

3.5 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Summary of Bioavailability Studies of Doxorubicin Hydrochloride Liposome Injection (Analyte: Free Doxorubicin)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (±SD) (%CV)						Study Report Location
					T _{max} (h) [#]	C _{max} (ng/mL)	AUC _{0-t} (ng.h/mL)	AUC _{0-∞} (ng.h/mL)	t _{1/2} (h)	λ _z (1/h)	
591-13	<p>Primary Objective: To assess the bioequivalence of the sponsor's test product [Doxorubicin Hydrochloride liposome injection 20 mg / 10 mL (2 mg / mL) of Dr. Reddy's Laboratories Ltd, India] relative to that of reference product [Doxorubicin Hydrochloride liposome injection 20 mg / 10 mL (2 mg / mL) of Sun Pharmaceutical Industries Limited, India] in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug.</p> <p>Secondary Objective: To monitor the safety of the patients, who are exposed to the Investigational Medicinal Product.</p>	A multicentre, open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study.	<p>Test Product-T: Doxorubicin Hydrochloride Liposome Injection 20mg /10 mL (2 mg / mL) Dose: 50mg/m² Dosage Form: Liposomal Injection Route: Intravenous Batch No. 500082</p>	N = 49 [M-0 / F-49] Patients Age Mean: 47.9 (31-59)	8.000 (1.250 - 120.167)	1152.791 ± 365.3941 (31.7)	135505.469 ± 41819.0718 (30.9)	144325.677 ± 51590.3711 (35.7) [*]	74.335 ± 25.3528 (34.1) [^]	0.011 ± 0.0043 (40.5) [*]	5.3.1.2: study-report-Page 9 and 64 of 186
			<p>Reference Product-R: Doxorubicin Hydrochloride Liposome Injection 20 mg / 10 mL (2 mg / mL) Dose: 50mg/m² Dosage Form: Liposomal Injection Route: Intravenous Batch No. JKM7084A</p>		12.000 (1.500 - 120.000)	1196.529 ± 499.7332 (41.8)	160053.190 ± 62047.3375 (38.8)	169208.518 ± 64756.3479 (38.3) [^]	91.997 ± 27.9585 (30.4) [^]	0.008 ± 0.0028 (33.3) [^]	

[#]T_{max} is represented as median (min-max) value. ^{*}N=43 and [^]N=38

Summary of Bioavailability Studies of Doxorubicin Hydrochloride Liposome Injection (Analyte: Liposome Encapsulated Doxorubicin)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (±SD) (%CV)						Study Report Location
					T _{max} (h) [#]	C _{max} (ng/mL)	AUC _{0-t} (ng.h/mL)	AUC _{0-∞} (ng.h/mL)	t _{1/2} (h)	λ _z (1/h)	
591-13	<p>Primary Objective: To assess the bioequivalence of the sponsor's test product [Doxorubicin Hydrochloride liposome injection 20 mg / 10 mL (2 mg / mL) of Dr. Reddy's Laboratories Ltd, India] relative to that of reference product [Doxorubicin Hydrochloride liposome injection 20 mg / 10 mL (2 mg / mL) of Sun Pharmaceutical Industries Limited, India] in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug.</p> <p>Secondary Objective: To monitor the safety of the patients, who are exposed to the Investigational Medicinal Product.</p>	A multicentre, open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study.	<p>Test Product-T: Doxorubicin Hydrochloride Liposome Injection 20 mg / 10 mL (2 mg / mL) Dose: 50mg/m² Dosage Form: Liposomal Injection Route: Intravenous Batch No. 500082</p>	N = 49 [M-0 / F-49] Patients Age Mean: 47.9 (31-59)	2.000 (0.950 - 8.000)	42685.478 ± 6654.2614 (15.6)	3758871.59 ± 907251.068 3 (24.1)	3931301.008 ± 989422.4144 (25.2) [*]	67.482 ± 17.2121 (25.5) [*]	0.011 ± 0.0035 (31.8) [*]	5.3.1.2: study-report-Pagell and 65 of 186
			<p>Reference Product-R: Doxorubicin Hydrochloride Liposome Injection 20 mg / 10 mL (2 mg / mL) Dose: 50mg/m² Dosage Form: Liposomal Injection Route: Intravenous Batch No. JKM7084A</p>		2.000 (1.250 - 4.000)	41672.724 ± 5592.9792 (13.4)	4038053.41 ± 950216.684 1 (23.5)	4280851.290 ± 1114132.871 3(26.0)	75.106 ± 18.8455 (25.1)	0.010 ± 0.0030 (30.1)	

[#]T_{max} is represented as median (min-max) value. ^{*}N=47

**Table 2. Reanalysis of Study Samples
Reanalysis of Study Samples for Study 591-13 (Encapsulated Doxorubicin)**

Study No. 591-13, Encapsulated Doxorubicin Additional information in 5.3.1.4								
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	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Significant variation in response of internal standard	6.0	5.0	0.5 %	0.4 %	5.0	5.0	0.4 %	0.4 %
Processing error (No ISTD response was obtained)	1.0	1.0	0.1 %	0.1 %	1.0	1.0	0.1 %	0.1 %
Significant drug concentration in pre-dose sample of patient	2.0	0.0	0.2 %	0.0 %	2.0	0.0	0.2 %	0.0 %
Processing error (less than 5% of mean ISTD response)	0.0	1.0	0.0 %	0.1 %	0.0	1.0	0.0 %	0.1 %
Patient sample analysis did not meet the analytical run acceptance criteria, as more than 20% of LLOQ area response was obtained at RT of analyte in all the Blank QC samples.	0.0	29.0	0.0 %	2.3 %	0.0	29.0	0.0 %	2.3 %
Patient sample analysis did not meet the analytical run acceptance criteria, as three out of four working standard LMQC samples were not within the acceptance criteria.	24.0	24.0	2.0 %	1.9 %	24.0	24.0	2.0 %	1.9 %
Patient sample analysis did not meet the analytical run acceptance criteria, as seven out of sixteen formulation QC samples were not within the acceptance criteria.	24.0	24.0	2.0 %	1.9 %	24.0	24.0	2.0 %	1.9 %
Patient sample analysis did not meet the analytical run acceptance criteria, as more than 20% of LLOQ area response was obtained at RT of analyte in all the Blank QC samples.	24.0	24.0	2.0 %	1.9 %	24.0	24.0	2.0 %	1.9 %
Total	81.0	108.0	6.6 %	8.6 %	80.0	108.0	6.5 %	8.6 %

Total Assay for Test Product (T): 1227 and Total assay for Reference Product (R):1291

Reviewer’s Note:

In the table above, there are two sections with the same repeat reason “*Patient sample analysis did not meet the analytical run acceptance criteria, as more than 20% of LLOQ area response was obtained at RT of analyte in all the Blank QC samples*”. The first section indicating 29 repeats in the reference product are from Subject (b) (6). The second section indicating 24 repeats for test and reference products are from Subject (b) (6).

Reanalysis of Study Samples for Study 591-13 (Free Doxorubicin)

Study No. 591-13, Free Doxorubicin Additional information in 5.3.1.4								
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	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Processing error (No ISTD response was obtained)	0.0	1.0	0.0 %	0.1 %	0.0	1.0	0.0 %	0.1 %
Poor chromatography	1.0	0.0	0.1 %	0.0 %	1.0	0.0	0.1 %	0.0 %
Concentration above highest standard	1.0	9.0	0.1 %	0.7 %	1.0	9.0	0.1 %	0.7 %
Significant variation in response of internal standard	5.0	8.0	0.4 %	0.6 %	5.0	8.0	0.4 %	0.6 %
Patient sample analysis did not meet the analytical run acceptance criteria, as more than 20% of LLOQ area response was obtained at RT of analyte in Standard Blank sample.	24.0	24.0	2.0 %	1.9 %	23.0	24.0	1.9 %	1.9 %
Patient sample analysis did not meet the analytical run acceptance criteria, as three out of four working standard LMQC samples were not within the acceptance criteria.	24.0	24.0	2.0 %	1.9 %	24.0	24.0	2.0 %	1.9 %
Patient sample analysis did not meet the analytical run acceptance criteria, as more than 20% of LLOQ area response was obtained at RT of analyte in Standard Blank sample.	27.0	24.0	2.2 %	1.9 %	27.0	24.0	2.2 %	1.9 %
Patient sample analysis did not meet the analytical run acceptance criteria, as all four DQC samples failed to meet the acceptance criteria.	2.0	8.0	0.2 %	0.6 %	2.0	8.0	0.2 %	0.6 %
Total	84.0	98.0	7.0 %	7.7 %	83.0	98.0	6.9 %	7.7 %

Total Assay for Test Product (T): 1227 and Total assay for Reference Product (R):1291

Reviewer’s Note:

- In the table above, there are two sections with the same repeat reason “*Patient sample analysis did not meet the analytical run acceptance criteria, as more than 20% of LLOQ area response was obtained at RT of analyte in all the Blank OC samples*”. The first section indicating 24 repeats for both test and reference products are from Subject (b) (6). The second section indicating repeats for test (27) and reference (24) products are from Subject (b) (6) respectively.
- Per the Bio Analytical Report (DARRTS, ANDA208657, SDN2, Module5.3.1.4), sample IDs C03201, A02201, A04201 and B03201 were reanalyzed in duplicate under the reason ‘**significant drug concentration in pre-dose sample of subject**’. All these pre-dose samples were obtained at period 2. However, the repeats for these subjects are not included in the table above. The firm provided the justification as follows:

As per SOP No. (b) (4) if more than 20% of total pre-dose samples of second/subsequent period show significant drug concentration, none of the pre-dose sample of second/subsequent period is required to be reanalyzed. In this study, **more than 20% of pre-dose samples of second/subsequent period showed concentration above LLOQ**, hence none of the samples should be reanalyzed. However, sample IDs C03201, A02201, A04201 and B03201 were reanalyzed in duplicate under the reason '**significant drug concentration in pre-dose sample of subject**', which is an SOP deviation. This had happened because analysis of patient samples was carried out in phase manner as the samples were received periodically from different sites. Also repeat analysis and incurred sample reanalysis were performed in phase manner after completion of analysis of received study samples. Therefore, sample IDs C03201, A02201, A04201 and B03201 were reanalyzed in duplicate under the reason '**significant drug concentration in pre-dose sample of subject**'. **After analyzing more numbers of periodically received study samples, it came to notice that, in more than 20% of predose sample of second period, significant drug concentration (equal to or greater than LLOQ) was obtained and hence as per SOP No. (b) (4), any of the pre-dose samples were not required to be reanalyzed. This has no impact on the final outcome of data, since the original concentrations of pre-dose sample ID: C03201, A02201, A04201 and B03201 have been accepted and reported.**

Table 3. SOPs Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	Preparation of calibration curve and quality control samples and defining analytical run organization and its acceptance criteria
		Repeat analysis and acceptance of results

Is there any other particular concern related to repeat analysis that should be investigated further?	No
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Comments from the Reviewer on Repeat Analysis:

- For the fasting BE study #591-13, the reanalysis of study samples included a total of 15.2% (6.6% test; 8.6% reference) re-assay repeats for Encapsulated Doxorubicin and a total of 14.7% (7.0% test; 7.7% reference) re-assay repeats for Free Doxorubicin. There were no PK repeats.
- In the Incurred Sample Reanalysis, approximately 76.0% and 89.8% of repeated samples were within 20% of the original values for encapsulated doxorubicin and free doxorubicin, respectively, in the fasting study. Overall, the repeat analyses for the fasting study are acceptable.

3.6 *In Vitro* Dissolution

Location of DB Dissolution Review	Drug release test will be reviewed by Office of Pharmaceutical Quality (OPQ).
Submitted Method (USP, FDA, or Firm)	FDA-recommended Dissolution Method
Recommended Method (details below) for the current ANDA	Develop a method to characterize in vitro release, starting at pH 6.00 ± 0.05 and at 47°C ± 0.5°C. Replicate for 12 dosage vials.
Medium	N/A
Volume (mL)	N/A
USP Apparatus type	N/A
Rotation (rpm)	N/A
Specifications	N/A
Do the data meet the recommended specifications at S1, L1, A1, or B1 acceptance criteria?	N/A
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	N/A
If no, reason why F2 not calculated	N/A
Is method acceptable?	The method of drug release test will be reviewed by OPQ.
If not then why?	N/A

3.7 Waiver Request(s) For ER Release Dosage Forms

Strengths for which waivers are requested, if applicable	N/A
Waiver regulation cited?	N/A (The firm submitted the waiver request for 50 mg /25 mL [21CFR320.22(d)(2)])
Proportional to strength tested <i>in vivo</i> ?	N/A
Is dissolution acceptable?	Drug release test/method will be reviewed by OPQ.
Waivers granted?	N/A
If not then why?	N/A

3.8 Batch Information

Note: The firm was requested to submit the following batch information for test and reference products including the manufacture date of the test lots and the expiration date of the RLD lots.

Study type	Test- Doxorubicin Hydrochloride Liposome Injection 20mg/10mL				Reference- Doxorubicin Hydrochloride Liposome Injection 20mg/10mL (Sun Pharma)			
	Lot No.	Potency (Assay)	Lot size (3301 vials)		Manufacture date	Lot number	Potency (Assay)	Expiration date
			Theoretical	Actually bottled				
Bioequivalence study	500082	100.3% (2.01 mg)	(b) (4)		Nov 2013	JKM7084A	98.1% (1.96 mg)	May 2015
In-Vitro equivalence study	500080	100.4% (2.01 mg)			Nov 2013	JKM2306A	98.1% (1.96 mg)	Sep 2014
	500082	100.3% (2.01 mg)			Nov 2013	JKM3342A	99.1% (1.98)	Oct 2014
	500083	102.5% (2.05 mg)			Nov 2013	JKM7084A	98.1% (1.96 mg)	May 2015

Note: The intended commercial batch size is the same as the theoretical bio-batch size (i.e., (b) (4) vials)⁶.

⁶ DARRTS, ANDA208657, SDN1, Module 3.2.P.3.2, dated 10/8/2015

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study 591-13

4.1.1.1 Study Design

Table 4. Study Information

Study Number	591-13
Study Title	A multicenter, open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, cross-over bioequivalence study of Doxorubicin Hydrochloride Liposome Injection 20 mg / 10 mL (2 mg / mL) of Dr. Reddy's Laboratories Ltd, India, with that of Doxorubicin Hydrochloride Liposome Injection 20 mg / 10 mL (2 mg / mL), Manufactured by: Sun Pharmaceutical Ind. Ltd, India; Distributed by: Caraco Pharmaceutical Laboratories, Ltd., Detroit, MI 48202 in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug under fasting condition
Study Type	<input checked="" type="checkbox"/> <i>In-vivo</i> BE <input type="checkbox"/> <i>In-vitro</i> BE <input type="checkbox"/> Permeability <input type="checkbox"/> Other
Submission Location	Study Report: 5.3.1.2 Validation Report: 5.3.1.4 Bio-analytical Report: 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Refer Annexure No. I
Principal Clinical Investigator (Name, Email)	Refer Annexure No. I
Dosing Dates	Refer Annexure No. II
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)
Analysis Dates	20 October 2014 to 09 April 2015 for Encapsulated Doxorubicin 15 October 2014 to 11 April 2015 for Free Doxorubicin
Principal Analytical Investigator	(b) (4)
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20° C to -80° C)	(a) 142 days at -65±10°C (09 September 2014 to 29 January 2015 for patient No. (b) (6) for Encapsulated Doxorubicin and 175 days at -65±10°C (09 September 2014 to 03 March 2015 for patient No. (b) (6) for Free Doxorubicin (b) At -65 ± 10 °C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Analyte 1: Encapsulated Doxorubicin: 268 days at -65 ± 10°C (b) (4) and 167 days at -22 ± 5°C (b) (4) Analyte 2: Free Doxorubicin: 289 days at -65 ± 10°C (b) (4) and 186 days at -22 ± 5°C (w) (4)
LTSS Data Location	Analyte 1: Encapsulated Doxorubicin: Long-Term Storage Stability Data is presented in Method Validation Report # (b) (4) Location: Module 5, 5.3.1.4, Appendix 16.6, Page 14 & 15 of 26 (Addendum-III) , and Page 12 & 13 of 23 (Addendum-IV) Analyte 2: Free Doxorubicin: Long-Term Storage Stability Data is presented in Method Validation Report # (b) (4) Location: Module 5, 5.3.1.4, Appendix 16.6, Page 13 & 15 of 28 (Addendum-IV) , and Page 11 & 12 of 23 (Addendum-V)

Table 5. Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Doxorubicin Hydrochloride Liposome Injection, 20mg/10mL (2mg/mL)	Doxorubicin Hydrochloride Liposome Injection, 20mg/10mL (2mg/mL)
Manufacturer	(b) (4)	Sun Pharmaceutical Ind. Ltd, Halol-389350, Gujarat, India.
Batch/Lot No.	500082	JKM7084A
Manufacture date	Nov 2013	N/A
Expiration Date	N/A	May 2015
Strength	20mg/10mL	20mg/10mL
Dosage Form	Injectable, Liposomal	Injectable, Liposomal
Bio-batch size	(b) (4) vials	N/A
Production Batch Size	(b) (4) vials	N/A
Potency	100.3 % (2.01 mg)	98.1% (1.96 mg/mL)
Content Uniformity (mean, % CV)	109.0, 0.9	N/A
Dose Administered	50 mg / m ²	50 mg / m ²
Route of Administration	Intravenous infusion	Intravenous infusion

Reviewer's Note: In the Quality Overall Summary-CMC (ANDA208657, SDN1, Module 2.3), the firm states that Acceptance Value of Content Uniformity of Batch 500082 is 5.4. This AV does not match with a %mean content uniformity of 109.0 or even 100.3 (based on mean potency). The reviewer back-calculated the %mean content uniformity as 104.64, when using 5.4 and 0.9 as AV and %CV value, respectively. However, all the values are within specification and therefore, acceptable.

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Sixty female ovarian cancer patients were enrolled in the study. Forty nine subjects completed the study in its entirety. Data from a total of 49 subjects were included in the pharmacokinetic and statistical analyses.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	10 (Center A through K). No patient was dosed in Center G.
Washout Period	At least 28 days
Randomization Scheme (Sequence of T and R)	Yes (sequence of TR and RT)

Blood Sampling Times	<p>As per the protocol, a total of 24 blood samples (Post-dose samples of 4 mL each & 1 pre-dose sample of 6 mL) were collected in each period before start of infusion (Pre-dose) (within 60 minutes prior to dosing), during infusion (0.083, 0.167, 0.333, 0.500 and 0.750 hours), at the end of infusion (1.000 hour) and after end of infusion (1.250, 1.500, 2.000, 3.000, 4.000, 6.000, 8.000, 12.000, 16.000, 24.000, 48.000, 96.000, 120.000, 168.000, 216.000, 264.000 and 336.000 hours after the start of infusion). Samples at and after 48 hours post-dose were collected on an ambulatory basis.</p>
Blood Sample Processing & Storage (include storage temperature)	<p>The blood samples were collected in K2 EDTA vacutainers. (b) (4)</p> <div style="background-color: #cccccc; height: 150px; width: 100%; margin: 5px 0;"></div> <p><i>Note:</i> First aliquot was used for analysis of free doxorubicin and second aliquot was used for analysis of liposome encapsulated doxorubicin and third lot was use as back up lot for both the analytes. If the plasma volume of the sample was less than the above mentioned quantity, one can add the Glycerol (98%, LR grade) in ratio of 20 % of the available plasma sample.</p> <p>All the samples were stored upright in a box containing dry ice or in a freezer at a temperature – 55°C or colder for interim storage until shipment to (b) (4) for analysis. Samples were packed with dry ice for transport, no interruption of the freeze cycle was allowed. Shipment was done separately for all lots. Temperature was recorded using calibrated temperature recording device during shipment. After receiving the samples by (b) (4) the Samples were stored at -65 ± 10°C until completion of analysis at (b) (4)</p>

Comments on Study Design:

- The fasting study was designed as an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study in female ovarian cancer patients in 11 centers. Dexamethasone Injection 8 mg (to avoid hypersensitivity reaction) and Granisetron Injection 2 mg IV (antiemetic) were administered to all the patients before starting of infusion in both the periods.
- Patients were administered a 50 mg/m² dose of Doxorubicin HCl Liposome Injection (either test or reference product) as intravenous infusion on the first day

of chemotherapy cycle under fasting conditions. The subjects were on overnight fasting for at least 10.00 hours pre-dose to 4.00 hours post-dose in each period. Per BE Guidance⁷, *if the health conditions of patients prevent fasting, a non-high-fat diet was provided during the study. Alternatively, the treatment was initiated 2 hours after a standard (non-high-fat) breakfast.* All subjects were housed in the clinical facility from at least 11 hours prior to dosing until at least 24 hours post dose in each period. The in-house period and fasting period are acceptable.

- All subjects had washout period of ≥ 28 days, as per protocol.
- The fasting BE study design is **adequate**.

⁷ Bioequivalence Recommendations for Specific Drug Products for Doxorubicin HCl Liposome Injection posted at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf> (Recommended Feb 2010; Revised Nov 2013, Dec 2014)

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 591-13			
Parameters		Treatment Groups	
		Test Product N = 49	Reference Product N = 49
Age (years)	Mean ± SD	47.9 ± 6.98	47.9 ± 6.98
	Range	31-59	31-59
Age Groups	< 18	0 (0%)	0 (0%)
	18-40	08 (16.33%)	08 (16.33%)
	41-64	41 (83.67%)	41 (83.67%)
	65-75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	0 (0%)	0 (0%)
	Female	49 (100%)	49 (100%)
Race	Asian	49 (100%)	49 (100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean ± SD	24.2 ± 3.69	24.2 ± 3.69
	Range	16.4-32.3	16.4-32.3
Other Factors		NA	

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. 591-13								
Patient No.	Reason for dropout / Replacement	Period	Replaced?	Replaced with				
(b) (6)	The patient was withdrawn from the study in Period-I on other condition as per Investigator's judgement.	I	No	NA				
	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">Time and date of infusion of last IMP</td> <td style="width: 70%;">Last IMP administered</td> </tr> <tr> <td style="text-align: center;">(b) (6)</td> <td style="text-align: center;">Reference Product-R</td> </tr> </table>				Time and date of infusion of last IMP	Last IMP administered	(b) (6)	Reference Product-R
	Time and date of infusion of last IMP				Last IMP administered			
(b) (6)	Reference Product-R							
0940 hours (b) (6)	Reference Product-R							
	The patient was withdrawn from the study in Period-I due to death.	I	No	NA				
	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">Time and date of infusion of last IMP</td> <td style="width: 70%;">Last IMP administered</td> </tr> <tr> <td style="text-align: center;">0940 hours (b) (6)</td> <td style="text-align: center;">Reference Product-R</td> </tr> </table>				Time and date of infusion of last IMP	Last IMP administered	0940 hours (b) (6)	Reference Product-R
	Time and date of infusion of last IMP				Last IMP administered			
0940 hours (b) (6)	Reference Product-R							
0930 hours (b) (6)	Reference Product-R							
	The patient was withdrawn from the study in Period-I due to adverse event.	I	No	NA				
	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">Time and date of infusion of last IMP</td> <td style="width: 70%;">Last IMP administered</td> </tr> <tr> <td style="text-align: center;">0930 hours (b) (6)</td> <td style="text-align: center;">Reference Product-R</td> </tr> </table>				Time and date of infusion of last IMP	Last IMP administered	0930 hours (b) (6)	Reference Product-R
	Time and date of infusion of last IMP				Last IMP administered			
0930 hours (b) (6)	Reference Product-R							
1015 hours (b) (6)	Reference Product-R							
	The patient was withdrawn from the study in Period-I as the infusion completed in 01 hour 08 minutes.	I	No	NA				
	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">Time and date of infusion of last IMP</td> <td style="width: 70%;">Last IMP administered</td> </tr> <tr> <td style="text-align: center;">1015 hours (b) (6)</td> <td style="text-align: center;">Reference Product-R</td> </tr> </table>				Time and date of infusion of last IMP	Last IMP administered	1015 hours (b) (6)	Reference Product-R
	Time and date of infusion of last IMP				Last IMP administered			
1015 hours (b) (6)	Reference Product-R							
1035 hours (b) (6)	Reference Product-R							
	The patient was withdrawn from the study in Period-I due to adverse event.	I	No	NA				
	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">Time and date of infusion of last IMP</td> <td style="width: 70%;">Last IMP administered</td> </tr> <tr> <td style="text-align: center;">1035 hours (b) (6)</td> <td style="text-align: center;">Reference Product-R</td> </tr> </table>				Time and date of infusion of last IMP	Last IMP administered	1035 hours (b) (6)	Reference Product-R
	Time and date of infusion of last IMP				Last IMP administered			
1035 hours (b) (6)	Reference Product-R							
0950 hours (b) (6)	Reference Product-R							

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Study No. 591-13					
Patient No.	Reason for dropout / Replacement		Period	Replaced?	Replaced with
(b) (6)	The patient was withdrawn from the study in Period-I as infusion was interrupted due to technical problem in infusion pump.		I	No	NA
	Time and date of infusion of last IMP	Last IMP administered			
	1025 hours (b) (6)	Reference Product-R			
(b) (6)	The patient was withdrawn from the study in Period-II as infusion was interrupted due to blockage of vein of patient.		II	No	NA
	Time and date of infusion of last IMP	Last IMP administered			
	1138 hours (b) (6)	Test Product-T			
(b) (6)	The patient was withdrawn from the study in Period-I due to death.		I	No	NA
	Time and date of infusion of last IMP	Last IMP administered			
	1005 hours (b) (6)	Test Product-T			
(b) (6)	The patient was withdrawn from the study in Period-II as per Sponsor's discretion.		II	No	NA
	Time and date of infusion of last IMP	Last IMP administered			
	0906 hours (b) (6)	Reference Product-R			
(b) (6)	The patient was withdrawn from the study in Period-I due to death.		I	No	NA
	Time and date of infusion of last IMP	Last IMP administered			
	1100 hours (b) (4)	Reference Product-R			

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. 591-13 Fasting Bioequivalence Study	
	Test Product (N=52)	Reference Product (N=59)
Body as a whole		
Asthenia	12 (23.08%)	10 (16.95%)
Pain	01 (1.92%)	01 (1.69%)
Pyrexia	03 (5.77%)	02 (3.39%)
Cardiovascular		
Cardio-respiratory arrest	01 (1.92%)	0
Tachycardia	0	01 (1.69%)
Gastrointestinal		
Abdominal pain	02 (3.85%)	01 (1.69%)
Abdominal pain upper	0	01 (1.69%)
Ascites	02 (3.85%)	01 (1.69%)
Constipation	04 (7.69%)	04 (6.78%)
Diarrhoea	01 (1.92%)	01 (1.69%)
Diarrhoea haemorrhagic	0	01 (1.69%)
Gastritis	01 (1.92%)	0
Intestinal obstruction	0	01 (1.69%)
Mouth ulceration	02 (3.85%)	0
Nausea	06 (11.54%)	09 (15.25%)
Stomatitis	03 (5.77%)	0
Vomiting	08 (15.38%)	07 (11.86%)
Other organ system		
Anaemia	04 (7.69%)	03 (5.08%)
Leukopenia	0	01 (1.69%)
Neutropenia	0	01 (1.69%)
Thrombocytopenia	0	01 (1.69%)
Anaphylactic reaction	0	01 (1.69%)
Hypersensitivity	0	02 (3.39%)
Bacterial infection	01 (1.92%)	0
Urinary tract infection	0	01 (1.69%)
Blood bicarbonate decreased	0	02 (3.39%)

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Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Study No. 591-13 Fasting Bioequivalence Study	
	Test Product (N=52)	Reference Product (N=59)
Blood creatinine increased	0	02 (3.39%)
Blood potassium increased	0	01 (1.69%)
Blood urea increased	0	01 (1.69%)
Blood uric acid increased	0	01 (1.69%)
Gamma-glutamyltransferase increased	02 (3.85%)	0
Red blood cells urine	0	01 (1.69%)
Cachexia	0	01 (1.69%)
Decreased appetite	0	01 (1.69%)
Hyperchloraemia	0	01 (1.69%)
Hypermagnesaemia	0	01 (1.69%)
Hypernatraemia	0	01 (1.69%)
Hypertriglyceridaemia	0	02 (3.39%)
Hyperuricaemia	0	01 (1.69%)
Hypoalbuminaemia	01 (1.92%)	01 (1.69%)
Hypocalcaemia	0	01 (1.69%)
Hypochloraemia	0	01 (1.69%)
Hypokalaemia	0	03 (5.08%)
Hypophosphataemia	0	01 (1.69%)
Arthralgia	01 (1.92%)	0
Back pain	01 (1.92%)	01 (1.69%)
Insomnia	01 (1.92%)	0
Renal failure acute	0	01 (1.69%)
Cough	02 (3.85%)	0
Dyspnoea	0	01 (1.69%)
Palmar-plantar erythrodysesthesia syndrome	0	01 (1.69%)
Hypotension	0	01 (1.69%)
Chills	0	01 (1.69%)
Death	0	01 (1.69%)
Total (Number of AEs)	59	80
Total (Number of patients who experienced AEs)	26 (50.00%)	27 (45.76%)

Reviewer's Note: There were 3 (1 test, 2 references) deaths. Thus, the numbers of death for test and reference listed in the table above are incorrect.

Was the adverse event (AE) profile observed during the fasting bioequivalence study comparable for the test and reference product? Please comment.

A total of 139 AEs were reported by 40 patients during the conduct of study. Fifty-nine (59) AEs were reported after receipt of test product and 80 adverse events were reported after receipt of reference product. The most frequently reported adverse events were Pyrexia (5 instances), Anaemia (7 instances), Constipation (8 instances), Nausea (15 instances), Vomiting (15 instances) and Asthenia (22 instances).

The causality assessment was judged as certain for 3 AEs, possible for 35 AEs, probable/likely for 14 AEs and unlikely for 87 AEs to the study drug administered.

Are there any serious AEs or death? If so, are they reported to the OGD Safety Committee?

There were 3 deaths [Patient Nos. (b)(6)]. Patient (b)(6) experienced serious adverse events (cardio pulmonary arrest/death) nineteen days after administration of the test product. Patients (b)(6) experienced serious adverse events following administration of the reference product. Patients (b)(6) were dropped from the study due to anaphylaxis (severe)/allergic reactions (moderate)/hypersensitivity (moderate) following administration of the reference product.

Subjects Experienced Severe Adverse Events During Study

Subject	Event	Test/Ref. (Period)	Start time and date of last infusion ⁸	End time and date of last infusion ⁸	Time and date of event ⁹	Time of event post-dose
(b)(6)	Intestinal Obstruction/Hyperuricemia/Acute renal failure	R (I)			(b)(6)	9 days
	Anemia					14 days
	Death					23 days
	Death (Cardio Pulmonary Arrest)	T (I)				19 days
	Bloody diarrhea	R (I)				23 days
	Thrombocytopenia					23 days
	Death					41 days
	Anaphylaxis	R (I)				0 day

⁸ DARRTS, ANDA208657, SDN1, Module 5.3.1.2, Section 16.2.5. Compliance and/or Drug Concentration Data Listing, dated 10/08/2015

⁹ DARRTS, ANDA208657, SDN1, Module 5.3.1.2, Section 16.2.7. Adverse Events, dated 10/08/2015

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The Division of Bioequivalence (DB) submitted a clinical consultation to the Division of Clinical Review (DCR) to ask if the adverse event (cardio pulmonary arrest /death) associated with the test formulation should be of a safety concern (see Section 4.4).

The Medical Officer concluded that the death of patient (b) (6) during the BE study #591-13 is unlikely to be related to the administration of the test product; therefore, it does not indicate a safety concern for the test product (see Section 4.4 for details).

Are there any other safety concerns based on the AE profile?

None

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. 591-13		
Type	Patient #s (Test T)	Patient #s (Ref. R)
Dosing Related	(b) (6)	
Lab Related		
PK Sample Related		
PK Sample Related (Sample Storage at Clinical Site: Temperature went above -55°C at Site H)		
PK Sample Related (Sample Storage at Clinical Site: Temperature went above -55°C) (Deviations for Patient Nos. F01 and F02 were observed after the last visit of the study)		
PK Sample Related (Sample Storage at Bioanalytical Site: Temperature went above -65 ± 10°C) (Deviations for Patient Nos. (b) (6) were observed after the last visit of the study)		
Restriction Related		
Scheduled Assessment(s) Related (Deviation for Patient No. (b) (6) was observed after the last visit of the study)		
Scheduled Visit Related		
IMP Related (IMP temperature during shipment, excursion was 8.5 °C at Site A and C)		

^Withdrawn Patient

Refer [Appendix No. 16.2.2](#) - Protocol deviations for detail.

Test T: Test Product-T

Ref. R: Reference Product-R

Comments on Dropouts/Protocol Deviations/Adverse Events:

- Eleven patients did not complete the study.
 - Patients (b) (6) were withdrawn from the study in Period-I due to **adverse event.**
 - Patients (b) (6) were withdrawn from the study in Period-I due to **death.**
 - Patients (b) (6) were withdrawn from the study due to some technical issues or firm's/investigator's decisions.

- Post-dose samples were collected within ± 2 minutes of the scheduled time for all the patients. The ambulatory samples scheduled at and after 48.000 hour were collected with an allowable deviation of 2 hours. The actual time of sample collection was used in the PK analyses of plasma concentration data. Therefore, no impact is foreseen on the outcome of the study.

4.1.1.3 Bioanalytical Results

Table 11. Sample Analysis Calibration and Quality Control Fasting Study (Encapsulated Doxorubicin)

Bioequivalence Study No. 591-13 Analyte Name: Encapsulated Doxorubicin								
Parameter	Standard Curve Samples							
Standard Ids	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng/mL)	150.039	300.078	3000.776	9011.338	30037.793	45034.173	54062.632	60069.591
Inter day Precision (%CV)	2.7	5.6	5.3	4.1	4.6	4.3	3.8	4.8
Inter day Accuracy (%Actual)	101.5	97.3	96.9	100.3	100.2	103.5	103.2	97.2
Linearity r2	0.9881 to 0.9995							
Linearity Range (ng /mL)	150.039 to 60069.591							
Sensitivity/LOQ (ng/mL)	150.039							

Bioequivalence Study No. 591-13 Analyte Name: Encapsulated Doxorubicin				
Parameter	Quality Control Samples			
Quality Control Sample Ids	HQC	MQC	LMQC	LQC
Concentration (ng/mL)	45444.640	28175.677	6198.649	446.303
Inter day Precision (%CV)	6.1	6.7	7.1	7.9
Inter day Accuracy (%Actual)	105.0	104.6	103.7	99.5

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Bioequivalence Study No. 591-13				
Analyte Name: Encapsulated Doxorubicin				
Parameter	Formulation Quality Control Samples			
Quality Control Sample Ids	HQC	MQC	LMQC	LQC
Concentration (ng/mL)	45732.225	27439.335	6036.654	446.712
Inter day Precision (%CV)	7.0	8.3	8.2	10.7
Inter day Accuracy (%Actual)	105.4	104.7	100.7	99.8

Fasting Study (Free Doxorubicin)

Bioequivalence Study No. 591-13								
Analyte Name: Free doxorubicin								
Parameter	Standard Curve Samples							
Standard Ids	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8
Concentration (ng/mL)	5.015	10.030	100.301	301.204	1004.014	1505.268	1807.044	2007.827
Inter day Precision (%CV)	2.6	5.7	5.7	4.7	4.3	5.1	3.5	4.8
Inter day Accuracy (%Actual)	102.4	95.5	93.5	99.8	100.4	104.0	104.4	100.3
Linearity r ²	0.9877 to 0.9997							
Linearity Range (ng /mL)	5.015 to 2007.827							
Sensitivity/LOQ (ng/mL)	5.015							

Bioequivalence Study No. 591-13				
Analyte Name: Free Doxorubicin				
Parameter	Quality Control Samples			
Quality Control Sample Ids	HQC	MQC	LMQC	LQC
Concentration (ng/mL)	1534.061	1012.480	202.496	14.985
Inter day Precision (%CV)	7.0	7.3	7.1	9.9
Inter day Accuracy (%Actual)	105.2	103.1	103.6	97.3

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Bioequivalence Study No. 591-13				
Analyte Name: Free doxorubicin				
Parameter	Formulation Quality Control Samples			
Quality Control Sample Ids	HQC	MQC	LMQC	LQC
Inter day Precision (%CV)	12.0	11.9	9.2	11.0

Note: Per the Bio Analytical Report (DARRTS, ANDA208657, SDN2, Module 5.3.1.4), nominal concentration of Free Doxorubicin was not possible to generate for liposomal quality control samples. Therefore, % accuracy was also not possible to evaluate for liposomal QCs. Therefore, only global precision was evaluated for liposomal formulation quality control samples¹⁰.

Note: Per the Bio Analytical Report (DARRTS, ANDA208657, SDN2, Module 5.3.1.4), as the working standard to be used for the preparation of CC/QC samples was non-liposomal, it did not mimic the study sample analysis requirement as liposomal formulation was dosed to the patients. Hence to check the reproducibility and extraction efficiency of Encapsulated Doxorubicin and Free Doxorubicin from the liposomal samples (subject samples), the Quality Control samples prepared from both working standard as well as from liposomal doxorubicin standard (Reference / Test Formulation) were used in the analytical run organization and no. of formulation QCs were equivalent to the no. of normal QC at each level.

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	Yes (See comments below)
Are there any concerns related to sample analysis (including reanalysis, run rejection, etc.)?	No

Were 20% of chromatograms included?	Yes (20% for Encapsulated Doxorubicin: subjects (b) (6), 27% for Free Doxorubicin: subjects # (b) (6))
--	--

Reviewer's comment:

- The standard curve (i.e., 5.015 - 2007.827 ng /mL for Free Doxorubicin) covers majority of plasma concentrations of Free Doxorubicin in the fasting BE study. The highest free doxorubicin concentration observed was 3823.267 ng/mL. Dilution integrity for free doxorubicin was validated up to 8048.355 ng/mL in the original Addendum for Method Validation (b) (4).
- The standard curve (i.e., 150.039 – 60069.591 ng /mL for Encapsulated Doxorubicin) covers majority of plasma concentrations of Encapsulated Doxorubicin in the fasting BE study. The highest encapsulated doxorubicin concentration observed was 70323.06 ng/mL. Dilution integrity for encapsulated doxorubicin was validated up to 99595.409 ng/mL in the original Addendum and up to 179270.323 ng/mL in Addendum I for Method Validation (b) (4).

¹⁰ DARRTS, ANDA208657, SDN1, Module 5.3.1.4, Bio-Analytical Report, dated 10/08/2015

Table 12. SOPs Dealing with Sample Analysis

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	PREPARATION OF CALIBRATION CURVE AND QUALITY CONTROL SAMPLES AND DEFINING ANALYTICAL RUN ORGANIZATION AND ITS ACCEPTANCE CRITERIA

Comments on Study Assays:

- The results of the fasting study assay are adequate.

4.1.1.4 Pharmacokinetic Results

**Table 13. Arithmetic Mean Pharmacokinetic Parameters
Free Doxorubicin - Reviewer Calculated**

Fasting Bioequivalence Study, Study No. 591-13, N=49									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
Analyte: Free Doxorubicin									
AUC _{0-t} (ng*hr/ml)	135505.5	30.86	70223.72	272055.3	160053.2	38.77	76687.32	367174.1	0.85
#AUC _∞ (ng*hr/ml)	126653.1	53.63	0.00	329477.1	131222.9	69.51	0.00	376314.8	0.97
C _{max} (ng/mL)	1152.791	31.70	567.45	2582.05	1196.529	41.77	577.73	3823.27	0.96
T _{max} * (hr)	8.000	.	1.25	120.17	12.000	.	1.50	120.00	0.67
Kel (hr ⁻¹)	0.009	57.33	0.00	0.03	0.006	66.17	0.00	0.01	1.44
T _{1/2} (hr)	65.233	52.40	0.00	147.05	71.345	64.33	0.00	164.93	0.91

* T_{max} values are presented as median, range.

Elimination phase was not well captured for 9 tests and 8 references using SAS Program CONTINU, which was excluded from the AUC_∞ calculation.

Encapsulated Doxorubicin - Reviewer Calculated

Fasting Bioequivalence Study, Study No. 591-13, N=49									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	%CV	Min	Max	
Analyte: Encapsulated Doxorubicin									
AUC _{0-t} (ng*hr/ml)	3758872	24.14	2046510	6322843	4038053	23.53	2154338	5882568	0.93
#AUC _∞ (ng*hr/ml)	3770840	33.08	0.00	7229444	4280851	26.03	2173091	6684681	0.88
C _{max} (ng/mL)	42685.48	15.59	28200.79	70323.06	41672.72	13.42	31116.60	53368.85	1.02

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Tmax* (hr)	2.000	.	0.95	8.00	2.000	.	1.25	4.00	1.00
Kel (hr⁻¹)	0.011	38.60	0.00	0.02	0.010	30.09	0.01	0.02	1.07
T1/2 (hr)	64.728	33.35	0.00	113.68	75.106	25.09	31.48	114.83	0.86

* Tmax values are presented as median, range.

Elimination phase was not well captured for 2 test product-treated samples using SAS Program CONTINU, which was excluded from the AUC_∞ calculation.

Table 28. Geometric Means and 90% Confidence Intervals - Firm Calculated

Summary of Statistical Analysis - Fasting BE Study (Analyte: Free Doxorubicin) Using Actual Time

Doxorubicin Hydrochloride Liposome Injection 20 mg/10mL (2 mg/mL) (No of subjects completed = 49)						
Dose (1×50 mg/m ²)						
Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals						
Fasting Bioequivalence Study (Project No.591-13)						
Parameter	Test	N	RLD	N	Ratio (%)	90% C.I.
AUC _{0-t}	131811.678	49	149455.085	49	88.2	81.53 - 95.41
AUC _{0-∞}	142219.803	43	162458.893	38	87.5	80.26 - 95.48
C _{max}	1115.191	49	1135.266	49	98.2	89.46 - 107.86

Summary of Statistical Analysis - Fasting BE Study (Analyte: Liposome Encapsulated Doxorubicin) Using Actual Time

Doxorubicin Hydrochloride Liposome Injection 20 mg/10mL (2 mg/mL) (No of subjects completed = 49)						
Dose (1×50 mg/m ²)						
Least Squares Geometric Means, Ratio of Means and 90% Confidence Intervals						
Fasting Bioequivalence Study (Project No.591-13)						
Parameter	Test	N	RLD	N	Ratio (%)	90% C.I.
AUC _{0-t}	3755898.185	49	4001851.965	49	93.9	90.73 - 97.09
AUC _{0-∞}	3961104.631	47	4193151.618	49	94.5	90.83 - 98.24
C _{max}	43043.872	49	42138.965	49	102.1	99.38 - 104.99

Table 29. Geometric Means and 90% Confidence Intervals – Reviewer Calculated Analyte: Free Doxorubicin (Using Nominal Time)

Doxorubicin Hydrochloride Liposome Injection, Dose: 1 x 50 mg/m ² (2 mg/mL)					
Fasting Bioequivalence Study No. 591-13, N=49					
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Free Doxorubicin					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng*hr/ml)	131799.9	149789.1	0.88	81.49	95.01
AUC _∞ (ng*hr/ml)	141501.2	162003.2	0.87	79.88	95.51
C _{max} (ng/mL)	1113.55	1136.42	0.98	89.49	107.30

Analyte: Encapsulated Doxorubicin (Using Nominal Time)

Doxorubicin Hydrochloride Liposome Injection, Dose: 1 x 50 mg/m ² (2 mg/mL) Fasting Bioequivalence Study No. 591-13, N=49 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Encapsulated Doxorubicin					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng*hr/ml)	3691428	3900685	0.95	91.35	98.04
AUC _∞ (ng*hr/ml)	3873384	4103843	0.94	90.86	98.04
C _{max} (ng/mL)	42195.20	41333.79	1.02	99.44	104.80

**Table 30. Additional Study Information
Free Doxorubicin**

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CONTINU (CALCKE was also used later)	
Reason(s) for Selecting Above SAS Program Macro	The elimination phase was not well captured using CONTINU. The AUC _∞ for all subjects were calculated using CALCKE later in this review.	
Root mean square error, AUC _{0-t}	0.2241	
Root mean square error, AUC _∞	0.2161	
Root mean square error, C _{max}	0.2649	
	Test	Reference
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	9	8
first measurable drug concentration as C _{max}	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	43	0.94	0.81	1.00
Reference	38	0.91	0.81	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	See the following CALCKE section.			

Encapsulated Doxorubicin

DB SAS Program Macros Used (CONTINU, CONTINU2 or CALCKE)	CONTINU (CALCKE was also used later)	
Reason(s) for Selecting Above SAS Program Macro	The elimination phase was not well captured using CONTINU. The AUC _∞ for all subjects were calculated using CALCKE later in this review.	
Root mean square error, AUC _{0-t}	0.1032	
Root mean square error, AUC _∞	0.1078	

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Root mean square error, C _{max}	0.0767	
	Test	Reference
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	2	0
first measurable drug concentration as C _{max}	0	0
Were the subjects dosed as more than one group?	No	

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	47	0.96	0.87	0.99
Reference	49	0.95	0.88	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.		See the following CALCKE section.		

Overall Comment:

- A total of 60 subjects were enrolled in the study with 49 subjects completing study periods. Eleven subjects (i.e., Subject (b) (6) (b) (6)) were dropped out from the study. PK and statistical analyses were performed on data obtained from 49 subjects. Minimum 48 subjects are needed to establish BE, as per power calculation.
- The analysis model used in the reviewer's calculation is: Model Y= GROUP SEQ GROUP*SEQ SUB(SEQ*GROUP) PER(GROUP) TRT and GROUP*TRT, where GROUP, SEQ, PER, SUB and TRT are class variables for group, sequence, period, subject and treatment, respectively. The 90% confidence intervals were calculated based on the model with the above variables.

The study was conducted in 10 centers, although no subject completed the study in center K. Therefore, there are 9 centers (groups) to be evaluated in this statistical analysis. An analysis of variance was performed to test for the 9 groups by treatment interaction (Group*Treatment) using the SAS program. There was no statistically significant difference ($p \geq 0.1$) for the group*treatment term for LC_{max} ($P = 0.7180$), LAUCT ($P = 0.5380$) and LAUCI ($P = 0.7357$) for free doxorubicin. However, there were statistically significant differences ($p < 0.1$) for the group*treatment term for LC_{max} ($P = 0.0417$), LAUCI ($P = 0.0480$) and LAUCT ($P = 0.0271$) for encapsulated doxorubicin.

Per the Division of Bioequivalence practice (see Section 4.6), when the GRP*TRT interaction is statistically significant ($P < 0.1$), the **bioequivalence should be demonstrated in at least one of the groups**, provided that group meets the minimum requirements for a complete bioequivalence study. Three out of the 9 centers had < 3 subjects, which is not adequate for the group effect

analysis¹¹. Therefore, two centers were combined for the following centers: D (n=2) + E (n=3), F (n=2) + H (n=6) and I (n=3) + J (n=2).

The reviewer-calculated 90% confidence intervals for T/R ratios for encapsulated doxorubicin for 6 groups (3 combined) are summarized in the table below.

Geometric Means and 90% Confidence Intervals of Each Group - Reviewer Calculated

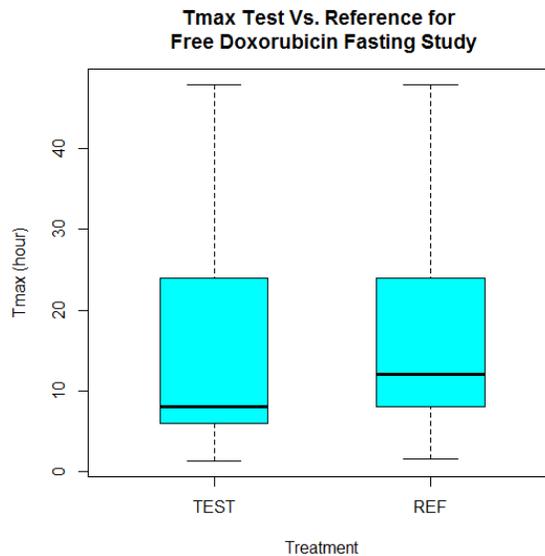
			Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
LAUCT		# of Subjects	Test	Reference	(T/R)	Lower	Upper
Group 1	A	8	4182322	4364308	0.96	90.60	101.36
Group 2	B	7	3642519	4166113	0.87	81.53	93.76
Group 3	C	16	3385095	3546195	0.95	88.88	102.52
Group 4	D + E	5	3791048	4627131	0.82	69.56	96.51
Group 5	F + H	8	4018209	3783351	1.06	96.15	117.31
Group 6	I + J	5	3573559	3638888	0.98	81.86	117.81
LCMAX		# of Subjects	Test	Reference	(T/R)	Lower	Upper
Group 1	A	8	43329.17	41164.51	1.05	99.33	111.54
Group 2	B	7	41559.03	43924.22	0.95	91.16	98.20
Group 3	C	16	39875.92	38672.60	1.03	98.28	108.18
Group 4	D + E	5	42448.84	45079.26	0.94	83.78	105.83
Group 5	F + H	8	46574.18	42943.37	1.08	97.55	120.58
Group 6	I + J	5	43864.54	42246.12	1.04	91.46	117.88
LAUCI		# of Subjects	Test	Reference	(T/R)	Lower	Upper
Group 1	A	8	4388658	4634498	0.95	89.24	100.48
Group 2	B	7	3745701	4381864	0.85	76.76	95.20
Group 3	C	16	3571489	3717022	0.96	89.26	103.43
Group 4	D + E	5	4114326	5039682	0.82	69.68	95.65
Group 5	F + H	8	4177638	3935632	1.06	95.40	118.11
Group 6	I + J	5	3621488	3758581	0.96	77.36	120.01

The 90% confidence intervals for the least squares geometric means of $\ln AUC_{0-t}$, $\ln C_{max}$ and $\ln AUC_{0-\infty}$ are within the acceptable limits of 80 – 125% except for $\ln AUC_{0-t}$ in Group 4 (Center D + E) and $\ln AUC_{0-\infty}$ in Group 2 (B), Group 4

¹¹ According to the DB's current practice, the data from any site with fewer subjects (< 3 subjects) could be pooled with data from another site, preferably with low number of subjects, if all of the subjects have similar demographics.

(Center D + E) and Group 6 (I + J), as listed in the table above. Since at least one of the groups meet the bioequivalence criteria, the test product meets the minimum requirements for a complete bioequivalence study, and how the smaller groups were combined has no significant effect on the BE outcome.

- For free doxorubicin and encapsulated doxorubicin, no first measurable drug concentration was C_{max} . There were 17 (test 9, ref 8) pre-dose concentrations for free doxorubicin as opposed to 2 (both test) pre-dose concentrations for encapsulated doxorubicin, mainly because there is lot more encapsulated doxorubicin present at 336 hours (28 days) than that for free doxorubicin (see mean Plasma Concentration Tables below). No pre-dose concentration was $>5\%$ of the corresponding C_{max} value.
- The median T_{max} values (range) for free doxorubicin for test and reference products were 8 hrs (1.25-120.167 hrs) and 12 hrs (1.5-120.0 hrs), respectively, with a T/R ratio of 0.67. Considering that the sampling time at 8 hours and 12 hours are contiguous and the range of the T_{max} distribution of test and reference are overlapped, the observed t_{max} difference would not make any difference in the clinical outcome. Moreover, this drug product is intended for long-term use, not acute effect.



Note: The box and whisker plot shows median, quartiles and 95% confidence intervals.

- The reviewer-calculated 90% confidence intervals for T/R ratios for $LAUC_{0-t}$ and LC_{max} for free doxorubicin are within the acceptable limits of 80% - 125% and similar to those reported by the firm. However, the lower bound of the 90% confidence interval for T/R ratio for $LAUC_{0-\infty}$ was below the acceptable limit (i.e.,

79.88). This is due to using the nominal sampling time instead of the actual sampling time in this statistical analysis.

Using ACTUAL time points for Free Doxorubicin

- Since the firm used actual time points for the statistical analysis, the reviewer used Phoenix to conduct the statistical analysis using actual time points. The subjects who displayed AUC_{0-t}/AUC_∞ ratios less than 0.80 (4 tests; 8 references) were excluded from this analysis, since AUC_∞ would not be calculated accurately for these subjects (See CALCKE section below). It should be noted that the firm also used lower number of subjects (n=38) for AUC_∞ analysis.

As shown in the table below, the 90% confidence interval for T/R ratio for LAUC_{0-∞} for free doxorubicin now meets the acceptable BE criteria.

Geometric Means and 90% Confidence Intervals – Reviewer Calculated using Phoenix (Using Actual Time)

Doxorubicin Hydrochloride Liposome Injection, Dose: 1 x 50 mg/m ² (2 mg/mL) Fasting Bioequivalence Study No. 591-13, N=47 (N=38 for AUC _{inf}) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals						
Free Doxorubicin						
Dependent	RefGeoLSM	TestGeoLSM	Ratio_%Ref_	CI_90_Lower	CI_90_Upper	Power
Ln(AUCINF_pred)	74549.64	74795.38	100.33	88.98	113.13	0.92
Ln(AUClast)	71533.48	72223.80	100.97	89.54	113.85	0.92
Ln(Cmax)	1110.27	1131.08	101.87	91.97	112.85	0.97

Pharmacokinetic and Statistical Analysis using SAS Program CALCKE:

- Since the elimination phase was not defined for many subjects using SAS Program CONTINU, the reviewer used SAS Program CALCKE for the statistical analysis and specified terminal linear range for Kel calculation.

As shown in the table below, the lower bound of the 90% confidence interval for T/R ratio for LAUC_{0-∞} was below the acceptable limit (i.e., 77.67) using SAS Program CALCKE.

Geometric Means and 90% Confidence Intervals – Reviewer Calculated using SAS Program **CALCKE**

Analyte: Free Doxorubicin (Using Nominal Time)

Doxorubicin Hydrochloride Liposome Injection, Dose: 1 x 50 mg/ m2 (2 mg/ mL) Fasting Bioequivalence Study No. 591-13, N=49 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Free Doxorubicin					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng*hr/ml)	131201.2	149684.0	0.88	81.18	94.64
AUC _∞ (ng*hr/ml)	144563.6	172209.2	0.84	77.67	90.73
C _{max} (ng/mL)	1113.55	1136.42	0.98	89.49	107.30

Analyte: Encapsulated Doxorubicin (Using Nominal Time)

Doxorubicin Hydrochloride Liposome Injection, Dose: 1 x 50 mg/ m2 (2 mg/ mL) Fasting Bioequivalence Study No. 591-13, N=49 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Encapsulated Doxorubicin					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (ng*hr/ml)	3681243	3898162	0.94	91.09	97.90
AUC _∞ (ng*hr/ml)	3980044	4107210	0.97	90.14	104.17
C _{max} (ng/mL)	42195.20	41333.79	1.02	99.44	104.80

Free Doxorubicin

Root mean square error, AUC _{0-t}	0.2239
Root mean square error, AUC _∞	0.2268
Root mean square error, C _{max}	0.2649

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	49	0.91	0.65	0.99
Reference	49	0.87	0.59	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	See comments below			

Encapsulated Doxorubicin

Root mean square error, AUC _{0-t}	0.1052
Root mean square error, AUC _∞	0.2111
Root mean square error, C _{max}	0.0767

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	49	0.94	0.14	0.99
Reference	49	0.95	0.82	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	See comments below			

- There were 12 AUC_{0-t}/AUC_∞ ratios less than 0.80 (4 tests; 8 references) for free doxorubicin. The half-life of these subject were relatively longer (mean 252.8 hours) compared to the mean half-life for the reference product in this study (i.e., 92.0 hours).

There was one AUC_{0-t}/AUC_∞ ratios less than 0.80 (test) for encapsulated doxorubicin. The half-life of this subject was longer (10611.2 hours) compared to the mean half-life for the reference product in this study (i.e., 75.1 hours).

The following 12 concentration-time curves for test and reference for free doxorubicin and one concentration-time curve for test product for encapsulated doxorubicin show that there were multiple peaks at the terminal phase which caused longer terminal half-life than actual terminal half-life. Thus, calculating AUC_∞ excluding these AUC_{0-t}/AUC_∞ < 0.8 may be acceptable.

**Table 13. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study
Mean plasma free doxorubicin concentrations (ng/mL)**

Time (hr)	Test (n=49)		Reference (n=49)		Ratio (T/R)
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0.00	2.28	277.21	1.40	241.95	1.63
0.08	42.37	72.50	46.30	82.56	0.92
0.17	72.17	63.97	84.87	81.28	0.85
0.33	152.26	59.65	166.55	94.49	0.91
0.50	234.37	51.75	252.20	90.56	0.93
0.75	367.52	46.47	369.11	77.48	1.00
1.00	531.60	41.95	517.42	62.58	1.03
1.25	581.08	66.34	530.62	60.31	1.10
1.50	565.38	44.53	591.63	56.66	0.96
2.00	631.65	45.28	633.89	59.03	1.00
3.00	721.16	33.79	717.41	50.08	1.01
4.00	781.86	34.41	760.17	63.56	1.03
6.00	804.81	38.95	754.23	45.01	1.07
8.00	886.59	30.38	842.27	35.86	1.05
12.00	859.39	33.98	926.06	53.57	0.93
16.00	840.28	33.81	875.44	39.58	0.96
24.00	821.39	36.91	908.27	33.44	0.90
48.00	782.11	33.57	877.96	51.97	0.89
96.00	584.55	36.20	689.84	40.28	0.85
120.00	494.41	40.05	598.19	51.23	0.83
168.00	326.02	49.83	407.15	50.15	0.80
216.00	236.17	53.21	293.54	51.96	0.80
264.00	152.21	62.55	211.26	49.99	0.72
336.00	84.90	70.55	141.05	69.46	0.60

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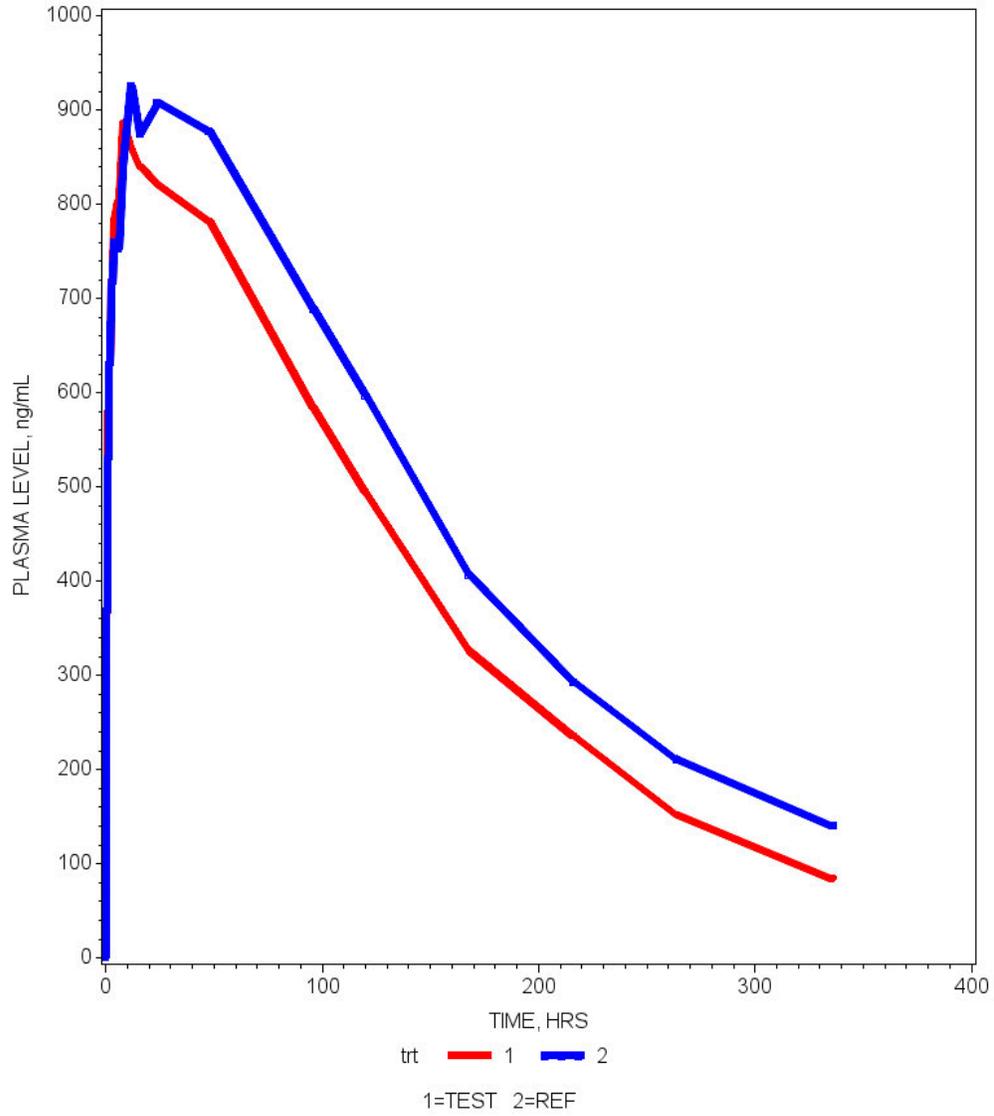
Mean plasma encapsulated doxorubicin concentrations (ng/mL)

Time (hr)	Test (n=49)		Reference (n=49)		Ratio
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	11.99	502.22	0.00	.	.
0.08	2176.08	46.86	2490.92	53.04	0.87
0.17	4577.11	29.83	5219.52	40.27	0.88
0.33	10512.95	23.25	10793.77	27.12	0.97
0.50	16672.27	18.52	17572.44	21.22	0.95
0.75	25724.88	14.90	26348.76	16.77	0.98
1.00	36679.49	13.83	36147.75	15.68	1.01
1.25	38896.75	13.68	38813.37	14.00	1.00
1.50	39942.10	14.28	38715.52	14.26	1.03
2.00	39208.83	15.25	38743.66	16.23	1.01
3.00	39590.45	14.95	38744.83	16.01	1.02
4.00	38771.97	14.37	38301.67	15.10	1.01
6.00	36897.93	20.33	36193.18	15.64	1.02
8.00	35724.49	15.80	36179.49	13.52	0.99
12.00	32386.68	15.87	33277.78	19.50	0.97
16.00	30857.69	14.90	31396.19	17.41	0.98
24.00	28923.01	16.98	29284.93	19.22	0.99
48.00	22657.67	20.93	24318.25	21.13	0.93
96.00	15371.66	26.84	16260.98	24.62	0.95
120.00	12086.04	34.18	13362.35	29.98	0.90
168.00	7487.48	36.78	8314.15	39.16	0.90
216.00	4709.83	46.90	5534.71	42.38	0.85
264.00	2893.32	57.95	3599.36	52.16	0.80
336.00	1624.78	94.06	1955.37	63.23	0.83

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Linear plot of mean plasma concentration vs. time profile for free doxorubicin (N=49)

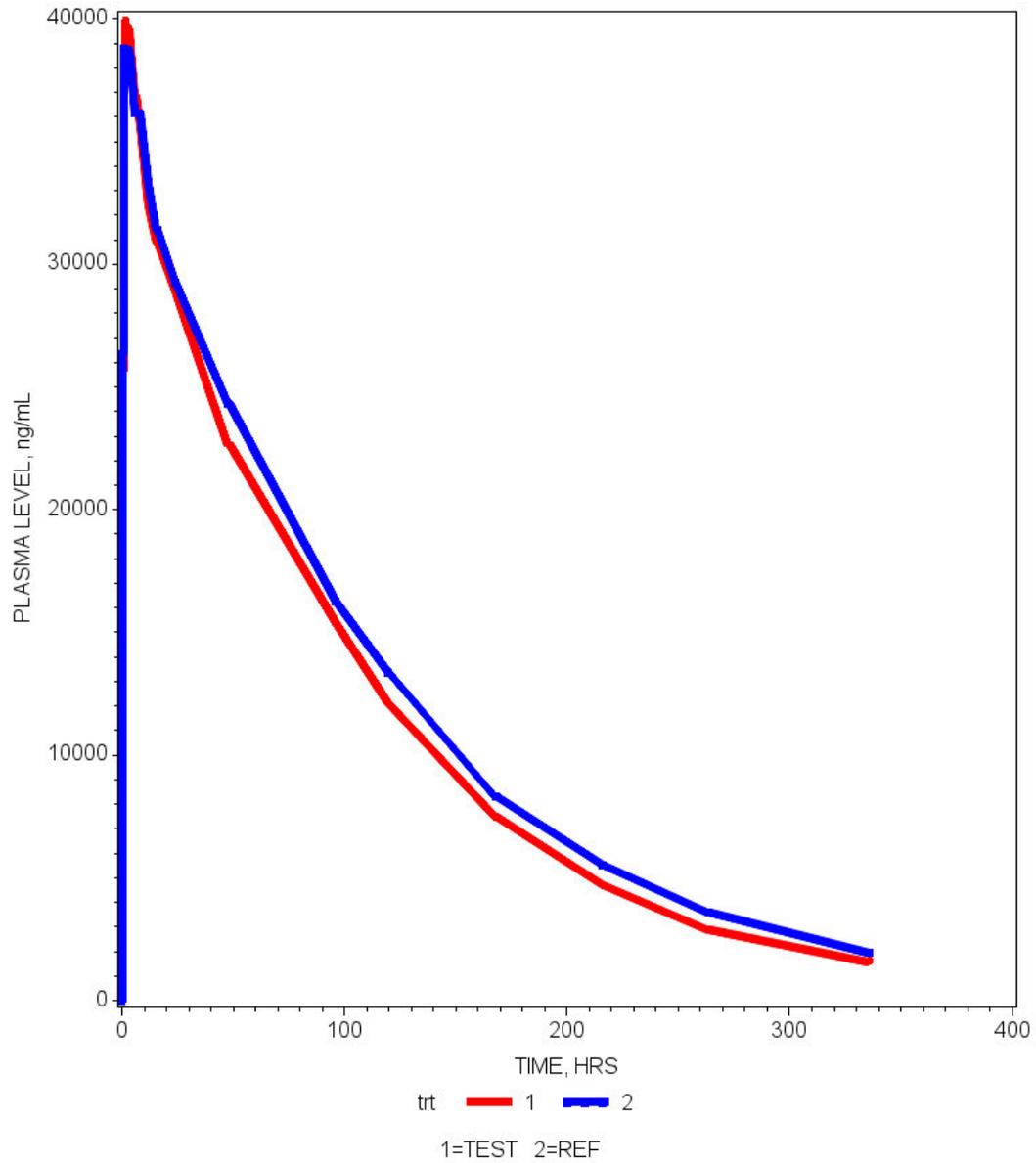
PLASMA Free Doxorubicin LEVELS
Doxorubicin HCl Liposome Injection, ANDA 208657
UNDER Fasted CONDITIONS
DOSE= 1x50 MG/m²



ANDA 208657
Single-Dose Fasting Bioequivalence Study Review

Linear plot of mean plasma concentration vs. time profile for encapsulated doxorubicin
(N=49)

PLASMA Encapsulated Doxorubicin LEVELS
Doxorubicin HCl Liposome Injection, ANDA 208657
UNDER Fasted CONDITIONS
DOSE= 1x50 MG/m2



4.1.2 *In Vitro*-Test Review

4.1.2.1 Liposome Size Distribution by Dynamic Light Scattering

4.1.2.1.1 Study Information

Study No.	Not applicable	
Study Site	(b) (4)	
Principal Investigator	A. Akhilesh Reddy	
Study Dates	Batch Number	Study Dates
	500080	14/11/2013
	500082	21/11/2013
	500083	23/11/2013
	JKM2306A	30/01/2014
	JKM3342A	30/01/2014
	JKM7084A	23/05/2014
SOP No.	(b) (4)	
SOP Effective Date	SOP Number	Effective Date
	(b) (4)	
SOP Title	(b) (4)	
Testing Method Description	(b) (4)	
Testing Equipment Used (e.g., name, model)		
Operating Conditions for Testing Equipment used (e.g., Temperature, humidity, etc.)		

Reviewer's Note

In Vitro Liposome Size Distribution Study Review

- The liposome size distribution was determined by **dynamic light scattering** using (b) (4) which provided liposome size distribution (D10, D50, D90) and span [(D90 - D10)/D50].
- Evaluation was done on samples from 10 vials from each of the three batches of Dr. Reddy's product (test product) and the three lots of Reference listed drug product i.e. Doxorubicin Hydrochloride Liposomal Injection, 2 mg/mL, manufactured by SUN Pharmaceutical Ind. Ltd.
- The study information of DSD test is **adequate**.

Product Information

Test Formulation	Doxorubicin Hydrochloride liposomal injection 2 mg/mL		
Manufactured By	Manufactured for: Dr. Reddy's Laboratories Ltd. Manufactured by: (b) (4)		
Batch No.	Test 1	Test 2	Test 3
	500080	500082	500083
Reference Formulation	Doxorubicin Hydrochloride liposomal injection 2 mg/mL		
Manufactured By	Sun Pharmaceutical Ind. Ltd, India Halol-Baroda Highway, Halol-389 350, Gujarat, INDIA. Distributed by: Caraco Pharmaceutical Laboratories, Ltd., Detroit, MI.		
Lot No.	Reference 1	Reference 2	Reference 3
	JKM2306A	JKM3342A	JKM7084A

Note: The firm was requested to submit the batch information for test and reference products including the manufacture date of the test lots and the expiration date of the RLD lots (See below).

In Vitro Liposome Size Distribution Study Review

Study type	Test- Doxorubicin Hydrochloride Liposome Injection 20mg/10mL				Reference- Doxorubicin Hydrochloride Liposome Injection 20mg/10mL (Sun Pharma)			
	Lot No.	Potency (Assay)	Lot size (3301 vials)		Manufacture date	Lot number	Potency (Assay)	Expiration date
			Theoretical	Actually bottled				
Bioequivalence study	500082	100.3% (2.01 mg)	(b) (4)		Nov 2013	JKM7084A	98.1% (1.96 mg)	May 2015
In-Vitro equivalence study	500080	100.4% (2.01 mg)			Nov 2013	JKM2306A	98.1% (1.96 mg)	Sep 2014
	500082	100.3% (2.01 mg)			Nov 2013	JKM3342A	99.1% (1.98)	Oct 2014
	500083	102.5% (2.05 mg)			Nov 2013	JKM7084A	98.1% (1.96 mg)	May 2015

4.1.2.1.2 Validation Summary Table

4.1.2.1.2.1 Precision

Treatment (Batch/Lot No.)	Parameter (Unit)	N	Mean	Std	Min	Max	Median	Range	Geo-metric Mean	%CV
Test (500080 + 500082+ 500083)	D ₁₀ (nm)	90	(b) (4)							
	D ₅₀ (nm)	90								
	D ₉₀ (nm)	90								
	SPAN	90								
Reference (JKM2306A + JKM3342A + JKM7084A)	D ₁₀ (nm)	90								
	D ₅₀ (nm)	90								
	D ₉₀ (nm)	90								
	SPAN	90								

Note: The method validation study should be conducted using the reference product.

RLD

Treatment	Batch/Lot No.	Parameter (Unit)	N	Mean	Std	Min	Max	Median	Range	Geo- metric Mean	%CV
Reference (Doxorubicin Hydrochloride Liposome Injection 2 mg/mL)	JKM2306A	D ₁₀ (nm)	30	(b) (4)							
		D ₅₀ (nm)	30								
		D ₉₀ (nm)	30								
		SPAN	30								
	JKM3342A	D ₁₀ (nm)	30								
		D ₅₀ (nm)	30								
		D ₉₀ (nm)	30								
		SPAN	30								
	JKM7084A	D ₁₀ (nm)	30								
		D ₅₀ (nm)	30								
		D ₉₀ (nm)	30								
		SPAN	30								

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Test

Treatment	Batch/Lot No.	Parameter (Unit)	N	Mean	Std	Min	Max	Median	Range	Geo-metric Mean	%CV
Test (Doxorubicin Hydrochloride Liposome Injection 2 mg/mL)	500080	D ₁₀ (nm)	30	(b) (4)							
		D ₅₀ (nm)	30								
		D ₉₀ (nm)	30								
		SPAN	30								
	500082	D ₁₀ (nm)	30								
		D ₅₀ (nm)	30								
		D ₉₀ (nm)	30								
		SPAN	30								
	500083	D ₁₀ (nm)	30								
		D ₅₀ (nm)	30								
		D ₉₀ (nm)	30								
		SPAN	30								

The firm re-conducted the validation studies and provided the following results using different batches.

Reference Product-JKP2573A

	D10	D50	D90	Span
Mean	(b) (4)			
% RSD				
Range				

Test Product-500237

	D10	D50	D90	Span
Mean	(b) (4)			
% RSD				
Range				

4.1.2.1.2.2 Intermediate Precision (by lot and by date)

Reviewer's Note:

The firm did not provide the intermediate precision and was requested to submit the method validation including intermediate precision (by date) and intermediate precision (by analyst). The firm re-conducted the validation studies and provided the following results.

Reference Product-JKP2573A

Intermediate Precision (by Date)

Day 1	D10	D50	D90	Span (b) (4)
Mean				
% RSD				
Day 2				
Mean				
% RSD				
% Difference (Day 1 vs Day2)				
Inter day % RSD				

Intermediate Precision (by Analyst)

Analyst 1	D10	D50	D90	Span (b) (4)
Mean				
% RSD				
Analyst 2				
Mean				
% RSD				
% Difference (Analyst 1 vs Analyst 2)				
Inter Analyst %RSD				

The firm also submitted the method validation study results using the test product as follows:

Test Product-500237

Intermediate Precision (by Date)

Day 1	D10	D50	D90	Span (b) (4)
Mean				
% RSD				
Day 2				
Mean				
% RSD				
% Difference (Day 1 vs Day2)				
Inter day % RSD				

Intermediate Precision (by Analyst)

Analyst 1	D10	D50	D90	Span (b) (4)
Mean				
% RSD				
Analyst 2				
Mean				
% RSD				
% Difference (Analyst 1 vs Analyst 2)				
Inter Analyst %RSD				

Comments on Method Validation:

- Per the summary tables of the method validation, the method validation study is found adequate.

4.1.2.1.3 Results Summary –

Calculated by the Firm

D50									
	Mean		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		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)								

Calculated by the Reviewer

D ₅₀ Summary									
	Mean		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		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)								

*Note: Based on the reviewer’s calculation, the within lot variability (%CV) of span for the test Lot 3 (b) (4) was slightly higher than the firm’s calculation (b) (4). The between lot variabilities of span for both test and reference are slightly lower than those calculated by the firm. However, the differences will not have impact on the outcomes of the study.

Summary of PBE Results (D50 mcm and Span) N=180 (Firm Calculated)

Variable	Geometric mean		Geometric Mean Ratio (%)T/R	Test Variability	Reference Variability	Standard Deviation		SigmaT/SigmaR Ratio
	Test	Reference				Sigma T	Sigma R	
D50	(b) (4)							
Span	(b) (4)							

Variable	Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Result
D50	(b) (4)			
Span	(b) (4)			

Summary of PBE Results (D50 mcm and Span) N=180 (Reviewer Calculated)

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Variable	Mean (log Scale)		Mean Ratio (log Scale)	Standard Deviation		Sigma T /Sigma R Ratio
	Test	Reference		Sigma T	Sigma R	
D50						(b) (4)
Span						
Variable	Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE		
D50						(b) (4)
Span						

Comments:

- Liposome size distribution by dynamic light scattering was performed on 3 lots of 10 vials each for the test and RLD.
- Based on the reviewer’s calculation using all 3 samples of each vial (i.e., sample #1-3 for each vial), the constant-scaled BE approach was applied for span and D50. The results of PBE statistical analyses for both D50 and span meet the PBE criteria and are similar to those calculated by the firm.
- The firm provided individual measurements of the time-history plots for the liposome size distribution study per the DB request. The time-history plots of particle size distribution data of test (500080, 500082 and 500083) and reference (JKM7084A, JKM2306A and JKM3342A) lots appear to be acceptable.
- The *in vitro* liposome size distribution study is **adequate**.

4.2 Formulation Data

S. No.	Components	Quantity (mg/mL)	Quantity (mg/vial)		%w/v
			20 mg/10mL	50 mg/25mL	
1.	Doxorubicin Hydrochloride USP	2 mg/mL	20 mg	50 mg	(b) (4)
2.	Cholesterol NF	3.19 mg/mL	31.9 mg	79.75 mg	
3.	Fully hydrogenated soy phosphatidylcholine (HSPC)	9.58 mg/mL	95.8 mg	239.5 mg	
4.	N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE)	3.19 mg/mL	31.9 mg	79.75 mg	
5.	Ammonium Sulfate NF	Approximately 2 mg/mL	Approximately 20 mg	Approximately 50 mg	
6.	Histidine USP	(b) (4)			
7.	Sucrose NF				
8.	Sodium Hydroxide NF				
9.	Hydrochloric acid NF				
10.	(b) (4)				
11.		(b) (4)			
12.					

Doxorubicin hydrochloride is encapsulated in long-circulating liposomes for intravenous administration. (b) (4)

The main components in the liposomal formulation are Lipid components i.e. MPEG 2000-DSPE, Fully hydrogenated soy phosphatidylcholine (HSPC) and Cholesterol. All the excipients in the Doxorubicin Hydrochloride Liposome Injection, 2 mg/ml were selected considering the route of administration i.e. parenteral route and sterile dosage form.

Not to be released under FOIA Comparative Composition

Component	Dr. Reddy's Laboratories Limited Test (mg/mL)	Sun Pharmaceuticals RLD (mg/mL) ANDA203263	Ortho Biotech Doxil® (mg/mL) NDA050728
Doxorubicin Hydrochloride	2.00	2.00	2.00
Cholesterol HP, NF	3.19	3.19	3.19
Fully Hydrogenated Soy Phosphatidyl Choline	9.58	9.58	9.58
MPEG-Distearoyl Phosphatidylethanolamine	3.19	3.19	3.19
Ammonium Sulfate, NF#	Approximately 2 mg/mL	Approximately 2 mg/mL	2*
Histidine USP	(b) (4)		
Sucrose, NF	(b) (4)		
Sodium Hydroxide, NF	(b) (4) (pH 6.5)	(b) (4) (pH adjustment)	(b) (4) (pH 6.5)
Hydrochloric Acid, NF	(b) (4) (pH 6.5)	(b) (4) (pH adjustment)	(b) (4) (pH 6.5)

(b) (4)

Reviewer's Comments

Per the control correspondence #11-0539¹², the proposed formulation of Doxorubicin Hydrochloride Liposome Injection submitted by Dr. Reddy's Laboratories Limited was determined to be Q1 and Q2 the same as that of Doxil[®] (NDA052728), the RLD product at the time of submission of the control.

Per the comparative composition table above, Dr. Reddy's test product formulation is qualitatively (Q1) but not quantitatively (Q2) the same as that of Sun Pharma Global's product, the current RLD (ANDA203263). The amount of the histidine in the test product is within $\pm 5\%$ (b) (4) of the corresponding excipient in the reference product, but the sucrose concentration (b) (4) exceeds the allowable $\pm 5\%$ difference.

However, during the review of ANDA203263 (Sun Pharma Global's Doxorubicin Hydrochloride Liposome Injection), the Division of Bioequivalence (DB) determined the formulation of the test product to be acceptable¹⁴, even though the test product formulation was not quantitatively (Q2) the same as that of Doxil[®]¹⁵. Please refer to Section 4.2 Formulation Data of the ANDA203263 DB review¹⁴ for details.

¹² Control Correspondence #11-0539 <\\cdsnas\OGDS6\CONTROLS\2011-docs\11-0539.pdf>

¹³ (Test-Reference)/Reference *100

¹⁴ DARRTS, ANDA203263, REV-BIOEQ-01(General Review), dated 2/16/2012

¹⁵ The formulation of Sun Pharma's product was considered to be acceptable for the following reasons:

- The Division of Clinical Review (DCR) consult found 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.
- As per ANDA203263 Chemistry review "The function of Sucrose is to maintain isotonicity. It is not part of the liposome composition. In other words, (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 firm submitted an in vivo bioequivalence study demonstrating bioequivalence of the test product.

The arguments used in the DB review of ANDA203263 (Sun Pharma Global's Doxorubicin Hydrochloride Liposome Injection) are also applicable to find the difference in sucrose content of the current test product to that of the current RLD product acceptable. (b) (4)

Overall, the formulation of the test product in the current application is acceptable.

Is there an overage of the active pharmaceutical ingredient (API)?	No. See the comments above.
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?	N/A
If no, are additional data or Pharm/Tox consult necessary?	N/A
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 RLD product dose-proportional?	N/A
Are all strengths of the test formulation acceptable	Yes
Additional Attachment for Formulation Calculations	N/A

4.3 In Vitro Drug Release Data

Drug Release Test Review Path	Drug release test will be reviewed by OPQ.
--------------------------------------	--

Table 24. Drug Release Data



(b) (4)

Reviewer's Comments:

There is no USP method for this product. The dissolution database for Doxorubicin Hydrochloride Liposome Injection recommends the firm to develop a method to characterize *in vitro* drug release.

DISSOLUTION PROFILE (pH 6.5 Buffer at 47°C)

	Test Product	Reference Listed Drug
Product	: Doxorubicin Hydrochloride Liposome Injection	Doxorubicin Hydrochloride Liposome Injection
Strength	: 20mg/10mL	20mg/10mL
Batch No./ Lot No.	: 500082	JKM7084A
Manufactured by	: (b) (4)	Sun Pharmaceutical India Ltd.
Manufactured for	: Dr. Reddy's Laboratories Limited	Not applicable
Manufacture Date	: November, 2013	Not applicable
Expiration Date	: To be established	05/2015
Apparatus	: Culture tube & incubation in water bath	Culture tube & incubation in water bath
Speed of Rotation	: Not applicable	Not applicable
Medium	: pH 6.5 Buffer (Ammonium Chloride and L-Histidine) - Dissolution in QC release media	pH 6.5 Buffer (Ammonium Chloride and L-Histidine) - Dissolution in QC release media
Volume	: 4mL Dissolution Medium & 4mL sample (1:1)	4mL Dissolution Medium & 4mL sample (1:1)
Temperature	: 47°C	47°C
STP No.	: K/STP/FPS/311	K/STP/FPS/311
Analytical Reference No	: U5/FP/022/13	U5/MS/634/14

In-vitro release data of Test product (Batch No: 500082)

pH 6.5 Buffer at 47°C

Time (hour)	% Dissolved												Min.	Max. (b) (4)	Mean	%CV	
	Vial-1	Vial-2	Vial-3	Vial-4	Vial-5	Vial-6	Vial-7	Vial-8	Vial-9	Vial-10	Vial-11	Vial-12					
0.5																22.8	11.6
1																33.2	3.7
2																46.0	1.3
4																65.7	1.1
6																82.4	0.4
12																97.1	0.1
24																99.0	0.2
48																100.1	0.1

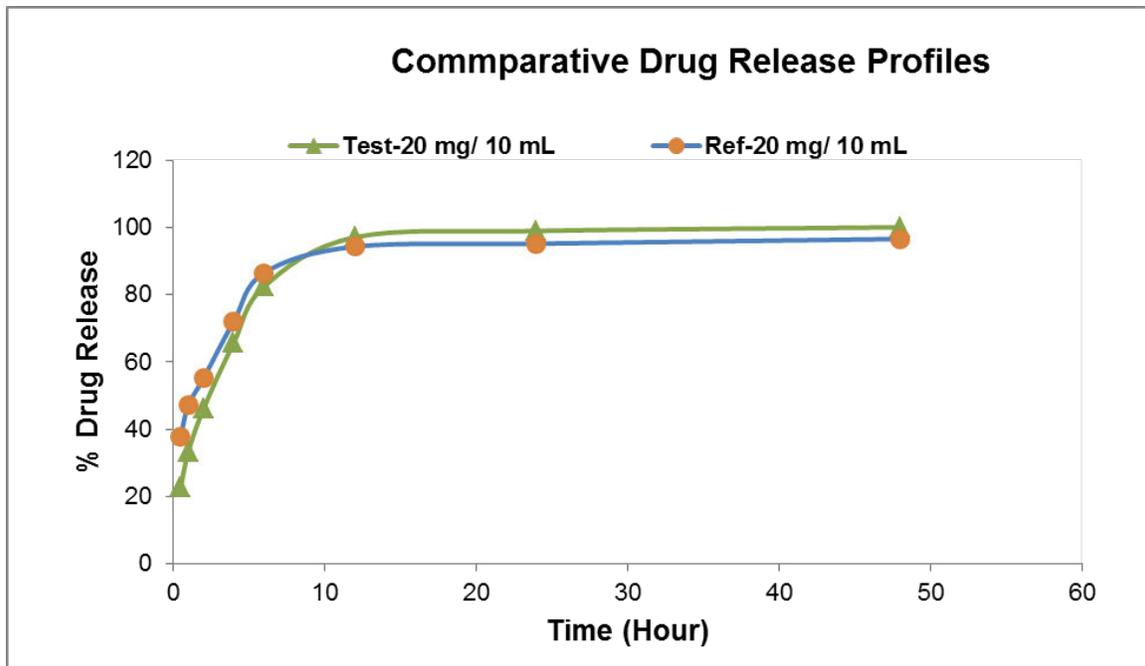
In-vitro release data of RLD product - Sun Pharma (Lot No: JKM7084A)

pH 6.5 Buffer at 47°C

Time (hour)	% Dissolved												Min.	Max. (b) (4)	Mean	%CV	
	Vial-1	Vial-2	Vial-3	Vial-4	Vial-5	Vial-6	Vial-7	Vial-8	Vial-9	Vial-10	Vial-11	Vial-12					
0.5																37.9	1.7
1																47.1	4.0
2																55.1	0.8
4																72.1	0.9
6																86.5	0.6
12																94.3	0.1
24																95.2	0.1
48																96.6	0.1

F2 values in pH 6.5 Buffer (having 2M Ammonium Chloride-0.2M Histidine)

F2 Metrics in pH6.5 buffer	
	Test vs. Reference
20 mg/10 mL (Test Batch #500082) vs 20 mg/10 mL (Reference Batch #JKM7084A)	50.45



The f_2 value for test vs reference calculated by the reviewer was greater than 50, which suggests that the drug release rate of test product is considered similar to that of reference product using the pH 6.5 buffer (having 2M Ammonium Chloride-0.2M Histidine) at 47°C.

4.4 DCR Consult Review

The DB has submitted a clinical consultation to the DCR to ask if the adverse event (**cardio pulmonary arrest /death**) associated with the test formulation should be of a safety concern.

The Medical Officer concluded that the death 19 days after administration of the test product of patient (b) (6) during the BE study #591-13 is unlikely to be related to the administration of the test product; therefore, it does **not indicate a safety concern for the test product**.

Patient (b) (6) was a 39-year old female with ovarian cancer. Her disease progressed/recurred after she completed a regime of platinum based chemotherapy. The patient received the test product and was discharge the following day. The patient visited the clinical site for ambulatory PK samples on 7 occasions. However, 19 days after administration of test drug, she presented to the test facility with nausea, vomiting, and abdominal distension without fever. Clinical findings were ascites, a solid mass in the lower abdomen, and sluggish bowel sounds. The investigator suspected sub-acute intestinal obstruction. Complete blood tests, liver function tests and renal function tests were not remarkable. The patient was treated with IV fluids, atropine, adrenaline, dopamine and hydrocortisone injection, antiemetics (ondansetron, metoclopramide), and antibiotics (cefoperazone aodium, ciprofloxacin and metronidazole). The patient suddenly got up from bed and collapsed. In spite of all

resuscitative measures, the patient died. An autopsy was not performed. The PK values, including AUC and Cmax, for subject (b) (6) are within the range of the study values. At the time of the event (and since day 14 post-dose), both plasma free doxorubicin and encapsulated doxorubicin levels were below the limit of quantitation suggesting that doxorubicin concentration in plasma was extremely low before the event took place.

After review of available data, a causal relationship between the death of patient (b) (6) and test product administration is considered unlikely. The event occurred 19 after taking the medication and when plasma doxorubicin levels were extremely low. The patient likely died from her disease progression, and the cause of death was cardio-pulmonary arrest.

Reviewer's Comments

Per the DCR consult, the severe adverse event (cardio pulmonary arrest /death) does not indicate a safety concern for the test product.

4.5 SAS Output

4.5.1 Fasting Study

Study #591-13

	Fasting Study Data	Fasting Study Codes (using nominal time)	Fasting Study Output
Free	 Fasting Doxorubicin Conc Pk data.xls	 Fasting Doxorubicin.sas	 208657_Fasted_table_Free Doxorubicin.d
Encapsulated	 Fasting Liposome Doxorubicin Conc Pk ( Fasting Liposome Doxorubicin.sas	 208657_Fasted_table_Encapsulated Doxc

4.6 Group Effect for Average Bioequivalence

(NOTE: A statistical consult has been requested for the ANDA 091073 regarding analyzing group effect in a reference-scaled average bioequivalence study design.)

Control Document No. 98-392

Bio Control Document No: 98-392
Reviewer: Barbara M. Davit
v:\firmsnz\^(b) (4)\controls\98-392a.doc

Firm: 

(b) (4)

Submission date: 10/30/98
Date finalized: 8/6/99

Addendum to the Review

Introduction:

The firm is requesting that the Division of Bioequivalence (DBE) comment on the appropriateness of the following dosing schemes to be used when bioequivalence study subjects are not recruited as a single group. Two proposed dosing schemes are shown below, for a drug with a one week washout period:

Dosing Scheme	11/1	11/8	11/15	11/22
1	Group 1 Period 1	Group 1 Period 2	Group 2 Period 1	Group 2 Period 2
2	Group 1 Period 1	Group 1 Period 2 Group 2 Period 1	Group 2 Period 2	

The firm is also requesting comment on the appropriate of the statistical model to be used in data analysis for the above bioequivalence study designs.

Comments:

CDER Quantitative Methods and Research Staff (QMRS) provided a written review commenting on the firm's proposals. The review is attached. The review written by the DBE primary reviewer is also attached.

Both Dosing Schemes are acceptable to QMRS. Dosing Scheme 1 is the classic two group design.

For both dosing schemes, the DBE recommends the following statistical model:

- Group
- Sequence
- Treatment
- Subject (nested within Group*Sequence)
- Period (nested within Group)
- Group-by-Sequence Interaction
- Group-by-Treatment Interaction

Subject (nested within Group*Sequence) is a random effect and all other factors are fixed effects. QMRS states that if SAS PROC GLM or equivalent software is used to analyze the study, including or not including this interaction will not change the confidence intervals. If SAS PROC MIXED is used, including this interaction might change the confidence intervals. By nesting the Period effect within Group, the model allows for the possibility that the effects of Period 1 and Period 2 in Group 1 may not be the same as the effects of Period 1 and Period 2 in Group 2.

An alternate model for Dosing Scheme 2 would include the following factors:

- Group
- Sequence
- Treatment
- Subject (nested within Group*Sequence)
- Week
- Group-by-Sequence Interaction
- Group-by-Treatment Interaction

The factor Week reflects which of the three weeks (11/1, 11/8, 11/15) the observations came from. If SAS PROC GLM or equivalent software is used to analyze the study, this model should produce the same confidence intervals as the model with Period (nested within Group).

For both models, if the Group-by-Treatment interaction test is not statistically significant ($p < 0.1$), the Group-by-Treatment term can be dropped from the statistical model.

If the Group-by-Treatment interaction is statistically significant ($p < 0.1$), DBE recommends that equivalence be demonstrated in one of the groups, provided that the group meets minimum requirements for a complete bioequivalence study. This is similar to the recommendation presented by QMRS as option #3 (see attached QMRS review). The firm should be cautioned that statistical analysis for bioequivalence studies dosed in more than one group should commence only after all subjects have been dosed and all pharmacokinetic parameters have been calculated. Statistical analysis to determine

bioequivalence within each dosing group should never be initiated prior to dosing the next group; otherwise the study becomes one of sequential design.

With both Dosing Schemes, if all of the following criteria are met, it may not be necessary to test for group effects in the model:

- the clinical study takes place at one site;
- all study subjects have been recruited from the same enrollment pool;
- all of the subjects have similar demographics;
- all enrolled subjects are randomly assigned to treatment groups at study outset.

In this latter case, the appropriate statistical model would include only the factors Sequence, Period, Treatment, and Subject (nested within Sequence).

Recommendations:

The following comments should be conveyed to the sponsor:

Both Dosing Schemes are acceptable to the Division of Bioequivalence.

The following statistical model can be applied to both Dosing Schemes.

Group
Sequence
Treatment
Subject (nested within Group*Sequence)
Period (nested within Group)
Group-by-Sequence Interaction
Group-by-Treatment Interaction

Subject (nested within Group*Sequence) is a random effect and all other factors are fixed effects. If SAS PROC GLM or equivalent software is used to analyze the study, including or not including this interaction will not change the confidence intervals. If SAS PROC MIXED is used, including this interaction might change the confidence intervals. By nesting the Period effect within Group, the model allows for the possibility that the effects of Period 1 and Period 2 in Group 1 may not be the same as the effects of Period 1 and Period 2 in Group 2.

An alternate model for Dosing Scheme 2 would include the following factors:

Group
Sequence
Treatment
Subject (nested within Group*Sequence)
Week
Group-by-Sequence Interaction
Group-by-Treatment Interaction

The factor Week in the statistical model for Dosing Scheme 2 reflects which of the three weeks the observations came from. If SAS PROC GLM or equivalent software

is used to analyze the study, this model should produce the same confidence intervals as the model with Period (nested within Group).

If the Group-by-Treatment interaction test is not statistically significant ($p \geq 0.1$), only the Group-by-Treatment term can be dropped from the statistical model.

If the Group-by-Treatment interaction is statistically significant ($p < 0.1$), **DBE requests that equivalence be demonstrated in one of the groups, provided that the group meets minimum requirements for a complete bioequivalence study.**

DBE cautions the firm that statistical analysis for bioequivalence studies dosed in more than one group should commence only after all subjects have been dosed and all pharmacokinetic parameters have been calculated. Statistical analysis to determine bioequivalence within each dosing group should never be initiated prior to dosing the next group; otherwise the study becomes one of sequential design.

If ALL of the following criteria are met, it may not be necessary to include Group-by-Treatment in the statistical model:

the clinical study takes place at one site;
all study subjects have been recruited from the same enrollment pool;
all of the subjects have similar demographics;
all enrolled subjects are randomly assigned to treatment groups at study outset.
In this latter case, the appropriate statistical model need include only the factors Sequence, Period, Treatment, and Subject (nested within Sequence).

Please be advised that the above comments are subject to revision by the Division of Bioequivalence.

Barbara M. Davit, Ph.D.
Team Leader
Review Branch III
Division of Bioequivalence

Rabinandra Patnaik, Ph.D.
Deputy Division Director
Division of Bioequivalence

Concur:

Date:

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

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cc: HFD-630, HFD-650 (Director), HFD-658 (Davit), Drug File, Division File

4.7 OSIS Inspection Report Review

Per Establishment Inspection Reports (EIR), the final classifications of clinical and analytical site inspections for Study 591-13 for the current application are listed in the tables below.

ID	Clinical Site	OSIS Final Classification
A	BIBI General Hospital & Cancer Centre, Telangana, India	Pending
B	Meenakshi Mission Hospital & Research Center Tamil Nadu, India ²⁰	NAI
C	City Cancer Centre, Vijayawada, India ¹⁶	NAI
D	Nirmal Hospital Pvt Ltd, Surat; Gujarat, India ¹⁷	NAI
E	Srinivasam Cancer Care Hospitals India Pvt. Ltd., Bangaluru, India ¹⁸	VAI (See comments below)
F	Curie Manavata Cancer Centre, Nashik, India ¹⁹	NAI
H	Acharya Harihar Regional Cancer Center Department of Radiation Oncology, Odisha India ²⁰	NAI
I	MNJ Institute of Medical Oncology and Regional Cancer Center, Hyderabad, India ²¹	NAI
J	Erode Cancer Centre Pvt. Ltd., Erode, India ²¹	NAI
K	Cancer Clinic & Nursing Home, Maharashtra, India ²⁰	NAI

Analytical Site	OSIS Final Classification
(b) (4)	VAI (See comments below)

Srinivasam Cancer Care Hospitals India Pvt. Ltd., Bangaluru, India (Clinical Site E)

The OSIS arranged an inspection of the clinical portion of Study 591-13 submitted to the current ANDA 208657 conducted at Srinivasam Cancer Care Hospitals India Pvt. Ltd., Bangaluru, India (Clinical Site E).

The final classification for this inspection is Voluntary Action Indicated (VAI). Per the EIR¹⁷, there is no specific deficiency observed for Study 591-13. The other issues listed for the other studies in this clinical site in the EIR will not affect the results of Study 591-13.

¹⁶ GDRP, ANDA-208657-ORIG-1, Site: CITY CANCER CENTRE, EIR Review_ANDAs (b) (4) 208657 Final-all signed.pdf, dated 04/27/2016

¹⁷ GDRP, ANDA-208657-ORIG-1, Site: NIRMAL HOSPITAL PRIVATE LTD, EIR Review-ANDA208657-Nirmal-(b) (4).pdf, dated 04/18/2016

¹⁸ GDRP, ANDA-208657-ORIG-1, Site: SRINIVASAM CANCER CARE HOSPITALS INDIA PRIVATE LIMITED, EIR Review Memo for Srinivasam Bangaluru India_Final.pdf, dated 06/04/2016

¹⁹ GDRP, ANDA-208657-ORIG-1, Site: CURIE MANAVATA CANCER CENTRE, Final EIR Review ANDA 208657 at Curie.pdf, dated 06/10/2016

²⁰ GDRP, ANDA-208657-ORIG-1, Site: ACHARYA HARIHAR REGIONAL CANCER CENTRE, DEPARTMENT OF RADIATION ONCOLOGY, EIR Review ANDA208657.pdf, dated 04/14/2016

²¹ GDRP, ANDA-208657-ORIG-1, Site: MNJ INSTITUTE OF MEDICAL ONCOLOGY AND REGIONAL CANCER CENTER, Final EIR Review ANDA 208657 at Erode MNJ (2).pdf, dated 05/31/2016

²² GDRP, ANDA-208657-ORIG-1, Site: (b) (4) EIR review-Analytical with attachments.pdf, dated (b) (4)

The OSIS recommends that the data from the clinical portion of studies 591-13 conducted at Srinivasam Cancer Care Hospitals India Pvt. Ltd., be accepted for further Agency review.

The OSIS status of the clinical site at Srinivasam Cancer Care Hospitals India Pvt. Ltd for the current ANDA208657 is **adequate**.

(b) (4) **(Analytical Site)**
The OSIS arranged an inspection of the analytical portion of Study 591-13 submitted to the current ANDA 208657 conducted at (b) (4)
(b) (4)

The final classification for this inspection is VAI. Per the EIR²², the following Observation 2 was reported for the Method Validation Study # (b) (4) for Study 591-13.

(b) (4)

Per the EIR, the discrepancy in the sample tracking system was due to a technical error in the (b) (4) software. The OSIS concluded that this issue does not have impact on the study integrity. The other issues listed for the other studies in this analytical site in the EIR will not affect the results of Study 591-13.

The OSIS recommends that the data from the analytical portion of studies 591-13 conducted at (b) (4), be accepted for further Agency review.

The OSIS status of the analytical site at (b) (4) for the current ANDA208657 is **adequate**.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 208657
APPLICANT: Dr. Reddy's Laboratories Limited
DRUG PRODUCT: Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL and 50 mg/25 mL

The Division of Bioequivalence (DB) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{ See appended electronic signature page }

Ethan M. Stier, Ph.D., R.Ph.
Director,
Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Productivity Data

Completed Assignment for 208657 ID: 27830

Reviewer: Harigaya, Yoriko

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Doxorubicin HCl Liposome Injection 20 mg/10 mL and 50 mg/25 mL

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>		
27830	10/8/2015	ANDA Original	OB	1	1	Edit	Delete
				Total:	1		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208657

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

June 03, 2016

ANDA: 208657

Drug Product Name

Proprietary: N/A

Non-proprietary: Doxorubicin Hydrochloride Liposome Injection

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
10/08/2015	10/08/2015	N/A	03/03/2016

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor

Name: Dr. Reddy's Laboratories Limited

Address: Integrated Product Development Organization
Innovation Plaza, Survey Nos. 42, 45, 46 & 54
Bachupally, Quthbullapur Mandal,
Rangareddy Dist., Hyderabad,
Telangana, India-500 090

U.S. Agent

Name: Dr. Reddy's Laboratories, Inc.

Address: 107 College Road East, Princeton, NJ 08540

Representative: Srinivasa Rao

Telephone: 609-375-9922

Fax: 908-450-1476

Name of Reviewer: Samata Tiwari, 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 sterile drug product
- 3. **MANUFACTURING SITE:**

(b) (4)
- 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile liposome Injection, IV (Infusion), 20mg/10mL and 50mg/25mL, packaged in a single dose.
- 5. **METHOD(S) OF STERILIZATION:**

(b) (4)
- 6. **PHARMACOLOGICAL CATEGORY:** Indicated for the treatment of patients with ovarian cancer after failure of platinum-based chemotherapy.
- B. **SUPPORTING/RELATED DOCUMENTS:**

(b) (4)
- C. **REMARKS:**

This application in an e-CTD submission.

Filename: A208657MR01.doc
 Template version: OGD modified_AP_2014v6.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 are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology 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)
(u) (4)



B. Brief Description of Microbiology Deficiencies – See Section 3 “List of Microbiology Deficiencies and Comments.”

C. Contains Potential Precedent Decision(s) - Yes No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

(b) (4)





(b) (4)

Acceptable

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 208657 APPLICANT: Dr. Reddy's Laboratories Limited

DRUG PRODUCT: Doxorubicin Hydrochloride Liposome Injection

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows YES NO

Microbiology Deficiencies:



d)



(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 208657

Other Review(s)

ANDA 208657 – Doxorubicin HCl Liposome Injection 20mg/10mL and 50mg/25mL

(b) (4)

This type of liposomal product for injection is considered as a (b) (4) and “high risk” product. There is currently no formal risk assessment procedure/template available for this type of product.

As per the Draft Guidance on Doxorubicin HCl Liposome injection posted on December 2014, two studies, namely clinical and in vitro studies are recommended 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.

With respect to the in vitro study, below is the information/recommendation provided in the draft Guidance.

In Vitro Study:

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% upper confidence bound): D50 and SPAN [(i.e. D90-D10)/D50] or polydispersity index using the population bioequivalence approach.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional information:

Same drug product composition

Being a parenteral drug product, a generic doxorubicin HCl liposome injection must be qualitatively and quantitatively the same as the RLD or reference standard, 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. Currently, FDA has no recommendations for the type of studies that would be needed to demonstrate that differences in buffers, preservatives and antioxidants do not impact the safety/efficacy profile of the drug product.

Lipid excipients are critical in the liposome formulation. ANDA sponsors should obtain lipids from the same category of synthesis route (natural or synthetic) as found in the RLD or reference standard. 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 as suggested in the liposome drug products draft guidance¹. ANDA sponsors should have specification on lipid excipients that are similar to those used to produce the RLD or reference standard. Additional comparative characterization (beyond meeting specifications) of lipid excipients including the distribution of the molecular species should be provided.

Active liposome loading process with an ammonium sulfate gradient

In order to meet the compositional equivalence and other equivalence tests, an ANDA sponsor would be expected to use an active loading process with an ammonium sulfate gradient. The major steps include 1) formation of liposomes containing ammonium sulfate, 2) liposome size reduction, 3) creation of ammonium sulfate gradient, and 4) active drug loading. An active loading process uses an ammonium sulfate concentration gradient between the liposome interior and the exterior environment to drive the diffusion of doxorubicin into the liposomes^{2,3}.

Sponsors should use a Quality by Design approach to identify critical material attributes and critical process parameters, and guide process optimization. It is recommended to identify the

¹ Draft guidance for industry: Liposome drug products chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation, FDA (2002), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070570.pdf>

² A. Gabizon, H. Sheemda, Y. Barenholz. Pharmacokinetics of pegylated liposome doxorubicin: review of animal and human studies. Clin Pharmacokinet 42(5): 419-436 (2003)

³ F. Martin. Product evolution and influence of formulation on pharmaceutical properties and pharmacology, Advisory Committee for Pharmaceutical Science Presentation (Jul 2001), http://www.fda.gov/ohrms/dockets/AC/01/slides/3763s2_08_martin.ppt.

critical process parameters and critical material attributes by evaluating the sensitivity of liposome characteristics to changes in process parameters and attributes. The optimal values of critical process parameters should be selected based on comparison of resulting liposome characteristics to those of the RLD or reference standard.

Equivalent liposome characteristics

As with other locally acting products with complex bioequivalence requirements (such as nasal sprays and inhalation products), *in vitro* liposome characterization should be conducted on at least three batches of the ANDA and the RLD or reference standard products (at least one ANDA batch should be produced by the commercial scale process and used in the *in vivo* bioequivalence study). Attributes that should be included in the characterization of ANDAs claiming equivalence to the RLD or reference standard are:

- **Liposome composition:** Liposome composition including lipid content, free and encapsulated drug, internal and total sulfate and ammonium concentration, histidine concentration, and sucrose concentration should be measured. The drug-to-lipid ratio and the percentage of drug encapsulation can be calculated from liposome composition values.
- **State of encapsulated drug:** The doxorubicin in the RLD or reference standard is largely in the form of a doxorubicin sulfate precipitate inside the liposome. The generic doxorubicin HCl liposome must contain an equivalent doxorubicin precipitate inside the liposome.
- **Internal environment (volume, pH, sulfate and ammonium ion concentration):** The internal environment of the liposome, including its volume, pH, sulfate and ammonium concentration, maintains the precipitated doxorubicin. The measurements of total and free concentrations of components (including sulfate ions) described in liposome composition section allow the inference of the internal concentration inside the liposome.
- **Liposome morphology and number of lamellae:** Liposome morphology and lamellarity should be determined as drug loading, drug retention, and the rate of drug release from the liposomes are likely influenced by the degree of lamellarity.
- **Lipid bilayer phase transitions:** Equivalence in lipid bilayer phase transitions will contribute to demonstrating equivalence in bilayer fluidity and uniformity. The phase transition profiles of the raw lipid excipients and liposomes should be comparable to those of the RLD or reference standard.
- **Liposome size distribution:** Liposome size distribution is critical to ensuring equivalent passive targeting. The ANDA sponsor should select the most appropriate particle size analysis method to determine the particle size distributions of both test and reference product. The number of liposome product vials to be studied should not be fewer than 30 for each of the test and reference products (i.e., no fewer than 10 from each of three batches). See recommended study 2 (above) for details of the recommended statistical equivalence tests.

- Grafted PEG at the liposome surface: The surface-bound methoxypolyethylene glycol (MPEG) polymer coating protects liposomes from clearance by the mononuclear phagocyte system (MPS) and increases blood circulation time. The PEG layer thickness is known to be thermodynamically limited and estimated to be in the order of several nanometers. The PEG layer thickness should be determined.
- Electrical surface potential or charge: Surface charge on liposomes can affect the clearance, tissue distribution, and cellular uptake. Liposome surface charge should be measured.
- In vitro leakage under multiple conditions: In vitro drug leakage testing to characterize the physical state of the lipid bilayer and encapsulated doxorubicin should be investigated to support a lack of uncontrolled leakage under a range of physiological conditions and equivalent drug delivery to the tumor cells. Below are some examples of proposed conditions.

Table 1. Examples of in vitro leakage conditions of doxorubicin liposomes

In Vitro Drug Leakage Condition	Purpose	Rationale
At 37°C in 50% human plasma for 24 hours	Evaluate liposome stability in blood circulation.	Plasma mostly mimics blood conditions.
At 37°C with pH values 5.5, 6.5, and 7.5 for 24 hours in buffer	Mimic drug release in normal tissues, around cancer cells, or inside cancer cells	Normal tissues: pH 7.3 Cancer tissues: pH 6.6 Insider cancer cells (endosomes and lysosomes): pH 5-6 (Endosome and lysosomes of cancer cells may be involved in liposome uptake and induce drug release).
At a range of temperatures (43°C, 47°C, 52°C, 57°C) in pH 6.5 buffer for up to 12 hours or until complete release	Evaluate the lipid bilayer integrity	The phase transition temperature (T_m) of lipids is determined by lipid bilayer properties such as rigidity, stiffness and chemical composition. Differences in release as a function of temperature (below or above T_m) will reflect small differences in lipid properties
At 37°C under low-frequency (20 kHz) ultrasound for 2 hours or until complete release.	Evaluate the state of encapsulated drug in the liposome.	Low-frequency ultrasound (20 kHz) disrupts the lipid bilayer via a transient introduction of pore-like defects and will render the release of doxorubicin controlled by the dissolution of the gel inside the liposome.

MEMORANDUM

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

DATE: Jan 19, 2017

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Amendment for EIR review covering ANDA 208657 for
clinical inspections conducted at Erode Cancer Centre
Pvt. Ltd., Erode, India and MNJ Institute of Medical
Oncology and Regional Cancer Center, Hyderabad, India

Amendment Summary

This review is to amend the EIR review covering ANDA 208657 finalized on May 25, 2016 (Attachment 1) to provide updated information on reserve sample collection at MNJ Institute of Oncology & Regional Cancer Center, Hyderabad, India (MNJ Institute). This EIR review amendment does not impact the Erode Cancer Centre Pvt. Ltd., Erode, India site.

On August 08, 2016, Office of Regulatory Affairs (ORA) investigator Anya D. Lockett-Evans initiated a site visit at MNJ Institute of Oncology & Regional Cancer Center, Hyderabad, India (MNJ Institute) for audit of a separate regulatory submission (b) (4). During this visit, investigator Lockett-Evans also collected reserve samples for study 591-13, which was submitted for ANDA 208657. Please note that as noted in the original EIR review, the reserve samples for study 591-13 were not collected during the previous inspection

conducted from February 01-04, 2016 by investigator Vickie J Kanion. Information on study 591-13 is provided below.

Application	Study	Sponsor
ANDA 208657	591-13	Dr. Reddy's Laboratories Ltd., India

Study 591-13: "A multicenter, open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, cross-over bioequivalence study of doxorubicin hydrochloride liposome injection 20 mg/10 mL (2 mg/mL) of Dr. Reddy's Laboratories Ltd, India, with that of doxorubicin hydrochloride liposome injection 20 mg/10 mL (2 mg/mL), manufactured by: Sun Pharmaceutical Ind. Ltd, India; distributed by: Caraco Pharmaceutical Laboratories, Ltd., Detroit, MI 48202 in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug under fasting condition"

Study Dates: July 3, 2014 (first patient, first visit)-April 9, 2015(last patient, last visit)

Recommendation

This EIR review amendment does not change the previous OSIS recommendation in the original EIR review for ANDA 208657 (finalized on May 25, 2016) that the clinical portion of study 591-13 conducted at MNJ Institute is acceptable for further Agency (FDA) review.

Xiaohan Cai -S

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Xiaohan Cai, Ph.D.
OSIS, DGDBE

**Stanley
Au -S**

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(Acting Team Lead)

Stanley Au, Pharm.D., BCPS
Team Lead (Acting)
OSIS, DGDBE

Seongeun
N. Cho -S

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Date: 2017.01.19 22:01:41 -05'00'

Seongeun Cho, Ph.D.

Director

OSIS, DGDBE

cc:

OSIS/Kassim/Taylor/Haidar/Miller/Nkah/Fenty-Stewart/Kadavil

OSIS/DGDBE/Cho/Skelly/Choi/Au/Cai

OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

OGD/OB/Conner

ORA/SEA/Harris/Rajaram

ORA/ KAN-DO/Hall/Kanion

ORAHQ/OMPTO/DMPTI/BIMO/Bukowczyk/Arline/Montemurro/Colon

Draft: XHC 1/18/17, XHC 1/19/17

Edit: SA 01/18/17, JC 01/19/2017

ECMS:

Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory
Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/MNJ
Institute of Oncology-Hyderabad-India/ANDA208657_Doxorubicin
Liposome Injection

OSI file# BE6993

FACTS: **11583191**

Attachments

Attachment 1: Original EIR review for ANDA 208657

M E M O R A N D U M

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

DATE: May 25, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering ANDA 208657 for clinical
inspections conducted at Erode Cancer Centre Pvt.
Ltd., Erode, India and MNJ Institute of Medical
Oncology and Regional Cancer Center, Hyderabad, India

Recommendations:

The Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS) arranged inspections of the following clinical study at Erode Cancer Centre Pvt. Ltd., Erode, India and MNJ Institute of Medical Oncology and Regional Cancer Center, Hyderabad, India (MNJ Institute). This reviewer recommends that the clinical portion of study 591-13 conducted at Erode Cancer Centre and MNJ Institute be accepted for further Agency review.

Application	Study	Study Site	Sponsor	Recommend
ANDA 208657	591-13	Erode Cancer Centre Pvt., Erode, India	Dr. Reddy's Laboratories Ltd., India	Acceptable
		MNJ Institute of Medical Oncology and Regional Cancer Center, Hyderabad, India		Acceptable

Study 591-13: "A multicenter, open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, cross-over bioequivalence study of Doxorubicin Hydrochloride Liposome Injection 20 mg/10 mL (2 mg/mL) of Dr. Reddy's Laboratories Ltd, India, with that of Doxorubicin Hydrochloride Liposome Injection 20 mg/10 mL (2 mg/mL), Manufactured by: Sun Pharmaceutical Ind. Ltd, India; Distributed by: Caraco Pharmaceutical Laboratories, Ltd., Detroit, MI 48202 in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug under fasting condition"

Study Dates: 12/09/14-04/03/15

Inspection:

ORA investigators Sunitha K. Rajaram and Vickie J Kanion audited the clinical portion of study 591-13 at Erode Cancer Centre during January 25-29, 2016 and at MNJ Institute during February 01-04, 2016, respectively. The audits included thorough reviews and examination of the facilities, personnel records, protocols, subject consent forms, subject records, test article accountability, and interviews and discussions with each site's management and staff. Reserve samples were collected at Erode Cancer Centre only. Reserve samples at MNJ Institute were not collected because the site shipped reserve samples to a 3rd party storage facility. Following the inspections, no Form FDA 483 was issued at Erode Cancer Centre or at MNJ Institute.

Conclusion:

Following evaluation of inspectional findings and the EIRs, this

reviewer concludes that data from the audited study at Erode Cancer Centre and MNJ Institute are reliable. Therefore, this reviewer recommends that the clinical portion of study 591-13 conducted at Erode Cancer Centre and MNJ Institute be accepted for further Agency review.

Xiaohan Cai, Ph.D.
OSIS, DGDBE

Final Site Classification:

NAI - Erode Cancer Centre Pvt. Ltd., Erode, India

FEI: 3009574457

NAI - MNJ Institute of Medical Oncology and Regional Cancer Center, Hyderabad, India

FEI: 3009078979

CC:

OSIS/Kassim/Taylor/Haidar/Miller/Nkah/Fenty-Stewart/Kadavil

OSIS/DGDBE/Cho/Skelly/Choi/Cai

OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

OGD/OB/Conner

ORA/SEA/Harris/Rajaram

ORA/KAN-DO/Hall/Kanion

ORAHQ/OMPTO/DMPTI/BIMO/Bukowczyk/Arline/Montemurro/Colon

Draft: XHC 04/18/2016; XHC 5/24/16

Edit: YMC 4/28/2016; MFS 5/24/16; JC 5/25/16

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/Erode Cancer Centre, Thindal, India/ANDA208657_Doxorubicin Liposome Injection

Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/MNJ Institute of Oncology-Hyderabad-India/ANDA208657_Doxorubicin Liposome Injection

OSI file# BE6993

FACTS: **11583191**

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

DATE: August 2, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Review of Establishment Inspection Report covering studies BP-1201 and 591-13 submitted to ANDA 205990 and ANDA 208657, respectively for Imatinib Mesylate 400 mg Immediate Release Tablet sponsored by Breckenridge Pharmaceuticals, Inc., USA and Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) sponsored by Dr. Reddy's Laboratories Ltd., India.

Inspection Summary:

This was a FY 2016 GDUFA in vivo bioequivalence site inspection. The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of studies BP-1201 and 591-13 conducted at Bibi Clinical Research Department, Hyderabad, India.

At the conclusion of the inspection, a significant issue was observed and Form FDA 483 was issued. The final classification for this inspection is official action indicated (OAI) because the firm failed to retain reserve samples for test article and reference drug product provided by the sponsor for bioequivalence (BE) testing [21 CFR 320.38/63]. This issue affected study BP-1201 only.

After reviewing the inspectional findings, I recommend that the data from study 591-13 be accepted for further Agency review. The data from the clinical portion of study BP-1201 conducted at Bibi Clinical Research Department should not be accepted for further Agency review.

Scope of the Inspection:

ANDA 205990:

Study Number: BP-1201

Study Title: "A prospective, open-label, randomized, multiple dose, two way crossover study, to compare the steady state bioequivalence of Imatinib Mesylate 400 mg Immediate Release Tablet manufactured by Stason Pharmaceuticals, Inc. Versus Gleevec[®] 400 mg Tablet manufactured by Novartis under fed conditions"

**Dates of
Clinical Study**

Conduct: January 28-July 18, 2013

ANDA 208657:

Study Number: 591-13

Study Title: "A multicenter, open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, cross-over bioequivalence study of Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) of Dr. Reddy's Laboratories Ltd., India with that of Doxorubicin HCl liposome injection 20 mg/10 mL (2 mg/mL); Manufactured by: Sun Pharmaceutical India Ltd., India; Distributed by: Caraco Pharmaceutical Laboratories, Ltd., Detroit, MI 48202 in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are already receiving or scheduled to start therapy with the reference list drug under fasting condition"

**Dates of
Study Clinical**

Conduct: July 3, 2014-April 9, 2015

The inspection of the clinical portion of above studies was conducted by the ORA Investigator Harry Brewer (NYK-DO) at Bibi Clinical Research Department, Hyderabad, India from March 28-April 1 and from April 4-7, 2016. The inspection included a thorough examination of the protocol, protocol amendments, study records,

informed consent forms, SOPs, IRB approvals, case report forms, and interviews/discussions with the firm's staff and management.

At the conclusion of the inspection, Form FDA 483 was issued to the firm (**Attachment-1**). The firm responded to Form FDA 483 on April 20, 2016 (**Attachment-2**). The Form FDA 483, the firm's response to Form FDA 483 and my evaluation follows.

- 1) **Samples of the test article and reference standard used in a bioequivalence study were not retained and released to FDA upon request as required in 21 CFR Part 320.38. Specifically, you received the test drug Imatinib Mesylate 400 mg (30 tablets) by Stason Pharmaceuticals and Reference Drug, Gleevec (Imatinib Mesylate 400 mg) (30 tablets) manufactured by Novartis Pharma Stein AG, on 01/17/13. You requested from the CRO an additional shipment of test and reference drugs in order to continue the dosing for fifth subject on 06/12/13. The remaining tablets (IPs-2 each) from the first shipment were used in the study and at the conclusion you returned to the CRO the remaining 25 tablets each from the second shipment on 08/13/13. You failed to retain the test articles from the first and second shipments which represented the test articles available during the study to the subjects.**

Firm's Response to Form FDA 483: The firm acknowledged the observation and stated that reserve samples were stored at the Site Management Organization (SMO) instead of storing them on site where the clinical study was conducted. Based on the previous FDA inspection conducted in August 2014, the firm revised their SOP to retain reserve samples for future BE studies at the third party site per regulatory requirements.

OSIS Assessment: The firm did not retain reserve samples of test and reference drug products used in study BP-1201 conducted during the period of January 28-July 18, 2013. Consequently, we cannot verify the authenticity of drug products used in study BP-1201. In contrast, the observation did not affect study 591-13. As a corrective action to a previous FDA 483 observation during an inspection of the site in August 2014, Bibi Clinical Research Department began retaining and storing reserve samples in a third party storage facility for studies conducted after September 2014. The reserve samples for study 591-13 were retained at a third party site under conditions consistent with product labeling. The reserve samples were returned to Bibi and collected by the FDA investigator.

The firm's response is adequate and provides sufficient details on how it plans to prevent recurrence of issues with reserve samples and comply with bioequivalence regulations in the future.

Recommendations:

After reviewing the EIR, inspectional observations, and the firm's response to Form FDA 483, I conclude that the clinical data generated from study BP-1201 are not reliable because the firm failed to retain reserve samples provided by the sponsor for bioequivalence testing [21 CFR 320.38(a)]. On the other hand, I recommend that the data from the clinical portion of study 591-13 be accepted for further Agency review.

Gajendiran Mahadevan, Ph.D.
DNDBE, OSIS

Final Classification:

Clinical Site:

OAI: Bibi Clinical Research Department, Hyderabad, India
FEI: 3003692761

CC:

OTS/OSIS/Kassim/Haidar/Taylor/Kadavil/Turner-Rinehardt/Fenty-
Stewart/Nkah/Miller/Johnson
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Mahadevan

CDER/OGD/OB/Conner

Draft: GM 07/21/2016
Edits: RCA 08/02/2016; AD 8/2/2016

BE File #: 6967 (ANDA 205990); 6993 (ANDA 208657);
O: BE\EIRCOVER\205990 and 208657.ima.dox.bib
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/
Clinical Site/Bibi Clinical Research Department, Hyderabad, India
/ANDA 205990_Imatinib Mesylate/ANDA 208657_Doxorubicin HCl

FACTS: 11574394

Gajendiran Mahadevan -S

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Gajendiran Mahadevan, Ph.D.

Ruben C. Ayala -S

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Ruben Ayala, Pharm.D.

Arindam Dasgupta -S

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Arindam Dasgupta, Ph.D.

M E M O R A N D U M

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

DATE: June 9, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering ANDA 208657 for a clinical
inspection conducted at Curie Manavata Cancer Centre,
Nashik, India

Recommendations:

The Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS) arranged an inspection of the following clinical study at Curie Manavata Cancer Centre, Nashik, India (Curie Manavata). This reviewer recommends that the clinical portion of study 591-13 conducted at Curie Manavata be accepted for further Agency review.

Application	Study	Study Site	Sponsor	Recommend
ANDA 208657	591-13	Curie Manavata Cancer Centre, Nashik, India	Dr. Reddy's Laboratories Ltd., India	Acceptable

Study 591-13: "A multicenter, open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, cross-over bioequivalence study of Doxorubicin Hydrochloride Liposome Injection 20 mg/10 mL (2 mg/mL) of Dr. Reddy's Laboratories Ltd, India, with that of Doxorubicin Hydrochloride Liposome Injection 20 mg/10 mL (2 mg/mL), Manufactured by: Sun Pharmaceutical Ind. Ltd, India; Distributed by: Caraco Pharmaceutical Laboratories, Ltd., Detroit, MI 48202 in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug under fasting condition"

Study Dates: 12/09/14-04/03/15

Inspection:

ORA investigator John A. Iwen audited the clinical portion of study 591-13 at Curie Manavata during April 11-15, 2016. The audit included a thorough review and examination of protocols, subject consent forms, subject records, and interviews and discussions with the site's management and staff. Reserve samples were collected for the audited study. Following the inspection, no Form FDA 483 was issued at Curie Manavata.

Conclusion:

Following evaluation of the EIR, this reviewer concludes that data from the audited study at Curie Manavata are reliable. Therefore, this reviewer recommends that the clinical portion of study 591-13 conducted at Curie Manavata be accepted for further Agency review.

Xiaohan Cai, Ph.D.
OSIS, DGDBE

Final Site Classification:

NAI - Curie Manavata Cancer Centre, Nashik, India
FEI: 3006429978

cc:

OSIS/Kassim/Taylor/Haidar/Miller/Nkah/Fenty-Stewart/Kadavil
OSIS/DGDBE/Cho/Choi/Skelly/Au/Cai
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OGD/OB/Conner

ORA/ KAN-DO/Hall/Iwen

Draft: XHC 6/6/16

Edit: YMC 6/8/16, JC 6/8/16

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL
SITES/Curie Manavata Cancer Center, India/ANDA208657_Doxorubicin
Liposome Injection

OSI file# BE6993

FACTS: **11583191**

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M E M O R A N D U M

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

DATE: June 4, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Ruben Ayala, Pharm.D.
Team Lead (Acting)
Division of New Drugs Bioequivalence Evaluation
Office of Study Integrity and Surveillance

and

Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Review of Establishment Inspection Report (EIR) Covering:

1. Study 14-VIN-060 Submitted to ANDA 208429, Imatinib Mesylate 400 mg Tablet Sponsored by Wockhardt Ltd., India
2. Study 14-VIN-106 Submitted to ANDA 208302, Imatinib Mesylate 400 mg Tablet Sponsored by Shilpa Medicare Ltd., India
3. Study 591-13 Submitted to ANDA 208657, Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) sponsored by Dr. Reddy's Laboratories Ltd., India

Inspection Summary:

This was a FY 2015 GDUFA in vivo bioequivalence clinical site inspection. The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of studies 14-VIN-

Page 2 - ANDA 208429, Imatinib Mesylate 400 mg Tablet Sponsored by Wockhardt Ltd., India; ANDA 208302, Imatinib Mesylate 400 mg Tablet Sponsored by Shilpa Medicare Ltd., India; ANDA 208657, Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) sponsored by Dr. Reddy's Laboratories Ltd., India

060, 14-VIN-106, and 591-13 conducted at Srinivasam Cancer Care Hospitals India Pvt. Ltd., Bangaluru, India.

At the conclusion of the inspection, deficiencies were observed and a one-item Form FDA 483 was issued. The final classification for this inspection is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings, I recommend that the data from the clinical portion of studies 14-VIN-060, 14-VIN-106, and 591-13 conducted at Srinivasam Cancer Care Hospitals India Pvt. Ltd., be accepted for further Agency review.

Scope of the Inspection:

ANDA 208429

Study Number: 14-VIN-060

Study Title: "A multicenter, open-label, randomized, balanced, two-treatment, two-period, two-sequence, two-way, crossover, multiple dose, comparative oral bioavailability study of Imatinib Mesylate Tablets 400 mg of Wockhardt Limited, India with Gleevec[®] (Imatinib Mesylate) Tablet 400 mg of Novartis Pharmaceuticals Corporation, East Hanover, NJ in adult human patients with chronic myeloid leukemia and/or gastrointestinal stromal tumor under fed steady-state condition."

Dates of

Study Conduct: September 6 - November 9, 2014

ANDA 208302

Study Number: 14-VIN-106

Study Title: "A multicenter, open-label, randomized, balanced, two-treatment, two-period, two-sequence, two-way, crossover, multiple dose, comparative oral bioavailability study of Imatinib Mesylate Tablets 400 mg of Shilpa Medicare Limited, India with Gleevec[®] (Imatinib Mesylate) Tablet 400 mg of Novartis Pharmaceuticals Corporation, East Hanover, NJ in adult human patients with chronic myeloid leukemia and/or gastrointestinal stromal tumor under fed steady-state condition."

Dates of

Study Conduct: November 1-December 26, 2014

Page 3 - ANDA 208429, Imatinib Mesylate 400 mg Tablet Sponsored by Wockhardt Ltd., India; ANDA 208302, Imatinib Mesylate 400 mg Tablet Sponsored by Shilpa Medicare Ltd., India; ANDA 208657, Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) sponsored by Dr. Reddy's Laboratories Ltd., India

ANDA 208657

Study Number: 591-13

Study Title: "A multicenter, open-label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) of Dr. Reddy's Laboratories Ltd., India with that of Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL), manufactured by Sun Pharmaceutical India Ltd., India distributed by Caraco Pharmaceutical Laboratories, Ltd., Detroit, MI 48202 in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug under fasting condition."

Dates of

Study Conduct: July 3, 2014 - April 9, 2015

Investigator Jennifer Johnson (FDA, India Office) inspected the clinical portion of above studies at Srinivasam Cancer Care Hospitals India Pvt. Ltd., Bangaluru, India during January 11-15, 2016. The inspection included a thorough examination of the protocol, protocol amendments, study records, case histories, informed consent forms, IRB approvals and correspondence, test article accountability, dispensation and storage, handling of biological samples, equipment calibration, employee training records, SOPs, case report forms, and interviews/discussions with the firm's staff and management.

At the conclusion of the inspection, deficiencies were observed and a one-item Form FDA 483 was issued to the firm (**Attachment-1**). The firm stated that it will not submit a response to the Form FDA 483. My evaluations of the deficiencies are following.

Observation 1:

- 1) **Failure to prepare or maintain case histories with respect to observations and data pertinent to the investigation. Specifically,**

Page 4 - ANDA 208429, Imatinib Mesylate 400 mg Tablet Sponsored by Wockhardt Ltd., India; ANDA 208302, Imatinib Mesylate 400 mg Tablet Sponsored by Shilpa Medicare Ltd., India; ANDA 208657, Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) sponsored by Dr. Reddy's Laboratories Ltd., India

Study 14-VIN-106: The site failed to maintain source documentation for the following information reported in the case Report Forms:

-Screening urine drug testing for 7 of 7 subjects

reviewed: [REDACTED] (b) (6)
[REDACTED] (b) (6).

Urine drug tests are used to determine subject eligibility.

-Urine pregnancy tests for 1 of 2 subjects of childbearing potential reviewed: [REDACTED] (b) (6)

[REDACTED]. The investigational product is Pregnancy Category D.

Study 14-VIN-060: The site failed to maintain a signed Informed Consent Document for Subject [REDACTED] (b) (6). The subject was randomized on [REDACTED] (b) (6).

The site failed to maintain source documentation for the following information reported in the Case Report Forms:
Day 0 urine drug testing for 8 of 8 subjects: [REDACTED] (b) (6)

[REDACTED] (b) (6)
[REDACTED] (b) (6). Urine drug tests are used to determine subject eligibility.

Firm's Response to Form FDA 483: During the closeout meeting, the Principal Investigator stated that he will not submit a response to the Form FDA 483.

OSIS Assessment of Observation for Study 14-VIN-106: The study protocol (Section 10.2, exclusion criterion #25) states that "positive results for drugs of abuse (benzodiazepines, opioids, amphetamines, cannabinoids, cocaine, and barbiturates) in urine tests on Day 0, Day 5, and Day 13 determine subject eligibility."

The firm appears to have conducted urine tests on all seven subjects mentioned above; however, source documents were not available during the inspection because the Contract Research Organization [REDACTED] (b) (4) monitoring the study, took them away and destroyed them. The firm did maintain a photocopy of Day 13 test results from subject [REDACTED] (b) (6), which match the results in the subject's CRF. Therefore, urine test results submitted to FDA appear to be valid despite the absence of source documents at the firm.

Page 5 - ANDA 208429, Imatinib Mesylate 400 mg Tablet Sponsored by Wockhardt Ltd., India; ANDA 208302, Imatinib Mesylate 400 mg Tablet Sponsored by Shilpa Medicare Ltd., India; ANDA 208657, Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) sponsored by Dr. Reddy's Laboratories Ltd., India

The study protocol (Section 10.2, exclusion criterion #5) states that female subjects who are pregnant, breast-feeding, or have a positive pregnancy test at baseline and throughout the study are excluded from the study. According to CRF, female subject (b) (6) tested negative for urine pregnancy at screening, Day 1, Day 5, and Day 13, but the source documents were not available during the inspection. The firm did maintain a photocopy of Day 1 test results from subject (b) (6), which match the results in the subject's CRF. Therefore, pregnancy test results submitted to FDA appear to be valid despite the absence of source documents at the firm.

OSIS Assessment for Study 14-VIN-060: Informed Consent Form (ICF) of Subject (b) (6) was not maintained at the clinical site; however, an audio-visual recording of subject's consent provided during the investigation was sufficiently valid enough to accept the data of this subject despite of the misplacement of one informed consent document at the clinical site.

According to subject eligibility criteria (Study Protocol, Section 10.2, exclusion criterion #25), the firm appears to have performed urine drug screening tests for all eight subjects reported in the observation; however, not maintained the source documents tested for all three days. The firm did archive photocopy of screening kit tested on Day 0 along with respective ICF of subjects that matched the identification number noted on the ICFs. Therefore, screening test results submitted to the Agency appear to be valid despite the absence of source documents at the firm.

The firm decided not to respond to the Form FDA 483 on how it plans to prevent future recurrence of the deficiencies; however, the ORA investigator emphasized the importance of maintaining the source documents at the clinical firm by the principal investigator.

Recommendations:

After reviewing the EIR, inspectional findings and observations, I conclude that the clinical data generated by Srinivasam Cancer Care Hospitals India Pvt. Ltd., Bangaluru, India for studies 14-VIN-060, 14-VIN-106, and 591-13 be accepted for further Agency review.

Gajendiran Mahadevan, Ph.D.
DNDBE, OSIS

Page 6 - ANDA 208429, Imatinib Mesylate 400 mg Tablet Sponsored by Wockhardt Ltd., India; ANDA 208302, Imatinib Mesylate 400 mg Tablet Sponsored by Shilpa Medicare Ltd., India; ANDA 208657, Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) sponsored by Dr. Reddy's Laboratories Ltd., India

Final Classification:

Clinical Site:

VAI: Srinivasam Cancer Care Hospitals India Pvt. Ltd., Bangaluru, India

FEI: 3006585888

CC:

OTS/OSIS/Kassim/Taylor/Haidar/Kadavil/Fenty-Stewart/Nkah/Miller/Johnson

OTS/OSIS/DGDBE/Cho/Skelly/Choi

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Mahadevan

CDER/OGD/OB/Conner

Draft: GM 05/24/2016

Edits: RCA 05/31/2016, 6/3/2016; AD 5/3/2016

BE File #: 6916(ANDA 208429); 6891(ANDA 208302); 6993(ANDA 208657)
O:BE\EIRCOVER\208429.ima.woc; \208302.ima.shi; \208302.dox.red;
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/
Clinical Site/ Srinivasam Cancer Care Hospitals India Pvt. Ltd.,
Bangaluru, India/ANDA 208429_Imatinib Mesylate; ANDA 205990_Imatinib
Mesylate; ANDA 208302_Doxrubicine

FACTS: 11540258 (ANDA 208429); 11529792 (ANDA 208302); 11529792
(ANDA 208657)

Page 7 - ANDA 208429, Imatinib Mesylate 400 mg Tablet Sponsored by Wockhardt Ltd., India; ANDA 208302, Imatinib Mesylate 400 mg Tablet Sponsored by Shilpa Medicare Ltd., India; ANDA 208657, Doxorubicin HCl Liposome Injection 20 mg/10 mL (2 mg/mL) sponsored by Dr. Reddy's Laboratories Ltd., India

**Gajendiran
Mahadevan -S**

Digitally signed by Gajendiran Mahadevan -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000820927,
cn=Gajendiran Mahadevan -S
Date: 2016.06.04 09:11:49 -04'00'

Gajendiran Mahadevan, Ph.D.

Ruben C. Ayala -S

Digitally signed by Ruben C. Ayala -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Ruben C. Ayala -S,
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Date: 2016.06.04 20:59:34 -04'00'

Ruben Ayala, Pharm.D.

Arindam Dasgupta -S

Digitally signed by Arindam Dasgupta -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=0012329705, cn=Arindam Dasgupta -S
Date: 2016.06.04 21:30:20 -04'00'

Arindam Dasgupta, Ph.D.

M E M O R A N D U M

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

DATE: May 25, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering ANDA 208657 for clinical
inspections conducted at Erode Cancer Centre Pvt.
Ltd., Erode, India and MNJ Institute of Medical
Oncology and Regional Cancer Center, Hyderabad, India

Recommendations:

The Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS) arranged inspections of the following clinical study at Erode Cancer Centre Pvt. Ltd., Erode, India and MNJ Institute of Medical Oncology and Regional Cancer Center, Hyderabad, India (MNJ Institute). This reviewer recommends that the clinical portion of study 591-13 conducted at Erode Cancer Centre and MNJ Institute be accepted for further Agency review.

M E M O R A N D U M

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

DATE: April 13, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Hasan Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of Establishment Inspection Report (EIR)
Covering ANDA 208657, Doxorubicin Hydrochloride Liposome
injection (2mg/ml), by Dr. Reddy's Laboratories Ltd.

SUMMARY:

Based on the review of inspectional outcomes, this OSIS reviewer recommends that the data from the clinical portion of Study **591-13** (ANDA 208657) conducted at (1) **Acharya Harihar Regional Cancer Center**, Department of Radiation Oncology, Odisha India, (2) **Cancer Clinic & Nursing Home**, Maharashtra, India, and (3) **Meenakshi Mission Hospital & Research Center** Tamil Nadu, India be accepted for further Agency review.

Study audited during the inspections

ANDA 208657

Study Number: 591-13
Study Title: "A multicenter, open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, cross-over bioequivalence study of Doxorubicin Hydrochloride Liposome Injection 20mg/10mL (2mg/mL) of Dr. Reddy's Laboratories Ltd, India, with that of Doxorubicin Hydrochloride Liposome Injection 20mg/10mL (2mg/mL), Manufactured by: Sun Pharmaceutical Ind. Ltd, India; Distributed by: Caraco Pharmaceutical

Laboratories, Ltd., Detroit, MI 48202 in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug under fasting condition"

ORA investigators audited the clinical portion of Study 591-13 at the following facilities (Table 1).

Table 1. Inspected Sites

Site Name	Study Date	Inspection Date	ORA Investigator	483 issued ?	Reserve Samples Collected?
Acharya Harihar Regional Cancer Center, Department of Radiation Oncology Clinical Research Cell, 2nd Fl, Annex Bldg, Medical Rd, Mangalabag, Cuttack, Odisha, 753007, INDIA	07/03/2014 to 05/09/2015	2/15/2016, 2/16/2016, 2/17/2016	Joy P. Matthias	NO	NO
Cancer Clinic & Nursing Home, Block No. 4-B, Hyatt Medicare, Plot No. 12 /2, Dr. N. B. Khare Marg, Dhantoli, Nagpur - 440 012, Maharashtra, India.	07/03/2014 to 05/09/2015	1/27/2016, 1/28/2016, 1/29/2016	Vickie J Kanion	NO	NO
Meenakshi Mission Hospital & Research Center, Lake Area, Melur Road, Madurai - 625 107, Tamil Nadu, India	07/03/2014 to 04/09/2015	2/1/2016, 2/2/2016, 2/3/2016	Sunitha Rajaram	NO	YES

At each clinical site, the audit included a review of a business organization, a thorough examination of study records, including source documents, case report forms (CRFs), concomitant medications, number of evaluable subjects, drug accountability, sample collection and traceability, clinical operations, communications between the CRO and the sponsor, dosing logs, and informed consent.

Reserve samples were collected only at Meenakshi Mission Hospital & Research Center. However, ORA investigators verified that each site (b) (4) third party, (b) (4) for storage at the conclusion of the study.

No objectionable conditions were observed during the inspections at any of the three sites above. At the conclusion of the inspections, ORA investigators did not issue Form FDA 483.

Conclusions:

Following a review of establishment inspectional reports (EIRs) and documentation for reserve samples and their storage, the data submitted to the Agency under Study 591-13 are found reliable. Therefore, this OSIS/DGDBE reviewer recommends that the results from the clinical portion of Study 591-13 conducted at Acharya Harihar Regional Cancer Centre, Cancer Clinic & Nursing Home, and Meenakshi Mission Hospital & Research Center be accepted for further Agency review (Table 2).

Table 2. Final OSIS/DGDBE Recommendation

Site Name/FEI#/Classification	Accept study data for further Agency review?
Acharya Harihar Regional Cancer Center, Department of Radiation Oncology Odisha, 753007, INDIA 3010659357 NAI	YES
Cancer Clinic & Nursing Home, Nagpur, India 3012069635 NAI	YES
Meenakshi Mission Hospital and Research Centre, Madurai, India 3006720617 NAI	YES

Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

CC:
OSIS/Kassim/Taylor/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah/Johnson
OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Irier
OSIS/DNDBE/Bonapace/Arindam

Draft: HI 3/25/16, 4/12/16
Edit: YMC 4/12/16 JC 4/12/16

OSIS File#: BE6993
FACTS #: 11583191

Hasan Irier -S
Digitally signed by Hasan Irier -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Hasan Irier -S,
0.9.2342.19200300.100.1.1=2001568214
Date: 2016.04.13 13:45:43 -04'00'

Seongeun N. Cho -S
Digitally signed by Seongeun N. Cho -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
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cn=Seongeun N. Cho -S
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M E M O R A N D U M

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

DATE: April 17, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Hasan Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of Establishment Inspection Report (EIR)
covering ANDA 208657, Doxorubicin Hydrochloride Liposome
injection (2mg/ml) by Dr. Reddy's Laboratories Ltd.

SUMMARY:

Based on the review of an inspectional outcome, this OSIS reviewer recommends that the data from the clinical portion of Study **591-13** (ANDA 208657) conducted at **Nirmal Hospital Pvt Ltd, Surat, Gujarat, India** be accepted for further Agency review.

Study audited during inspection

ANDA 208657

Study Number: 591-13

Study Title: "A multicenter, open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, cross-over bioequivalence study of Doxorubicin Hydrochloride Liposome Injection 20mg/10mL (2mg/mL) of Dr. Reddy's Laboratories Ltd, India, with that of Doxorubicin Hydrochloride Liposome Injection 20mg/10mL (2mg/mL), Manufactured by: Sun Pharmaceutical Ind. Ltd, India; Distributed by: Caraco Pharmaceutical Laboratories, Ltd., Detroit, MI 48202 in ovarian cancer patients whose disease has progressed or recurred after platinum based chemotherapy and who are

already receiving or scheduled to start therapy with the reference listed drug under fasting condition"

Study Dates: 07/03/2014 to 04/09/2015

ORA investigator Sunitha Rajaram, Ph.D. (Resident Post, Puget Sounds, WA) audited the clinical portion of Study 591-13 at the following facility (**Table 1**).

Table 1. Inspected Site

Site Name	Inspection Date	ORA Investigator	483 issued?
Nirmal Hospital Pvt Ltd Ring Rd, Civil Street; Near Kadiwala School; Surat 395 002; Gujarat, Indi	1/28/2016, 1/29/2016, 2/1/2016, 2/2/2016, 2/3/2016, 2/4/2016, 2/5/2016	Sunitha Rajaram	NO

During this inspection, ORA investigator reviewed and examined all informed consent documents, drug accountability, ethics committee approvals, monitoring documents, financial disclosure, training, source documents, inclusion/exclusion criteria, hospital records pertaining to the subjects enrolled, e-CRFs adverse event reporting and serious adverse event reporting. All files of the subjects enrolled in the study at the Nirmal Hospital Pvt Ltd were reviewed in their entirety. No discrepancies were noted between documentation of the source documents and the data listing information in the assignment materials. No adverse events nor protocol deviations were discovered that had not been reported previously. Reserve samples were collected by the ORA investigator during the inspection, and the collected reserve samples were submitted to CDER - Division of Pharmaceutical Analysis (DPA).

No objectionable conditions were observed during the inspection. At the conclusion of the inspection, ORA investigator did not issue Form FDA 483.

Conclusions:

Following a review of establishment inspectional report (EIR) and documentation for reserve samples and their storage, the data submitted to the Agency under Study 591-13 are found reliable. Therefore, this OSIS/DGDBE reviewer recommends that the results from

the clinical portion of Study 591-13 conducted at **Nirmal Hospital Pvt Ltd** be accepted for further Agency review (**Table 2**).

Table 2. Final OSIS/DGDBE Recommendation

Site Name/FEI#/Classification	Accept study data for further Agency review?
Nirmal Hospital Pvt Ltd, Surat; Gujarat, India 1000600925 NAI	YES

Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

CC:
OSIS/Kassim/Taylor/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah/Johnson
OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Irier
OSIS/DNDBE/Bonapace/Arindam

Draft: HI 04/15/16
Edit: YMC 04/15/16; JC 04/15/16

OSIS File#: BE6993
FACTS #: 11583191

Hasan Irier -S

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ou=FDA, ou=People, cn=Hasan Irier -S,
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Date: 2016.04.17 22:13:51 -04'00'

Seongeun
N. Cho -S

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0.9.2342.19200300.100.1.1=200033697
8, cn=Seongeun N. Cho -S
Date: 2016.04.18 07:15:17 -04'00'

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208657

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Approval Type: <input checked="" type="checkbox"/> FULL APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH)		
RPM: Dara Nardini Team: HC- Presto		Approval Date: 5/15/2017
<input checked="" type="checkbox"/> PI <input type="checkbox"/> PII <input type="checkbox"/> PIII <input type="checkbox"/> PIV (eligible for 180 day exclusivity) <input type="checkbox"/> Yes <input type="checkbox"/> No) <input type="checkbox"/> MOU <input checked="" type="checkbox"/> RX or <input type="checkbox"/> OTC		
ANDA #: 208657 Applicant: Dr. Reddy's Laboratories Limited Established Product Name: Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL) Single-dose Vials		
Basis of Submission (RLD): 50718/ Doxil Liposome Injection/ Janssen Research and Development, LLC. (Is ANDA based on an approved Suitability Petition? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No)		
Does the ANDA contain REMS? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No (If YES, initiate approval action 6 weeks prior to target action date)		
Regulatory Project Manager Evaluation:		Date: 5/4/2017
<input type="checkbox"/> Previously reviewed and tentatively approved (if applicable) --- Date N/A		
Date of Application 10/8/2015	Original Received Date 10/8/2015	Date Acceptable for Filing 10/8/2015
YES	NO	DMF (b) (4) - AQ NAI 12/23/16
<input checked="" type="checkbox"/>	<input type="checkbox"/>	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A) Date of Acceptable Quality 5/10/2017 Date of Acceptable Dissolution 3/28/2017 Date of Acceptable Bioequivalence 6/24/2016 Date of Acceptable Labeling 10/13/2016
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Was a CR issued throughout the life of the ANDA? If Yes, date last CR letter was issued: 12/27/2016
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Are consults pending for any discipline?
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES → Verify a second filing review was completed and that all disciplines completed new reviews <input type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Is there a pending Citizen Petition (CP)?
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: 5/8/2017
<input checked="" type="checkbox"/>	<input type="checkbox"/>	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed Enter Date
Draft Approval/Tentative Approval Letter		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task
Review Discipline/Division Endorsements		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Division of Legal and Regulatory Support Endorsement completed, Date 5/11/2017
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Paragraph IV Evaluation completed (if applicable), Date N/A
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Quality Endorsement completed, Date 5/15/2017
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Bioequivalence Endorsement completed, Date 5/15/2017
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Labeling Endorsement completed, Date 5/10/2017
<input type="checkbox"/>	<input checked="" type="checkbox"/>	REMS Endorsement (if applicable), Date N/A
RPM Team Leader Endorsement and Action Package Verification		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	RPM Team Leader Endorsement completed, Date 5/15/2017
Final Decision and Letter Sign-off		

Lead Division: Program Management **Effective Date:** 10/1/2014 Page 1 of 10

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:
[OGD QMS Approved Documents](#)



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

<input checked="" type="checkbox"/>	<input type="checkbox"/>	Final Decision recommending approval/tentative approval completed, Date 5/15/2017
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter electronically signed, Date: 5/15/2017
<u>Project Close-Out</u>		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Notify applicant of approval and provide a courtesy copy of the electronically signed letter
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed <u>Enter Date</u>
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information

This page to be completed by the RPM

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 5/11/2017

Name/Title: MHS

Contains GDEA certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Pediatric Exclusivity System RLD = _____ NDA# _____ Date Checked _____ Nothing Submitted <input type="checkbox"/> Written request issued <input type="checkbox"/> Study Submitted <input type="checkbox"/>
(required if sub after 6/1/92)	
Patent/Exclusivity Certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	
If Para. IV Certification- did applicant:	
Notify patent holder/NDA holder Yes <input type="checkbox"/> No <input type="checkbox"/>	
Was applicant sued w/in 45 days: Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has case been settled: Yes <input type="checkbox"/> No <input type="checkbox"/>	
Date settled:	
Is applicant eligible for 180 day	
Is a forfeiture memo needed: Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Type of Letter:	
<input checked="" type="checkbox"/> APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH)	
<input type="checkbox"/> OTHER:	
Comments:	
ANDA submitted on 10/8/2015, BOS= NDA 50718 Doxil, no relevant patent statement provided. ANDA ack for filing on October 8, 2015 for the 2 mg/mL, 10 mL and 25 mL (b) (4) vial products.	
There are no remaining unexpired patents or exclusivities listed for the RLD Doxil. This ANDA is eligible for immediate Final AP.	

Lead Division: Program Management **Effective Date:** 10/1/2014

Page 2 of 10

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:

[OGD QMS Approved Documents](#)



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

2. **Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

3. **Quality Endorsement by the Office of Pharmaceutical Science**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

4. **Bioequivalence Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

5. **Labeling Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

6. **REMS Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

7. **RPM Team Leader Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

8. Final Decision

Date: 5/15/2017

Name/Title: cah

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
First Generic Approval
PD or Clinical for BE
Special Scientific or Reg. Issue

Date PETS checked for first generic drug _____

Comments:

ANDA received on 10/8/2015. The BOS= NDA 050718; Doxil, Janssen Research and Development LLC. The applicant provided a "no relevant patent" certification. There are no new or unexpired patents/exclusivities listed in the OB for this NDA (5/15/17). There are no issues listed on the policy alert list (5/8/17). Bio – Fasting study (50 mg/25 mL) and liposome size distribution study completed on the 2 mg/mL. Bio- is adequate per Harigaya on 6/24/16. Bio addendum completed by Harigaya/Chandaroy on 5/15/17 states Bio is adequate despite the OAI outcome for clinical site A. This site is tied to a different ANDA and drug product. Bio endorsement completed by Jiang on 5/15/17. Labeling is adequate per Kim/Jung on 10/13/16. Labeling endorsement completed by Jung on 5/10/17. OSIS memos dated 4/13/16 (Irier/Cho), 4/18/16 (Irier/Cho), 4/27/16 (Zhang/Dasgupta), 4/26/16 (Choi/Gupta/Cho), 5/25/16 (Cai/Cho), 6/4/16 (Mahadevan/Ayala/Dasgupta), 6/9/16 (Cai/Cho), 8/2/16 (Mahadevan/Ayala/Dasgupta) state the clinical portion should be accepted for further review. IQA completed for this ANDA – overall adequate per Zhang on 5/13/17 (Biopharmaceutics is adequate per Li/Eradiri/Zhang on 5/15/17; Drug Product is adequate per Zhang on 5/8/17; micro is adequate per Tiwari/Bhattacharya on 11/3/16, DMFs (b) (4) are adequate on 12/23/16 ((b) (4)), 10/27/16 ((b) (4)), and 6/17/15 ((b) (4)). The QE checklist was completed by Pleas/Simamora on 5/15/17. The checklist indicates OPQ reviews remain adequate including DMF and facilities. The quality endorsement was completed by Simamora on 5/15/17. The overall manufacturing inspection recommendation is approve (see screen shots below – there are no visible alerts in the platform at the time of this action). This ANDA is ready for Full Approval.

Lead Division: Program Management **Effective Date:** 10/1/2014

Page 4 of 10

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

Please ensure you are using the most current version of this Form. It is available at:

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Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

(b) (4)

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

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Title: Approval Routing Summary Form	Author: Heather Strandberg	

EES DATA:

Click here to enter text.



(b) (4)

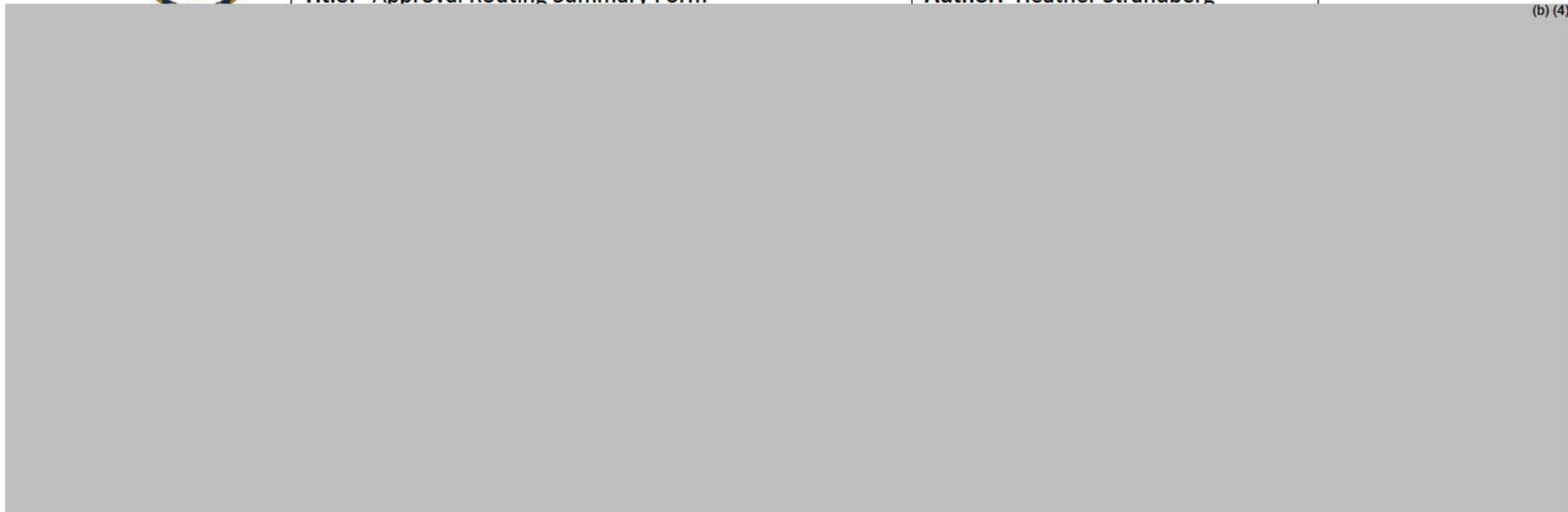
Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

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(b) (4)



Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

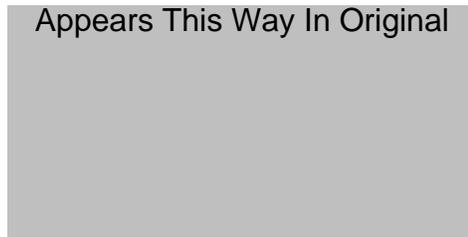
Please ensure you are using the most current version of this Form. It is available at:
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Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Application History:
Click here to enter text.

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Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

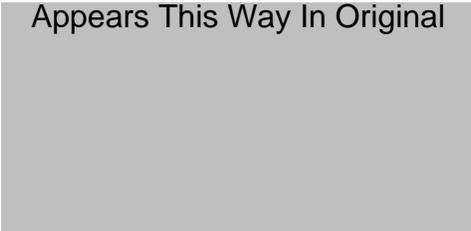


Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Orange Book Report:

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Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
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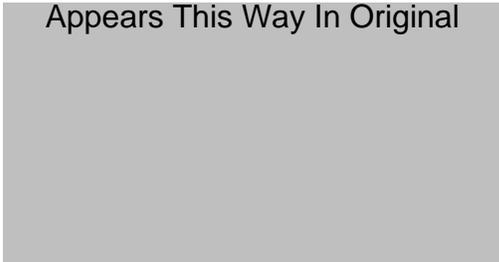
REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form

Appears This Way In Original





ANDA 208657

INFORMATION REQUEST

Dr. Reddy's Laboratories, Inc.
US Agent For Dr. Reddy's Laboratories Limited
Attention: Srinivasa Rao
Vice President and Head, Regulatory Affairs - North America
107 College Road East
Princeton, NJ 08540

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated October 8, 2015, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Doxorubicin Hydrochloride Liposome Injection, 20mg/10mL and 50mg/25mL.

We also refer to your February 16, 2017 submission, containing Quality Information.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 1 day, in order to continue our evaluation of your ANDA.

List of the Deficiencies:

A. Process

1.

2.

(b) (4)

If you do not submit a complete response by May 11, 2017 the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Please note, if information or data submitted exceeds the data requested in the IR/ECD this may result in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA).

If the submitted data is determined to be a tier 2 unsolicited amendment, this may affect the goal date.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Christina Pleas, Regulatory Business Process Manager, at 240-402-2873.

Sincerely,

Christina Pleas -S

Digitally signed by Christina Pleas, DN: cn=Christina Pleas, o=FDA, ou=FDA, email=christina.pleas@fda.hhs.gov

Christina Pleas, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



ANDA 208657

INFORMATION REQUEST

Dr. Reddy's Laboratories, Inc.
U.S. Agent For: Dr. Reddy's Laboratories Limited
Attention: Srinivasa Rao, Senior Director and Head Regulatory Affairs - North America
107 College Road East
Princeton, NJ 08540

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated October 8, 2015, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Doxorubicin Hydrochloride Liposome Injection, 20mg/10mL and 50mg/25mL.

We also refer to your February 16, 2017 submission, containing quality information.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 3 days, (Note for ANDA products: in general the requested date should not exceed 30 days per SOP 2501.01: Process for Issuing Deficiencies and Information Requests for Generic Drug Chemistry Review) in order to continue our evaluation of your ANDA.

List of the Deficiencies:

A. Biopharmaceutics

The proposed in vitro release acceptance criteria are permissive and not acceptable. Based on your batch release data and the new in vitro release data provided for batch (b) (4), we recommend that you implement the following acceptance criteria for your proposed drug product, and provide the revised specification table with the updated acceptance criteria for the in vitro release test.

Time	% released
2 hr	(b) (4) %
4 hr	(b) (4) %
8 hr	NLT (b) (4) %

If you do not submit a complete response by March 23, 2017 the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Please note, if information or data submitted exceeds the data requested in the IR/ECD this may result in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA).

If the submitted data is determined to be a tier 2 unsolicited amendment, this may affect the goal date.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Christina Pleas, Regulatory Business Process Manager, at 240-402-2873.

Sincerely,

Christina Pleas -S

Digitally signed by Christina Pleas, S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=HQ/OPD,
e=9.2342.10200390.100.1.1-201710492_cn=Christina.Pleas.S
Date: 2017.03.17 19:03:07 -0400

Christina Pleas, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



ANDA 208657

INFORMATION REQUEST

Dr. Reddy's Laboratories Inc.
U.S. Agent for: Dr. Reddy's Laboratories Limited
Attention: Srinivasa Rao, Senior Director & Head Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated October 8, 2015, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Doxorubicin Hydrochloride Liposome Injection, 20mg/10ml and 50mg/25ml.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 30 days, (Note for ANDA products: in general the requested date should not exceed 30 days per SOP 2501.01: Process for Issuing Deficiencies and Information Requests for Generic Drug Chemistry Review) in order to continue our evaluation of your supplemental ANDA.

List of the Deficiencies:

A. Drug Substance

1.

2.

(b) (4)

Send your submission through the Electronic Submission Gateway <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Christina Pleas, Regulatory Business Project Manager, at 240-402-2873.

Sincerely,

Christina Pleas -S

2025 RELEASE UNDER E.O. 14176

Christina Pleas, PharmD
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

EASILY CORRECTABLE DEFICIENCY

208657

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Dr. Reddy's Laboratories Limited

ATTN: Srinivasa Rao

Email: srao@drreddys.com

FROM: Danielle Russell

FDA CONTACT PHONE: 240-402-8772

Dear Sir or Madam:

This communication is in reference to your abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Doxorubicin Hydrochloride Liposome Injection, 20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL) Single-dose Vials .

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**EASILY CORRECTABLE DEFICIENCY
LABELING**

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Labeling Project Manager, Danielle Russell at 240-402-8772.

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.

We have completed our review and have the following comments:

Labeling Deficiencies determined based on your submission dated October 8, 2015:

1. GENERAL COMMENTS

- a. We strongly encourage you to assign different numbers for the Product Code, the middle digits of the NDC number to differentiate the 20 mg and 50 mg containers and ensure that the container and carton labels and package insert are updated to reflect the new numbers. When injectable products contain the same product concentration but a different total amount of drug, each of these injectable products should have a different product code assigned to help healthcare practitioners distinguish the difference in total drug content.
- b. Please revise the package type term “^{(b) (4)}” to “Single-dose” throughout your labeling pieces. We refer you to Guidance for Industry “Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use”, which is available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>.

2. CONTAINER LABEL

- a. Relocate the company logo to the bottom of the label.
- b. We recommend increasing the prominence of the active moiety name “DOXOrubicin Hydrochloride”.
- c. Relocate “Cytotoxic Agent/ Must be diluted” to appear on the top of the side panel.
- d. Include “Single-Dose Vial. Discard unused portion” right below the strength statement.
- e. Revise to read “LIPOSOMAL FORMULATION-DO NOT SUBSTITUTE FOR DOXORUBICIN HCL”.
- f. Revise the storage statement to read “Refrigerate, 2° - 8°C (36° - 46°F). Do not Freeze.” and relocate to appear above the usual dosage statement on the side panel.
- g. ^{(b) (4)}

3. CARTON LABELING

- a. Relocate the company logo to the bottom of the label.
- b. Relocate “Sterile/ Cytotoxic Agent/ MUST BE DILUTED PRIOR TO ADMINISTRATION” to appear below the usual dosage statement on the side panel.
- c. Include “Single-Dose Vial. Discard unused portion” right below the strength statement.
- d. Revise to read “LIPOSOMAL FORMULATION-DO NOT SUBSTITUTE FOR DOXORUBICIN HCL”.
- e. Revise the storage statement to read “Refrigerate, 2° - 8°C (36° - 46°F). Do not Freeze.” and relocate to appear right below “FOR INTRAVENOUS INFUSION ONLY” on the principal display panel.
- f. ^{(b) (4)}

- g. Revise the listing of the ingredients by grouping them into an active ingredient, liposomal carriers and the rest of the ingredients to improve its clarity and readability (*i.e.*, Each mL contains doxorubicin HCl, 2 mg. PEGYLATED 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, approximately 2 mg; sucrose; histidine; and hydrochloric acid and/or sodium hydroxide).

4. PRESCRIBING INFORMATION

- a. HIGHLIGHTS, Limitation statement: Revise the presentation of the established name to appear in upper case letters as such: **“These highlights do not include all the information needed to use DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION safely and effectively. See full prescribing information for DOXORUBICIN HYDROCHLORIDE LIPOSOME INJECTION.”**
- b. 12.3 Pharmacokinetics, Table 8, third column: Revise (b) (4)” to read “0.004”.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

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

Sincerely,

**Danielle E.
Russell -S**

Digitally signed by Danielle E. Russell
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=20014010
90, cn=Danielle E. Russell -S
Date: 2016.03.21 15:17:22 -04'00'

Danielle E. Russell, PharmD
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research