

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 50-718/S-50

Trade Name: Doxil®

Generic Name: doxorubicin hydrochloride liposome injection

Sponsor: Janssen Products, L.P.

Approval Date: December 28, 2015

Indications: For the treatment of ovarian cancer, AIDS-related Kaposi's Sarcoma and multiple myeloma.

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APPLICATION NUMBER:
NDA 50-718/S-50

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APPLICATION NUMBER:
NDA 50-718/S-50

APPROVAL LETTER



NDA 050718/S-050

SUPPLEMENT APPROVAL

Janssen Products, L.P.
Attention: Robyn Thomas, Associate Director, Global Regulatory Affairs
Janssen Research and Development, LLC
Welsh and McKean Roads
Spring House, PA 19477

Dear Ms. Thomas:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Doxil (doxorubicin HCl liposome injection), 20 mg/10mL and 50 mg/25 mL.

This Prior Approval supplemental new drug application provides for the addition of a new drug product manufacturing site, GlaxoSmithKline Manufacturing S.P.A., located in Torile (Parma), Italy and the following additional analytical testing sites: (b) (4)

as contractor testing sites for non-compendial excipients.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your September 1, 2015, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on December 8, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “Final Printed Carton and Container Labels for approved NDA 050718/S-050.” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

DATING PERIOD

The shelf life for Doxil manufactured at GSK Manufacturing S.P.A shall be 20 months when stored at 2 to 8°C.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 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>.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling and Carton and Container Labeling- reflecting the new manufacturing site: GlaxoSmithKline Manufacturing S.P.A, Torrile (Parma), Italy

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

/s/

JOSEPH E GOOTENBERG on behalf of PATRICIA KEEGAN
12/28/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-50

MEDICAL REVIEW(S)

FROM: Meredith K. Chuk, Medical Officer, DOP2
THROUGH: Marc Theoret, Team Leader, DOP2
TO: File
SUBJECT: Clinical review for NDA050718, S50 (SDN 978)
SUBMIT DATE: September 1, 2015
PRODUCT: Doxil (doxorubicin HCl liposome injection)
APPLICANT: Janssen Research & Development, LLC
REVIEW COMPLETION DATE: December 2, 2015

CLINIAL REVIEW EXECUTIVE SUMMARY:

NDA050718-S50 is a CMC supplement for a new manufacturing site for Doxil and includes the results of a bioequivalence (BE) study. This review focuses on the safety information provided in the clinical study report (CSR) and datasets for the BE study.

This reviewer did not identify any major safety concerns or new safety signals in this clinical trial with the use of either the test or reference Doxil product. The adverse events reported in the trial were consistent with the known safety profile of Doxil.

Please see review by Siriam Subramaniam, Ph.D., FDA Biopharmaceutics Reviewer for more complete details regarding the pharmacokinetic results of the BE study. Please see review by Zedong Dong, Ph.D., FDA Chemistry reviewer for details on the chemistry portion of the supplement.

BACKGROUND:

On September 1, 2015, Janssen submitted CMC Supplement 50 to NDA 050718 for a new manufacturing site, GlaxoSmithKline (GSK), Polo di Torriale, Italy.

SAFETY REVIEW:

NDA050718-S50 contains a CSR for the BE study DOXILNAP1004: "A Pivotal Bioequivalence Study of DOXIL®/CAELYX® Manufactured at a New Site in Subjects With Advanced or Refractory Solid Malignancies." The trial was a randomized, open-label, multiple-site, single-dose, 2-cycle, crossover BE study in patients with refractory malignancies. The primary objective of the trial was to investigate the bioequivalence of Doxil manufactured at a new site [GlaxoSmithKline (GSK), Polo di Torriale, Italy], and at a currently approved site (Ben Venue Laboratories, Bedford, Ohio, U.S.) based on the encapsulated doxorubicin pharmacokinetic parameters of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$. Secondary objectives included the evaluation of free doxorubicin based on arithmetic difference of total doxorubicin plasma concentrations minus encapsulated doxorubicin plasma concentrations, the safety of Doxil, and the investigator-determined response at the end-of-treatment visit. An additional objective of this trial was to demonstrate BE between DOXIL/CAELYX reference product and test product based on the total doxorubicin pharmacokinetic parameters of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ in patients with solid malignancies. The study included a Screening Phase followed by an Open-Label Treatment Phase consisting of two Doxil treatment cycles (28-days each). Patients could then enter the optional Extension Phase to continue to receive the reference Doxil for up to one year in the absence of disease progression or unacceptable toxicity. Patients were randomized (1:1) to one of two treatment sequence groups (Sequence AB or BA):

- Treatment A: Doxil, produced at the current manufacturing site (Ben Venue Laboratories, Bedford, Ohio, U.S.= reference product) administered by intravenous (IV) infusion over 90 minutes at a dose of 50 mg/m²
- Treatment B: Doxil, produced at a new manufacturing site [GlaxoSmithKline (GSK), Polo di Torriale, Italy] administered by IV infusion over 90 minutes at a dose of 50 mg/m²

Blood samples for pharmacokinetic studies of total and encapsulated doxorubicin were to be obtained at specified times over 26 days in Cycles 1 and 2. The main inclusion criteria included age 18 years or older, ECOG performance status 0-2, prior cumulative doxorubicin (or other anthracycline) exposure ≤ 360 mg/m², or prior cumulative epirubicin exposure of ≤ 720 mg/m², left ventricular ejection fraction (LVEF) within normal institutional limits, adequate liver and renal function, and adequate bone marrow reserve.

The trial was initiated on August 11, 2014, and the clinical data cutoff was April 28, 2015. Thirty-five patients were randomized; 29 were evaluable for the primary BE analysis. Thirty-five patients received at least one dose of study medication and are included in the safety review; 31 completed the treatment phase and 4 discontinued early (reasons for early discontinuation = death, adverse event (AE), withdrawal of consent, and progressive disease, each n=1). The most common diagnoses were breast cancer (9 patients) and ovarian cancer (6 patients). Three patients receiving Sequence BA died during the study, all reported as general deterioration of health, two of the three were reported to have disease progression and none were considered related to study drug. One patient in Sequence BA had an adverse event of general health deterioration that led to study drug discontinuation. Two patients receiving Treatment A (reference product) and four patients receiving Treatment B (test product) had treatment delays following cycle 1. One patient in Sequence AB had a dose reduction in cycle 2 for toxicity (stomatitis).

Serious adverse events (SAEs) were reported for 15 (43%) patients. More SAEs were reported in patients following Treatment B (32%) than Treatment A (18%); however, the events are all either consistent with either the safety profile of Doxil or anticipated in the patient population under study and only one SAE was considered drug-related by the investigator in each group. Review of the narratives of the two SAEs considered related to study drug (stomatitis in a patient following Treatment A and febrile neutropenia in a patient following Treatment B) revealed no new safety concerns. SAEs reported in more than one patient included general health deterioration (n=2 in Treatment B and n=1 in Treatment A), pulmonary embolism (n=2 in Treatment A and n=1 in Treatment B). Table 1 summarizes the SAEs reported in the trial.

Table 1: Serious Adverse Events

Table 14: Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study DOXILNAP1004)			
	All Cancer Types		
	Trt B ^a	Trt A ^a	Total
Analysis set: safety subjects	34	34	35
Number of subjects with serious TEAEs	11 (32.4%)	6 (17.6%)	15 (42.9%)
System Organ Class			
Preferred Term			
General disorders and administration site conditions	3 (8.8%)	4 (11.8%)	6 (17.1%)
General physical health deterioration	2 (5.9%)	1 (2.9%)	3 (8.6%)
Asthenia	1 (2.9%)	1 (2.9%)	1 (2.9%)
Device occlusion	0	1 (2.9%)	1 (2.9%)
Malaise	0	1 (2.9%)	1 (2.9%)
Pain	0	1 (2.9%)	1 (2.9%)
Infections and infestations	2 (5.9%)	1 (2.9%)	3 (8.6%)
Cellulitis	1 (2.9%)	0	1 (2.9%)
Pyelonephritis acute	1 (2.9%)	0	1 (2.9%)
Sepsis	0	1 (2.9%)	1 (2.9%)
Metabolism and nutrition disorders	3 (8.8%)	0	3 (8.6%)
Dehydration	1 (2.9%)	0	1 (2.9%)
Failure to thrive	1 (2.9%)	0	1 (2.9%)
Hypocalcaemia	1 (2.9%)	0	1 (2.9%)
Respiratory, thoracic and mediastinal disorders	2 (5.9%)	1 (2.9%)	3 (8.6%)
Pulmonary embolism	1 (2.9%)	1 (2.9%)	2 (5.7%)
Pleural effusion	1 (2.9%)	0	1 (2.9%)
Gastrointestinal disorders	0	2 (5.9%)	2 (5.7%)
Nausea	0	1 (2.9%)	1 (2.9%)
Stomatitis	0	1 (2.9%)	1 (2.9%)
Musculoskeletal and connective tissue disorders	1 (2.9%)	1 (2.9%)	2 (5.7%)
Back pain	1 (2.9%)	0	1 (2.9%)
Pain in extremity	0	1 (2.9%)	1 (2.9%)
Blood and lymphatic system disorders	1 (2.9%)	0	1 (2.9%)
Febrile neutropenia	1 (2.9%)	0	1 (2.9%)
Cardiac disorders	1 (2.9%)	0	1 (2.9%)
Myocardial infarction	1 (2.9%)	0	1 (2.9%)
Investigations	1 (2.9%)	0	1 (2.9%)
Weight decreased	1 (2.9%)	0	1 (2.9%)
Nervous system disorders	0	1 (2.9%)	1 (2.9%)
Dizziness	0	1 (2.9%)	1 (2.9%)
Renal and urinary disorders	0	1 (2.9%)	1 (2.9%)
Renal injury	0	1 (2.9%)	1 (2.9%)
Urinary fistula	0	1 (2.9%)	1 (2.9%)
Reproductive system and breast disorders	1 (2.9%)	0	1 (2.9%)
Perineal pain	1 (2.9%)	0	1 (2.9%)

^a A: DOXIL/CAELYX 50 mg/m² IV infusion manufactured at current site (BVL); B: DOXIL/CAELYX 50 mg/m² IV infusion manufactured at new site (GSK).

Note: Grade 5 toxicity events are excluded from toxicity frequency counts.

Note: Drug-related adverse events are adverse events with causality reported as possible, probable or very likely. A subject was counted once within each system organ class, preferred term and treatment. Adverse Events were coded using MedDRA Version 17.1.

[TSFAE06A.rtf] [JNJ-17302753\NAP1004\DBR_SUBMISSION\RE_CSR\tsfae06a.sas] 19MAY2015, 12:47

Source: CSR DOXILNAP1004; verified with AE xpt, ADAE.xpt

Note: patient DOXILNAP1004-00001017 had an SAE of asthenia reported during Treatment A and Treatment B

The most commonly reported (>20%) treatment-emergent AEs in all patients were fatigue (31%), anemia (29%), constipation (29%), vomiting (23%), neutropenia (20%), pyrexia (20%), and dyspnea (20%).

Treatment-emergent AEs are summarized in Table 2.

Table 2: Adverse Events $\geq 10\%$

Table 12: Treatment-emergent Adverse Events by System Organ Class and Preferred Term: TEAEs reported for $\geq 10\%$ of Total Subjects; Safety Analysis Set (Study DOXILNAP1004)			
	All Cancer Types		
	Trt B ^a	Trt A ^a	Total
Analysis set: safety subjects	34	34	35
Number of subjects with TEAE	30 (88.2%)	30 (88.2%)	33 (94.3%)
System Organ Class			
Preferred Term			
Gastrointestinal disorders	21 (61.8%)	22 (64.7%)	28 (80.0%)
Nausea	8 (23.5%)	11 (32.4%)	14 (40.0%)
Stomatitis	9 (26.5%)	9 (26.5%)	14 (40.0%)
Constipation	7 (20.6%)	5 (14.7%)	10 (28.6%)
Vomiting	4 (11.8%)	7 (20.6%)	8 (22.9%)
Abdominal pain	2 (5.9%)	3 (8.8%)	5 (14.3%)
Gastroesophageal reflux disease	4 (11.8%)	1 (2.9%)	5 (14.3%)
Diarrhoea	2 (5.9%)	2 (5.9%)	4 (11.4%)
Dry mouth	2 (5.9%)	2 (5.9%)	4 (11.4%)
General disorders and administration site conditions	14 (41.2%)	15 (44.1%)	23 (65.7%)
Fatigue	8 (23.5%)	5 (14.7%)	11 (31.4%)
Pyrexia	4 (11.8%)	4 (11.8%)	7 (20.0%)
Metabolism and nutrition disorders	12 (35.3%)	12 (35.3%)	19 (54.3%)
Decreased appetite	7 (20.6%)	6 (17.6%)	13 (37.1%)
Hypokalaemia	4 (11.8%)	3 (8.8%)	6 (17.1%)
Respiratory, thoracic and mediastinal disorders	13 (38.2%)	9 (26.5%)	18 (51.4%)
Dyspnoea	4 (11.8%)	3 (8.8%)	7 (20.0%)
Cough	4 (11.8%)	2 (5.9%)	5 (14.3%)
Pleural effusion	3 (8.8%)	1 (2.9%)	4 (11.4%)
Skin and subcutaneous tissue disorders	12 (35.3%)	10 (29.4%)	18 (51.4%)
Dry skin	4 (11.8%)	2 (5.9%)	6 (17.1%)
Palmar-plantar erythrodysesthesia syndrome	3 (8.8%)	2 (5.9%)	5 (14.3%)
Blood and lymphatic system disorders	11 (32.4%)	9 (26.5%)	14 (40.0%)
Anaemia	5 (14.7%)	7 (20.6%)	10 (28.6%)
Neutropenia	4 (11.8%)	4 (11.8%)	7 (20.0%)
Musculoskeletal and connective tissue disorders	8 (23.5%)	7 (20.6%)	12 (34.3%)
Back pain	2 (5.9%)	3 (8.8%)	5 (14.3%)
Nervous system disorders	9 (26.5%)	4 (11.8%)	10 (28.6%)
Neuropathy peripheral	4 (11.8%)	1 (2.9%)	5 (14.3%)
Psychiatric disorders	6 (17.6%)	4 (11.8%)	8 (22.9%)
Anxiety	3 (8.8%)	2 (5.9%)	5 (14.3%)
Insomnia	3 (8.8%)	2 (5.9%)	5 (14.3%)
Investigations	4 (11.8%)	4 (11.8%)	6 (17.1%)
Aspartate aminotransferase increased	1 (2.9%)	3 (8.8%)	4 (11.4%)

^a A: DOXIL/CAELYX 50 mg/m² IV infusion manufactured at current site (BVL); B: DOXIL/CAELYX 50 mg/m² IV infusion manufactured at new site (GSK).

Note: Grade 5 toxicity events are excluded from toxicity frequency counts.

Note: A subject was counted once within each system organ class, preferred term and treatment. Adverse Events were coded using MedDRA Version 17.1.

Source: adapted from Attachment [TSFAE02A](#) [JNJ-17302753\NAP1004\DBR_SUBMISSION\RE_CSR\tsfae02a.sas] 19MAY2015, 12:46

Source: CSR DOXILNAP1004; verified with AE xpt, ADAE.xpt

Reviewer Comments:

- 1. There were some minor differences in the frequency of certain AEs following each Treatment, A and B; however, the magnitude of these differences is not unexpected based on the relatively small size of the trial.*
- 2. All AEs were consistent with either the known safety profile of Doxil or were expected for the patient population under study.*

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/s/

MEREDITH K CHUK
12/04/2015

MARC R THEORET
12/04/2015

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APPLICATION NUMBER:
NDA 50-718/S-50

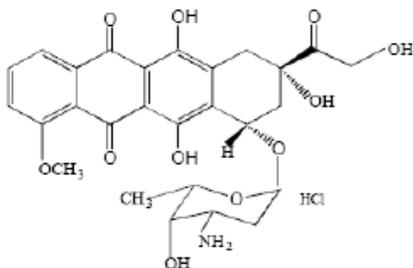
CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW
OF SUPPLEMENT

1. ORGANIZATION: OPQ-Office of Lifecycle Drug Product (OLDP)
2. NDA Number: 50718
3. SUPPLEMENT NUMBERS/DATES: S050 (PAS)
Letter date: September 1, 2015
Stamp date: September 1, 2015
4. AMENDMENTS/REPORTS/DATES: Response to Info. Request (SDN998)
Letter date: December 8, 2015
Stamp date: December 8, 2015
5. RECEIVED BY CHEMIST: September 10, 2015

6. APPLICANT NAME & ADDRESS
Janssen Products, L.P.
800/850 Ridgeview Drive
Horsham, PA 19044

7. NAME OF DRUG: Doxil®
8. NONPROPRIETARY NAME: Doxorubicin HCl Liposome Injection
9. CHEMICAL NAME/STRUCTURE: (8S,10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride
 $C_{27}H_{29}NO_{11} \cdot HCl$; Mol. Wt.: 579.99



10. DOSAGE FORM(S): Injection, liposomal suspension for intravenous infusion
11. POTENCY: 2mg/mL, as a single use vial containing either 20mg/10mL or 50mg/25mL
12. PHARMACOLOGICAL CATEGORY: Antineoplastic agent used in cancer treatment (see PI for further details)

13. HOW DISPENSED: X (Rx) (OTC)
14. RECORDS & REPORTS CURRENT: X Yes No
REVIEW RECORDS & REPORTS CURRENT X Yes No
15. RELATED IND/NDA/DMF: N/A

16. SUPPLEMENT PROVIDES FOR: Additional facility for the manufacture of Doxil (doxorubicin HCl liposome injection) at a (b) (4) commercial scale.

17. COMMENTS: Janssen Products, L.P. (Janssen) NDA 50718 for Doxil (doxorubicin HCl liposome injection) (Doxil) was approved November 17, 1995. Janssen has submitted a supplemental application, which proposes to add an additional manufacturing facility for Doxil. This submission contains CMC documentation for the new drug product manufacturing site as well as Labeling and a Bioequivalence Study Report (DOXILNAP1004). On September 25, 2015, Idara Udoh, M.S. (Senior Regulatory Health Project Manager, DOP2/Office of Hematology and Oncology Products) informed Janssen that the proposed supplemental application would be reviewed as Prior Approval Supplement (PAS) 50718/S050. The Initial Quality Assessment of 50718/S050 is available in Panorama. NDA 50718/S050 is managed by DOP2/Office of Hematology and Oncology Products.

Introduction/Background

Bulk Doxil was originally manufactured by BenVenue Laboratories (BVL) (Bedford, OH) at a (b) (4) commercial scale. The applicant proposed to (b) (4)

(b) (4)

1.14 Labeling

Janssen has provided draft carton and container labels (20mg and 50mg), which have been updated to include a statement that Doxil is manufactured at the GSK Parma facility. The Doxil package insert is also updated to include a statement that Doxil is manufactured at the GSK Parma facility.

The Doxil draft carton and container labels submitted in 50718/S050 has been reviewed by Division of Medication Error Prevention and Analysis (DMEPA) for evaluation from a medication errors perspective. DMEPA found the proposed container and carton labeling acceptable from a medication errors perspective. DMEPA noted that Janssen lists both TTY and GSK Parma on the same carton labeling (under the heading "Manufactured by"), instead of a carton for TTY and a separate carton for GSK Parma. DMEPA defers to the Office of Pharmaceutical Quality (OPQ) or other applicable office on whether Janssen's proposal to list both sites together on the same label is acceptable.

Janssen has provided their explanation for listing both manufacturing sites on the carton label instead of a carton for TTY and a separate carton for GSK Parma, in the 50718/S050 December 8, 2015, **Response to Information Request** document (**SDN998**). This document also provides updated carton and container labeling for Doxil. OPQ finds Janssen's explanation and the draft labeling acceptable form a CMC perspective.

Janssen provides in 50718/S050 the updated Doxil prescribing information (PI). The PI has been updated to include the Glaxo Parma address along with TTY and Alza Corporation under the heading "Manufactured by:". No other changes to the PI are proposed. The updated PI is acceptable from a CMC perspective.

Evaluation: Acceptable

18. CONCLUSIONS & RECOMMENDATIONS: Recommend approval of 50718/S050 from a CMC perspective.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo A. Rocca	Signed Electronically	
	_____	_____

20. BRANCH CHIEF NAME	SIGNATURE	DATE COMPLETED
Ramesh Raghavachari	Signed Electronically	
	_____	_____

cc:
OLDP/RRaghavachari
OLDP/LRocca
DOP2/PM/APatel

F/T by: LRocca, File: C:\Data\LR\Supplement\50718pm\S050(PAS)\50718_S-050Review1.docx

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/s/

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-50

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: 30 November 2015
From: Shawna L. Weis, Ph.D.
Pharmacologist
Division of Oncology Products 2/Division of Hematology Oncology Toxicology
Through: Whitney S. Helms, Ph.D.
Supervisory Pharmacologist
Division of Oncology Products 2/Division of Hematology Oncology Toxicology
To: File for NDA #50,718/S-50 (Doxil)

On 09 October 2015, the Applicant submitted the reports of the following nonclinical pharmacokinetic studies to support S-50 of NDA 50,718:



Because the determination of bioequivalence will be based on clinical data, these studies are not considered necessary to support the approval of the present supplement and will not be reviewed at this time. There are no outstanding pharmacology/toxicology issues that would prevent the approval of this supplement.

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/s/

SHAWNA L WEIS
12/01/2015

WHITNEY S HELMS
12/01/2015

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
NDA 50-718/S-50

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

December 17, 2015

NDA: 050718/S-050

Drug Product Name

Proprietary: DOXIL

Non-proprietary: Doxorubicin HCl liposome injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
9/1/2015	9/1/2015	N/A	9/30/2015
12/14/2015	12/14/2015	N/A	N/A

Submission History (for 2nd Reviews or higher) N/A

Applicant/Sponsor

Name: Janssen Products, LP

Address: 800/850 Ridgeview Drive, Horsham, PA 19044, USA

Representative: Robyn Thomas, Associate Director, Global Regulatory Affairs

Telephone: (215) 793-7021

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Name of Reviewer: Yuansha Chen, Ph.D.

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

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** NDA Prior Approval Supplement
2. **SUBMISSION PROVIDES FOR:** Proposing an additional manufacturing facility.
3. **MANUFACTURING SITE:**
GlaxoSmithKline Manufacturing S.P.A.
Strada Provinciale Asolana N. 90 (Loc.San Polo)
43056 Torrile (Pr), Italy
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection, IV, 2 mg/mL, packaged as 20 mg/10 mL in a 10 mL vial, and 50 mg/25 mL in a 30 mL vial, both single-dose vials
5. **METHOD(S) OF STERILIZATION:** (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Treatment of patients with AIDS related Kaposi's sarcoma, Metastatic Carcinoma of the Ovary, and Multiple Myeloma

- B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology review (b) (4) 050718s46.pdf (recommended) by R. Mello dated 8/26/2013 (b) (4) is referenced for (b) (4) the proposed manufacturing facility were approved in (b) (4) 050718s46.pdf).
- NDA 50-718/S-046 (b) (4) dated 9/22/2014 and the associated microbiology review n50718s046r2.pdf (acceptable) by R. Mello dated 1/18/2018 for the (b) (4)*

C. **REMARKS:** eCTD.

An information request letter was conveyed to the sponsor in 12/8/2015. The sponsor responded to the request in 12/14/2015. The original IR is included in the review followed by the information provided in the sponsor's response, both are in italics.

Filename: 050718s50.doc

Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
The submission is **recommended** for approval on the basis of sterility assurance.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** (b) (4)



- B. Brief Description of Microbiology Deficiencies –** None identified
- C. Contains Potential Precedent Decision(s) -** Yes No

III. Product Quality Microbiology Risk Assessment

- A. Initial Product Quality Microbiology Risk Assessment –** N/A
- B. Final Risk Assessment –** No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

IV. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Microbiologist/Yuansha Chen, Ph.D.
Microbiology Secondary Reviewer/Nandini Bhattacharya, Ph.D.
- C. CC Block**
cc: Field Copy

Yuansha
Chen -S

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-50

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW Division of Biopharmaceutics/Office of New Drug Products			
Application No.:	NDA 050718/S-050	Reviewer: Om Anand, Ph.D.	
Submission Date:	September 01, 2015 October 2, 2015 October 09, 2015 ¹		
Division:	Division of Oncology Products 2 [DOP 2]	Acting Biopharmaceutics Lead: Okpo Eradiri, Ph.D.	
Applicant:	Janssen Research & Development , LLC	Acting Branch Chief: Angelica Dorantes, Ph.D.	
Trade Name:	Doxil [®]	Date Assigned:	Sep 16, 2015
Generic Name:	Doxorubicin HCl liposome injection	Date of Review:	December 2, 2015
Indication:	Treatment of Multiple Myeloma	Type of Submission: Prior Approval Supplement (PAS)	
Dosage Form/ strengths	Liposome [20 mg/vial and 50 mg/vial]		
Route of Administration	Oral		
Type of Review:	Evaluation of: In-vitro release of doxorubicin from doxorubicin HCl liposome injection to support the proposed alternate manufacturing site.		

¹ Amendment to the Supplement

BIOPHARMACEUTICS REVIEW SUMMARY:

Background: Doxil[®] [Doxorubicin HCl liposome injection] is indicated in the treatment of multiple myeloma. Doxil[®] was previously manufactured by Ben Venue Laboratories (BVL) in Beford Ohio. (b) (4)

On 22 January 2015, supplement S-046 was approved, providing for the addition of TTY Biopharm (TTY) as a drug product manufacturing site. The current prior approval supplement (PAS 050) introduces an additional manufacturing site, GlaxoSmithKline (GSK), Polo di Torriale, Italy, for the manufacture of Doxil[®].

Submission: The Applicant submitted this PAS seeking approval of an additional drug product manufacturing site. This submission contains Chemistry, Manufacturing, and Controls documentation as well as Labelling, a Clinical Overview and Bioequivalence Study Report (DOXILNAP1004).

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of comparative multipoint in-vitro release data for the Doxil[®] [Doxorubicin HCl liposome injection] batches used in the bioequivalence study [DOXILNAP1004]. In addition, in-vitro release profiles of additional batches manufactured at GSK site have been evaluated.

RECOMMENDATION

The in-vitro release data support the approval of the additional drug product manufacturing site, GlaxoSmithKline (GSK), Polo di Torriale, Italy. From the Biopharmaceutics perspective, NDA 50718/S-50 for Doxil[®] [Doxorubicin HCl liposome injection] is recommended for **APPROVAL**.

Om Anand -S

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Signature

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products/OPQ

**Okponanabofa
Eradiri -S**

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Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ

BIOPHARMACEUTICS ASSESSMENT

The Supplement (PAS 50) introduces the following changes:

- Addition of GSK Parma as an additional drug product manufacturing and primary packaging site.



In support of the addition of GSK Parma as a manufacturing and primary packaging site, the following information is provided:

- Results of bioequivalence [DOXILNAP1004] and nonclinical studies comparing BVL/ (b) (4) and GSK Parma drug product batches.
- Comparative batch release data between (b) (4) commercial-scale batches ((b) (4) 20 mg and (b) (4) 50 mg batches) manufactured at GSK Parma and (b) (4) batches manufactured at BVL (b) (4) (3.2.P.5.4 Batch Analyses), as well as comparative characterization data between these (b) (4) GSK Parma batches and (b) (4) BVL batches (3.2.P.2.3 Manufacturing Process Development).
- Twelve month stability data from (b) (4) commercial-scale batches in the 20 mg/vial packaging presentation, and 9 month stability data from (b) (4) commercial-scale batch in the 50 mg/vial packaging presentation (3.2.P.8.3 Stability data), and a summary of data included (3.2.P.8.1 Stability Summary and Conclusion).
- Validation of the sterilization process (3.2.P.3.5 Process Validation and/or Evaluation).

The Biopharmaceutics review includes assessment of the in-vitro release of doxorubicin from doxorubicin HCl liposome injection to support the proposed alternate manufacturing site.

The qualitative and quantitative composition of Doxil[®] is presented below in table 1. The bulk liquid is (b) (4) into 10 and 30 mL vials.

Table 1: Qualitative and quantitative composition of doxorubicin HCl liposome injection

Component	Quality Reference	Function	Quantity (mg/mL) ^a
Doxorubicin Hydrochloride ^b	USP	Active	2.00
N-(Carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE)	Company Specification	Liposome Stealth Component	3.19
Fully hydrogenated soy phosphatidylcholine (HSPC)	Company Specification	Liposome Structure Component	9.58
Cholesterol	NF	Liposome Structure Component	3.19
Ammonium Sulfate ^c	ACS	(b) (4)	(b) (4)
Sucrose	USP/NF	Tonicity Agent	(b) (4)
Histidine	USP/NF	Buffer	
Hydrochloric Acid ^d	USP/NF	pH Adjuster	
Sodium Hydroxide ^d	USP/NF	pH Adjuster	
(b) (4)			
(b) (4)			

Table 2 provides the comparison of current and the proposed composition.

Table 2 Comparison of current and proposed batch formulae of doxorubicin HCl liposome injection

Component	BVL (b) (4) Process ^b	GSK Parma Process (b) (4)
Doxorubicin Hydrochloride	[REDACTED]	[REDACTED]
MPEG-DSPE		
Fully hydrogenated soy phosphatidylcholine (HSPC)		
Cholesterol		
Ammonium Sulphate		
Sucrose		
Histidine		
[REDACTED] (b) (4)		
Hydrochloric Acid		
Sodium Hydroxide		
[REDACTED] (b) (4)		

In vitro release drug assay (IVRA):

The in vitro release method is same as previously approved²:

Description of the method:

[REDACTED] (b) (4)

² DARRTS: NDA-050718: REV-QUALITY-21(Primary Review): 08/07/2013: Supplement-31 (Manufacturing (CMC)): DUAN, JOHN Z:

The Table 3 below provides the proposed and approved acceptance criteria for in vitro release drug assay:

Table 3: in vitro release drug assay acceptance criteria:

	Approved ³	Proposed
Time (hours)	% Release	
0.5	(b) (4) 0%	(b) (4) 0%
1.5	(b) (4) 0%	(b) (4) 0%
3	(b) (4) 0%	(b) (4) 0%
6	NLT (b) (4)	NLT (b) (4)

The Applicant provided only mean in vitro release data in [3.2.P.5.4 Batch Analyses (GSK Parma)] in submission dated 9/01/2015. This Reviewer summarized mean in vitro release profiles of the batches used in the BE study and commercial-scale batches ((b) (4) 20 mg and (b) (4) 50 mg batches) manufactured at GSK Parma and (b) (4) batches manufactured at BVL (b) (4), as provided below in Table 4. The f_2 values were calculated between the profiles of the batch # 4002 used in Bioequivalence Study # DOXILNAP1004 and (b) (4) commercial-scale batches ((b) (4) 20 mg and (b) (4) 50 mg batches) manufactured at GSK Parma:

³ DARRTS: NDA-050718: REV-QUALITY-21(Primary Review): 08/07/2013: DUAN, JOHN Z:

Table 4: Comparison of mean dissolution profiles of the batches used in the BE study and the commercial-scale batches

	20 mg/ vial-GSK	50 mg/ vial-GSK	20 mg/ vial- BVL/ (b) (4)
Time (hours)	(b) (4)		
0.5			
1.5			
3			
6			
<i>f2</i> *			

* *Similarity factor (f2)* comparison between the profiles of bio-lot 4002-GSK [Treatment B] and commercial lots manufactured at GSK; and bio-lot 4002-GSK [Treatment B] and bio-lots DJBS300- BVL/ (b) (4) & EDBS000- BVL/ (b) (4) [Treatment A].

In the Supplement, the Applicant provided only the mean in vitro release data, therefore, in an information request dated 24 November 2015, The Applicant was asked to provide the comparative multipoint dissolution profile data (n=12) of batch # 4002 [Treatment B] and lot numbers DJBS300 and EDBS000 [Treatment A] used in Bioequivalence Study # DOXILNAP1004. In addition, the Applicant was asked to explain the differences in in-vitro release profiles of batch # 4001[20 mg vs. 50 mg].

In a response to the information request dated 24 November 2015, the Applicant provided the individual unit data for batch # 4002 (n=12) used for multipoint in-vitro release profile comparison is provided in Table 5 below.

⁴ 4002 Bio-lot-Test: batch # 4002 [Treatment B] manufactured at GSK and used in Bioequivalence Study # DOXILNAP1004.

⁵ DJBS300 and EDBS000: lot numbers DJBS300 and EDBS000 [Treatment A] manufactured at BVL/ (b) (4) and used in Bioequivalence Study # DOXILNAP1004

Table 5: Individual In-vitro Release Assay Results for GSK Batch 4002

Run	Timepoint (hours)			
	0.5	1.5	3	6
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	25.5	53.4	78.5	100.4

The Applicant also submitted, the in-vitro release data for batch DJBS300 (BVL, (b) (4) batch 1306088) provided in Table 6. The Applicant stated that these data were generated on two composite samples which was the practice in place at the time of testing. The test method was subsequently modified to test 12 individual vials for comparative *f*₂ testing. The number of time points tested is greater than for GSK Batch 4002 as this was prior to the specification being in place which reduced the time points to 0.5, 1.5, 3, and 6 hours.

Table 6: Individual in-vitro release assay results for DJBS300 (BVL, (b) (4) Batch 1306088)

Composite #	Timepoint (hours)							
	0.25	0.5	1.0	1.5	2.0	3.0	4.0	6.0
1	(b) (4)							
2								
Average	21.2	29.9	42.8	53.4	62.4	78.5	88.4	99.6

In addition, the Applicant claimed that Batch EDBS000 (BVL, (b) (4) 1402452) was not initially released for commercial supply in the US, therefore it was not tested at release according to the approved IVRA method. This batch was later identified for use in the extension phase of the bioequivalence study DOXILNAP1004 and was placed on stability. The samples were tested at three months using the approved IVRA method. Six vials were tested in accordance with the method for standard release and stability testing. The three month IVRA stability data are provided in Table 7.

Table 7: Individual In-vitro release assay 3 month stability results for EDBS000 (BVL/ (b) (4) Batch 1402452)

Stability Time point	Run	Time point (hours)			
		0.5	1.5	3	6
3 month	1	(b) (4)			
3 month	2				
3 month	3				
3 month	4				
3 month	5				
3 month	6				

Furthermore, the Applicant explained the differences in in-vitro release profiles of batch # 4001[20 mg vs. 50 mg]. The Applicant stated that GSK batches 4001 (20 mg) and 4001 (50 mg) are not the same bulk product filled into two different size vials. These batches were manufactured from unique bulk formulations at different times. The differences in profile may be attributed to general batch to batch variability and inherent method variability. The Applicant further stated that the results from both of these batches meet the approved IVRA release specification.

Figure 1: Comparison of in-vitro release profile of batches used in the BE study

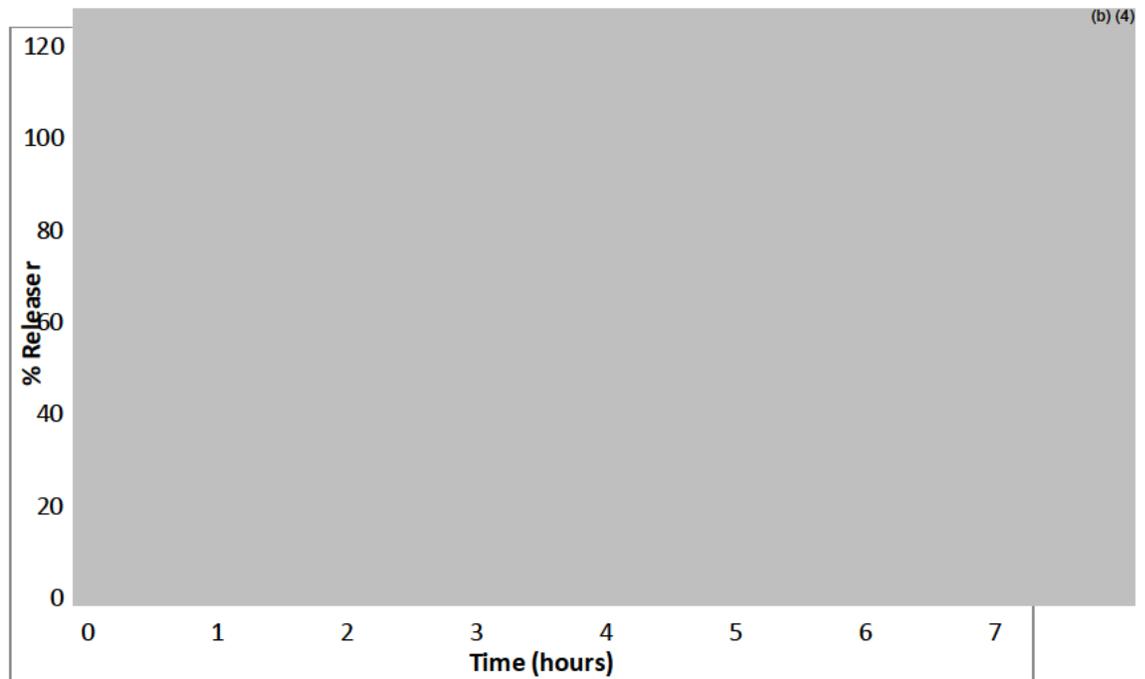


Figure 2: Comparison of in-vitro release profile of batches used in the BE study and the commercial-scale batches [20 mg /vial]

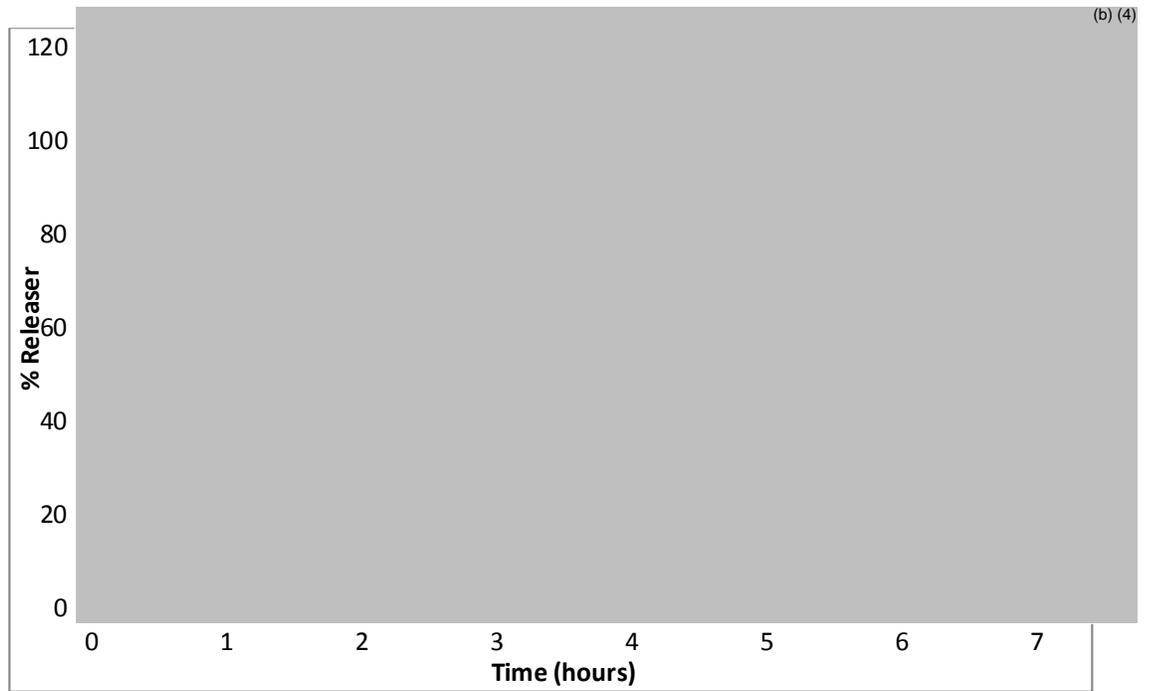
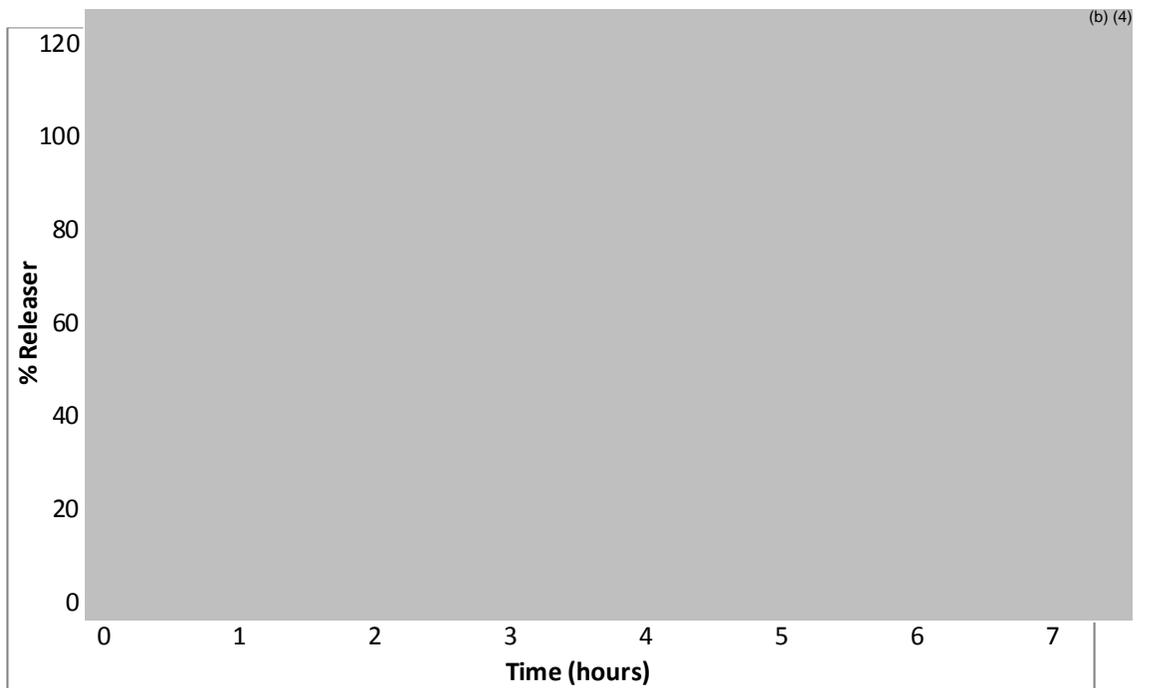


Figure 3: Comparison of in-vitro release profile of batches used in the BE study and the commercial-scale batches [50 mg /vial]



Reviewer's Assessment: SATISFACTORY

- The application includes a relative bioavailability study [DOXILNAP1004] that compares the Doxil[®] formulations manufactured at the proposed GSK facility and at the currently approved facility, Ben Venue Laboratories, Bedford, Ohio (“BVL facility”) using the same manufacturing process. The BE study was found acceptable by the Office of Clinical Pharmacology⁶.
- The in vitro release profiles, using the approved in vitro release drug assay (IVRA), of the batches used in the BE study are similar and acceptable (Figure 1).
- The vitro release profiles of the batch # 4002, manufactured as GSK, used in BE study and (b) (4) commercial-scale batches ((b) (4) 20 mg and (b) (4) 50 mg batches) manufactured at GSK Parma are also similar as demonstrated by the f_2 values in table 4 and figures 2-3. The in-vitro release profile of batch # 4001[20 mg/vial] is slightly slower and not similar [$f_2 < 50$] to the in-vitro release profile of batch # 4002 used in the BE study. The Applicant attributed the differences in profile to general batch to batch variability and inherent method variability. This Reviewer agrees with the Applicant explanation and notes that this batch meets the approved IVRA release acceptance criteria.
- The vitro release profiles of the (b) (4) of the commercial-scale batches (20 mg/vial and 50 mg/vial) are similar [table 4].
- The proposed acceptance criteria are same as the previously approved acceptance criteria (Table 3). The vitro release profiles of the batches, manufactured at GSK, used in BE study and (b) (4) commercial-scale batches meets the approved acceptance criteria.

Recommendation:

The in-vitro release data support the approval of the additional drug product manufacturing and primary packaging site, GlaxoSmithKline (GSK), Polo di Torriale, Italy. From the Biopharmaceutics perspective, NDA 50718/S-50 for Doxil[®] [Doxorubicin HCl liposome injection] is recommended for **APPROVAL**.

⁶ DARRTS: NDA-050718: REV-CLINPHARM-21(Primary Review): 11/30/2015: SUBRAMANIAM, SRIRAM: Supplement-50 (Manufacturing (CMC))

CLINICAL PHARMACOLOGY REVIEW

Submission Number	NDA 050718 / S50
Submission Date	09/01/2015
Submission Type	CMC Supplement
Brand Name	Doxil
Generic Name	Doxorubicin HCl Liposome Injection
Dosage Form	Intravenous Infusion, 2 mg/mL
Dosage Regimen	(b) (4) mg/kg/day
Indication	AIDS-related Kaposi's sarcoma, Ovarian cancer, and Multiple myeloma (in combination with bortezomib).
Sponsor	Janssen Products, LP
OND Division	Division of Oncology Products II
OCP Division	Division of Clinical Pharmacology V
OCP Reviewer	Sriram Subramaniam, Ph.D.
OCP Team Leader	Hong Zhao, Ph.D.

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1 EXECUTIVE SUMMARY

Janssen Products LP (hereon referred to as “Janssen”) submitted this CMC NDA supplement for the addition of a new manufacturing facility, GlaxoSmithKline in Plo di Torrile, Italy (“GSK facility”) for the manufacture of Doxil® (doxorubicin HCl liposome) Injection, 2 mg/mL. Doxil® Injection is indicated for the treatment of patients with AIDS-related Kaposi’s sarcoma, ovarian cancer, and multiple myeloma (in combination with bortezomib), and was originally approved November 17, 1995. Doxil® Injection is marketed as single-use vials, 20 mg/10 mL and 50 mg/25 mL.

The application includes a relative bioavailability study (NAP1004) that compares the Doxil formulations manufactured at the proposed GSK facility and at the currently approved facility, Ben Venue Laboratories, Bedford, Ohio (“BVL facility”) using the same manufacturing process. The primary objective of the study is to demonstrate bioequivalence (BE) between the Doxil formulations manufactured at the GSK and BVL facilities based on encapsulated doxorubicin pharmacokinetic (PK) parameters in patients with solid tumors, and secondary objective is to evaluate free doxorubicin estimated based on arithmetic difference of total doxorubicin and encapsulated doxorubicin plasma concentrations. An additional study objective was to demonstrate BE between the Doxil products based on the total doxorubicin PK parameters.

The BE study results showed that Doxil manufactured at the proposed GSK facility and the currently approved BVL facility are bioequivalent based on encapsulated doxorubicin. In addition, both Doxil products are bioequivalent based on total doxorubicin. The estimated free doxorubicin concentrations were not reliable for pharmacokinetic analysis.

1.1 RECOMMENDATIONS

This application is acceptable from a clinical pharmacology perspective. The Office of Clinical Pharmacology recommends approval of this NDA supplement.

1.2 POST-MARKETING REQUIREMENT AND POST-MARKETING COMMITMENT

There are no clinical pharmacology requested PMRs or PMCs.

Signatures

Sriram Subramaniam, Ph.D.
Reviewer
Division of Clinical Pharmacology V

Hong Zhao, Ph.D.
Acting Team Leader
Division of Clinical Pharmacology V

Cc: DDOP: CSO - I Udoh; MTL - M Chuk; MO – M Theoret
Deputy DD - B Booth; DD - A Rahman

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Janssen proposes to add a new manufacturing facility, GlaxoSmithKline in Plo di Torriale, Italy (“GSK facility”), to manufacture its Doxil® (doxorubicin HCl liposome) Injection, 2 mg/mL. Doxil Injection will be manufactured using the same manufacturing process as currently manufactured Doxil, and will be for the same indication, dose, and route of administration, as that of the approved Doxil® Injection. Doxil® Injection is marketed as single-use vials, 20 mg/10 mL and 50 mg/25 mL.

To assess the relative bioavailability (BA) of Janssen’s Doxil formulation manufactured at the proposed GSK facility, Janssen submitted a bioequivalence (BE) study (NAP1004) comparing pharmacokinetics (PK) of the Doxil product manufactured at the proposed GSK facility (Test) against Doxil manufactured at the currently approved facility (Reference), Ben Venue Laboratories, Bedford, Ohio (“BVL facility”) in patients with solid malignancies. The primary objective was to compare the PK parameters (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) of encapsulated doxorubicin of both Doxil products, and secondary objective was to evaluate free doxorubicin based on arithmetic difference of total doxorubicin and encapsulated doxorubicin plasma concentrations. The additional study objective was to demonstrate BE between the Doxil products based on the total doxorubicin PK parameters. A single dose of 50 mg/m² of Doxil was administered via intravenous infusion to patients with solid malignancies in each cycle.

Study NAP1004 demonstrated that the 90% confidence intervals of the geometric mean ratios of PK parameters (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) for the test and reference products are within the acceptable BE limits for encapsulated and total doxorubicin (see table below). However, the estimates of free doxorubicin concentrations did not provide meaningful data for PK analysis as the total doxorubicin and encapsulated doxorubicin concentrations were similar and often yielded negative values. Nonetheless, for the purpose of the study, the Doxil formulations manufactured at GSK and BVL facilities are comparable as they are bioequivalent based on PK parameters for encapsulated and total doxorubicin.

Parameter (unit)	Least Squares Geometric Mean		Test-to-Reference Ratio	90% Confidence Interval of Ratio
	Test (GSK)	Reference (BVL)		
Encapsulated Doxorubicin (N=29)				
AUC_{0-t} (h*µg/mL)	2843.59	2865.93	0.99	90.29-109.03
$AUC_{0-\infty}$ (h*µg/mL)	3013.59	3001.03	1.00	91.50-110.18
C_{max} (µg/mL)	32.36	32.48	0.97	97.05-102.33
Total Doxorubicin (N=29)				
AUC_{0-t} (h*µg/mL)	3076.03	3028.99	1.02	95.29-108.23
$AUC_{0-\infty}$ (h*µg/mL)	3243.21	3224.82	1.01	94.72-108.78
C_{max} (µg/mL)	31.90	30.87	1.03	100.34-106.42

2 BACKGROUND

04/14/14: FDA recommended estimation of free doxorubicin based on mass balance approach for BE Study NAP1002 to evaluate manufacturing site change (DARRTS I036778 Reference ID 3506500).

09/22/14: Janssen submitted BE Study NAP1002 as part of an earlier CMC supplement (S-46). The study used the same design as Study NAP1004.

12/15/14 Janssen provided an amended protocol for Study NAP1004. Per protocol, the primary objective of NAP1004 was to evaluate BE of both Doxil products based on the encapsulated doxorubicin PK parameters, the secondary objective was to evaluate free doxorubicin based on mass balance approach, and an additional objective was to demonstrate BE between the Doxil products based on the total doxorubicin PK parameters. The FDA found the protocol objectives acceptable (DARRTS I036778 Reference ID 367430).

01/29/15: Study NAP1002 was found acceptable by the FDA (N050718 S46, Panorama).

3 CLINICAL PHARMACOLOGY FINDINGS

Study NAP1004 was a global, multi-center, open label, single-dose, randomized, two-treatment, two-cycle crossover study to compare the bioavailability of Doxil manufactured at the proposed GSK facility (Test) against Doxil manufactured at the currently approved BVL facility (Reference) under fasting conditions. A total of 35 patients with solid tumors (9 males and 26 females) from 6 sites were recruited and 32 patients completed the study, with 29 evaluable patients.

The primary objective was to compare the PK parameters (C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$) of encapsulated doxorubicin of the test and reference products, and secondary objective was to evaluate free doxorubicin based on arithmetic difference of total doxorubicin and encapsulated doxorubicin plasma concentrations. The additional study objective was to compare the PK parameters of total doxorubicin between the two products.

The study consisted of two treatment cycles. The patients were randomized to one of two sequences (test in Cycle 1 then reference in Cycle 2, or reference in Cycle 1 then test in Cycle 2) for dosing. In each cycle, a single dose of 50 mg/m² (based on body surface area) of Doxil was administered on Day 1 by IV infusion over 90 minutes. If there was a >10% change in the patient's body surface area on Day 1 of Cycle 2 compared to Cycle 1, the dose in Cycle 2 was adjusted. The dosing of patients in Cycle 1 and Cycle 2 was separated by 28 days. In each period, blood samples were collected at pre-dose (0 hr), and at 0.25, 0.167, 0.5, 1, 1.5, 1.58, 1.75, 2, 3, 4, 6, 8, 24, 48, 72, 96, 168, 336, 504 and 600 hours post-dose.

Patients were dosed at least 2 hours after standard (non-high fat) breakfast, and a light meal (non-high fat) was served between 2 to 3 hours after dosing.

Patients with dose adjustments, interruption/delay in the infusion, greater than 3 week delay between cycles, or with insufficient PK samples¹ were considered not evaluable for

¹ *i.e.*, missed samples within 105 minutes after infusion, or >1 missed sample between 2 and 8 hours, 24 and 72 hours (Days 2 and 4), or 96 hours and 600 hours (Days 5 and 26).

bioequivalence (BE) assessment. Of the 35 patients, 33 patients completed both periods and 29 patients were considered evaluable for BE assessments. The patients excluded from BE assessments and reasons for their exclusion are listed in Table 1.

Table 1: Patients Excluded from BE Analyses

Patient ID	Site	Event	Excluded from BE
1012	BE00001	Withdrawn in Cycle 2 (Trt. A) due to DP. PK sampling halted after Day 8 (168 hrs) collection in Cycle 2.	Yes
1037	BE00001	Died in Cycle 2 (Trt. A). The last PK sampling was on Day 8 (168 hrs) of Cycle 2.	Yes
2007	ES00001	Suffered Grade 3 stomatitis during Cycle 1 (Trt. A). Dose reduced in Cycle 2. PK sampling halted after Day 22 (504 hrs) collection in Cycle 1.	Yes
3013	CA00013	PK sampling halted after Day 8 (168 hrs) collection in Cycle 2 (Trt. B).	Yes
3034	CA00013	Died in Cycle 1 (Trt. B). The last PK sampling was on Day 8 (168 hrs) of Cycle 1.	Yes
3033	US01273	Cycle 2 not performed as the patient required additional radiation therapy delaying Cycle 2 to >3-week window. PK sampling halted after Day 22 (504 hrs) collection in Cycle 1 (Trt. A).	Yes

Encapsulated and Total Doxorubicin

Prior to the study, it was established that the 90% confidence intervals (90% CI) of the geometric mean ratio for peak concentration (C_{max}), area under the concentration time curve (AUC) to the last time point (AUC_{0-t}) and AUC to infinity (AUC_{0-∞}) for encapsulated and total doxorubicin should be within 80%-125%. Summary BE statistics and descriptive statistics of the PK parameters of encapsulated and total doxorubicin are presented in **Error! Reference source not found.** and **Error! Reference source not found.**

Table 2: Summary BE Statistics, Study NAP1004 (n=29) (Reviewer's analysis)

Parameter (unit)	Least Squares Geometric Mean		Test-to-Reference Ratio	90% Confidence Interval of Ratio
	Test (GSK)	Reference (BVL)		
Encapsulated Doxorubicin				
AUC _{0-t} (h*µg/mL)	2843.59	2865.93	0.99	90.29-109.03
AUC _{0-∞} (h*µg/mL)	3013.59	3001.03	1.00	91.50-110.18
C _{max} (µg/mL)	32.36	32.48	0.97	97.05-102.33
Total Doxorubicin				
AUC _{0-t} (h*µg/mL)	3076.03	3028.99	1.02	95.29-108.23
AUC _{0-∞} (h*µg/mL)	3243.21	3224.82	1.01	94.72-108.78
C _{max} (µg/mL)	31.90	30.87	1.03	100.34-106.42

Table 3: Arithmetic PK Parameters of Doxorubicin, Study NAP1004

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
Encapsulated Doxorubicin (N=29)										
AUC _{0-t}	µg*hr/mL	3109.54	37.15	646.78	5270.93	3223.91	41.51	647.10	5477.68	0.96
AUC _{0-∞}	µg*hr/mL	3258.74	34.78	814.98	5355.21	3348.76	39.97	673.53	5578.78	0.97
C _{max}	µg/mL	33.069	19.68	19.40	45.20	33.13	18.75	18.90	42.30	1.00
T _{max}	hr	2.000	.	1.50	8.00	2.00	.	1.50	8.00	1.00
K _e	hr ⁻¹	0.010	45.48	0.01	0.03	0.01	69.10	0.01	0.04	0.82
THALF	hr	79.504	32.63	26.32	135.05	72.39	34.91	19.65	107.01	1.10
Total Doxorubicin (N=29)										
AUC _{0-t}	µg*hr/mL	3373.13	37.18	730.07	5450.40	3346.13	40.89	755.16	6034.10	1.01
AUC _{0-∞}	µg*hr/mL	3510.83	34.83	905.69	5530.97	3515.46	37.43	797.25	6145.59	1.00
C _{max}	µg/mL	32.44	17.49	21.40	42.10	31.46	18.43	19.40	42.10	1.03
T _{max}	hr	2.00	.	1.58	8.00	2.00	.	1.50	8.00	1.00
K _e	hr ⁻¹	0.010	52.86	0.01	0.03	0.01	53.91	0.01	0.03	0.98
THALF	hr	75.95	27.02	19.99	109.51	75.98	29.98	19.85	110.34	1.00

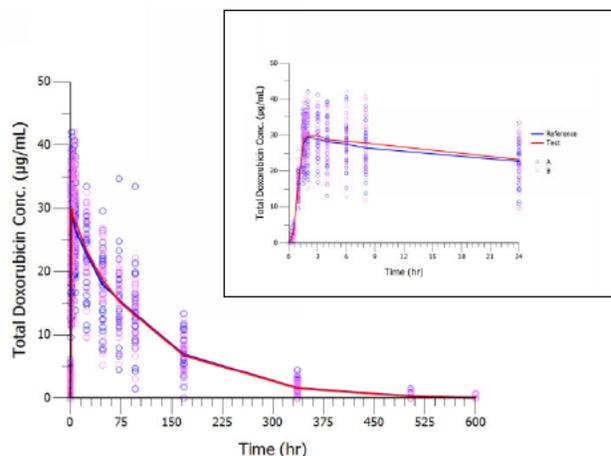
Since the study was conducted at 6 clinical sites, the reviewer evaluated the potential for site effect using the following statistical model: site, period nested within site, formulation, sequence, patient nested within sequence*site and the formulation*site interaction. No “site*treatment” interaction was observed for AUC and C_{max} for encapsulated and total doxorubicin.

Therefore, PK data from all the 6 sites were pooled for BE analysis. The 90% confidence intervals of the test-to-reference ratios of the geometric means for C_{max}, AUC_{0-t}, and AUC_{0-∞} are within the acceptable BE limits of 80% to 125% for encapsulated and total doxorubicin. While, the sponsor’s calculation of geometric means were not the same as the reviewer’s calculation, the sponsor’s 90% CIs and point estimates were confirmed by the reviewer and are within the acceptable 80-125% limits (Table 2, and Figure 1).

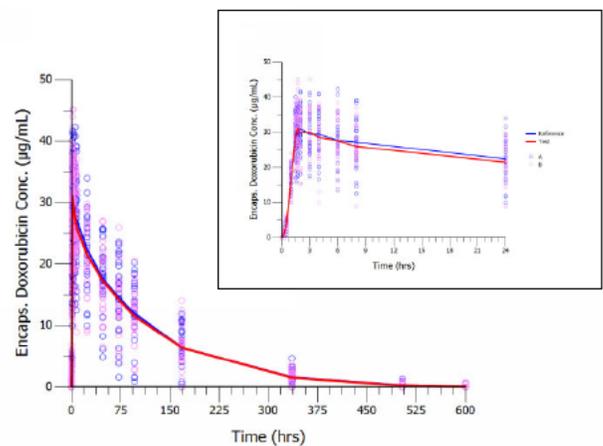
Therefore, the PK parameters C_{max}, AUC_{0-t} and AUC_{0-∞} for the Doxil formulations manufactured at GSK and BVL sites are bioequivalent for encapsulated and total doxorubicin.

Figure 1: Time-Mean Concentration Profile (linear scale: inset figures represent profiles of first 24 hours after start of infusion)

Encapsulated doxorubicin



Total doxorubicin



Free Doxorubicin:

Free doxorubicin was not measured in Study NAP1004. Instead, free doxorubicin concentrations were estimated using the mass balance approach, *i.e.*, the arithmetic difference between total and encapsulated doxorubicin at each time point for each patient. Because of the similarity in the concentrations of total and encapsulated doxorubicin, the differences across the individual time points were either small or negative.

The reviewer found that for 42% of the PK samples in Study NAP1004, the estimated free doxorubicin values were less than zero (*i.e.*, encapsulated concentrations were greater than total concentrations). Among the PK samples with positive (*i.e.*, greater than zero) free doxorubicin levels, 64% of the estimated free doxorubicin concentrations were within 10% of their total doxorubicin levels.

Considering that systemic encapsulated doxorubicin levels are reported to be at least 90% of the total doxorubicin² and the assay variability associated with the measurements of encapsulated and total doxorubicin concentrations (especially at the early absorption phase and elimination phase where the concentrations levels are relatively lower with greater assay variability), the reviewer is of the opinion that the mass balance approach (*i.e.*, difference of total and encapsulated) may not yield reliable estimates of free doxorubicin concentrations.

Also, for the purpose of the study, the free doxorubicin estimates may not be critical as the Doxil formulations manufactured at GSK and BVL facilities were found to be bioequivalent based on PK parameters for encapsulated and total doxorubicin.

Safety

The adverse event (AE) profile was comparable for test and reference products for the overall incidence of AEs (88.2% for each) and drug-related AEs (64.7% vs. 70.6%). The incidence of serious AEs was higher for test (11 patients) compared to reference (6 patients) products. However, the incidence of drug-related serious AEs was low and comparable (1 patient each). There were 3 deaths, 2 due to AEs (one each for test and reference) and 1 due to disease progression.

4 GENERAL ATTRIBUTES

4.1 GENERAL BIOPHARMACEUTICS

The Doxil is a liposomal formulation containing doxorubicin HCl for intravenous injection, 2 mg/mL.

Test Product

Name: Doxil (doxorubicin HCl liposome injection)

Formulation: Intravenous Injection, 2 mg/mL

Manufacturer: GSK, Batch No.: 4002

² *In vitro* and *in vivo* characterizations of PEGylated liposomal doxorubicin (2011). W Jiang, R Lionberger, and LX Yu. *Bioanalysis* 3(3):333-344.

Reference Product

Name: Doxil (doxorubicin HCl liposome injection)

Formulation: Intravenous Injection, 2 mg/mL

Manufacturer: BVL, Batch No.: DJBS300 and EDBS000

5 ANALYTICAL

5.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Encapsulated doxorubicin and total doxorubicin were assessed in the plasma of patients in Study NAP1004. Bioanalytical methods (b) (4) were developed for the quantification of encapsulated doxorubicin and total doxorubicin in human plasma over the range of 0.5 µg/mL to 50 µg/mL. The sponsor states that the method validation met the established acceptance criteria (see Section 5.4 for reviewer comments). The same methods were used in an earlier BE study (NAP1002) for manufacturing site change.

Briefly, for the encapsulated doxorubicin method, (b) (4)

(according to

(b) (4)

(b) (4)

(see Section 5.2 for preparation). Per the reviewer, this is not an issue as the QCs and study samples were processed similarly.

For total doxorubicin, doxorubicin in the calibration standards, QC samples, and study samples were extracted by (b) (4), and doxorubicin measured (according to (b) (4)

5.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The methods demonstrate suitable linearity (0.5 µg/mL to 50 µg/mL) for the assessment of encapsulated & total doxorubicin in human plasma. The linear range of the standard curve was established using (b) (4), and the range adequately met the needs of clinical study.

Calibration standards for both methods were prepared (b) (4)

For the encapsulated doxorubicin method, (b) (4)

5.3 What are the lower and upper limits of quantification (LLOQ/ ULOQ)?

The lower limit of quantification (LLOQ) and the upper limit of quantification (ULOQ) for encapsulated & total doxorubicin assays were 0.5 µg/mL and 50 µg/mL, respectively.

5.4 What are the accuracy, precision and selectivity at these limits?

The assay accuracy, precision, and selectivity results of encapsulated & total doxorubicin during validation are summarized in the table below (Table 4). The assay accuracy and precision in Study NAP1004 were 96.7-98.9% and 2.7-3.3% for total doxorubicin, and 98.4-100% and 6.4-7.3% for encapsulated doxorubicin. Less than 0.5% of total samples were reassayed in the study. See Sections 5.1, 5.3, 5.5 and 5.6 for details.

Table 4. Method Validation Summary for Quantitation of Encapsulated & Total Doxorubicin in Human Plasma

Information Requested	Encapsulated doxorubicin	Total doxorubicin
Analyte	Doxorubicin	Doxorubicin
Internal standard (IS)	(b) (4)	
Method description*	Solid phase extraction with LC/MS/MS method (see Section 5.1)	Protein precipitation extraction with LC/MS/MS method (see Section 5.1)
Blank Plasma	Commercial K ₂ EDTA plasma from cancer patients	
LLOQ	0.5 µg/mL	0.5 µg/mL
Standard curve concentrations	0.5 – 50 µg/mL	0.5 – 50 µg/mL
Recovery		100.8
QC concentrations	1.50, 10.0 and 37.5 µg/mL	1.50, 10.0 and 37.5 µg/mL
QC Intraday precision range	1.8 to 5.8%	1.4 to 3.2%
QC Intraday accuracy range	98% to 107.5%	94.7-98.2%
QC Interday precision range	3% to 5.5%	1.7 to 3.3%
QC Interday accuracy range	102% to 104%	95.3 to 96.6%
Bench-top stability*	6 hours in an ice-water bath	
Stock stability		217 days at -20C
	32 days at -20°C in diluent (0.1 % formic acid in methanol/water) 24 & 18 hours at room temperature under white light for doxorubicin and IS, respectively IS stock: Stable for 769 days at -20°C	
Dry Ice Stability* (to mimic storage/shipping)	3 days at -20°C, moved to dry ice for 96 hours and back to -20°C for 6 days	
Processed stability*	74 hours at room temperature	73.5 hours at room temperature
Freeze-thaw stability*	3 freeze-thaw cycles	
Long-term storage stability*	235 days at -20°C. 80 days at -30C, then 67 days at -20°C	975 days at -20°C
Dilution integrity	225 µg/mL diluted 6-fold	
Selectivity	The blank selectivity samples were within acceptance criteria No pyridoxine interference	No interfering peaks noted in blank plasma samples
Matrix effect	None in plasma blanks, and in blanks spiked at 1.5 and 37.5 µg/mL	
Whole blood stability		120 minutes at room temperature & 4°C

*Compared against freshly prepared calibrators

The sponsor stated that the precision and accuracy were demonstrated for the methods. However, since the quality controls (QC) used in the encapsulated doxorubicin method included only encapsulated doxorubicin, the reviewer requested Janssen to demonstrate the ability of the of the SPE to selectively extract encapsulated doxorubicin (*i.e.*, remove free doxorubicin from

the extracted study samples). In response to information request, Janssen provided method development results with QCs (b) (4)

The results indicate that the extraction procedure was capable of isolating encapsulated doxorubicin from free doxorubicin, with >99% recovery of encapsulated doxorubicin in the eluent.

5.5 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

The plasma samples in Study NAP1004 were stored for ~7.5 months (first sample collection to last day of analysis: August 11, 2014 to March 31, 2015) which is within the validated long-term frozen storage stability of encapsulated and total doxorubicin (see Table 4).

Long-term stability of encapsulated doxorubicin in human plasma was validated by assaying QC samples at high and low QC concentrations after storage at approximately -20°C for a period of 235 days against a freshly prepared calibration curve. The QC concentrations were within 15 % of their nominal concentrations.

In response to information request to clarify the long-term stability of total doxorubicin, Janssen stated that free doxorubicin frozen storage stability in human plasma was demonstrated for 201 days at -20°C. This information combined with stability of encapsulated doxorubicin in plasma and the acceptable ISR results (Section 5.6) indicate that the total doxorubicin is stable for the duration of storage of the study samples. In addition, long-term stability of total doxorubicin in human plasma was validated by assaying QC samples at high and low QC concentrations after storage at approximately -20 °C for a period of 235 days and 975 days against a freshly prepared calibration curve (Table 4).

Stability for encapsulated doxorubicin is indicated for 3 freeze-thaw cycles. Nonetheless, during Study NAP1004, majority of the samples were analyzed only once (i.e., one freeze-thaw cycle).

Short-term stability in human serum was validated for 6 hours in ice-bath using high and low QCs that were measured against freshly prepared calibration curve.

Dry-ice stability to simulate conditions during sample shipment and transit was demonstrated by evaluating stability samples that were stored for 3 days at -20°C, moved to dry ice for 96 hours and returned to -20°C for 6 days.

5.6 What is the QC sample plan?

For encapsulated doxorubicin method, QC samples were prepared (b) (4)

QCs were prepared at 1.5 µg/mL (QC A), 10.0 µg/mL (QC B) and 37.5.0 µg/mL (QC C) and stored at -20°C in Study NAP1004. For the total doxorubicin assay, Janssen clarified that the QCs were prepared (b) (4)

QCs were analyzed either in duplicates or triplicates in each analytical run. QC acceptance criteria: at least 67% (2/3) of the QC samples in each analytical run should be within ±15% of their respective nominal values. At least 50% (1/2) of the replicates at each concentration level must be within ±15% of their respective nominal value.

Study samples for encapsulated doxorubicin and total doxorubicin were analyzed approximately 7 months (March 6-31, 2015) and 6 months (February 14- March 27, 2015), respectively, after first sample collection in Study NAP1004. A total of 9 and 18 analytical runs were analyzed for total and encapsulated doxorubicin, respectively, in Study NAP1004. All runs met the QC acceptance criteria. The overall inter-run accuracy and precision during Study NAP-1004 was 96.7-98.9% and 2.7-3.3% for total doxorubicin, respectively and 98.4-100% and 6.4-7.3% for encapsulated doxorubicin, respectively. .

In addition, 120 samples each for total and encapsulated doxorubicin were reanalyzed for incurred sample reanalysis (ISR). The difference between the original and their reanalyzed concentrations (normalized to their mean concentrations) was within 20% for all ISR samples, demonstrating reproducibility in incurred samples. In addition, only 1 sample for total doxorubicin and 6 samples for encapsulated doxorubicin were reanalyzed as their original IS response was out of range.

6 OFFICE OF SCIENTIFIC INVESTIGATION INSPECTION

The analytical portions of bioequivalence study NAP1004 was conducted at (b) (4). The Office of Study Integrity and Surveillance (OSIS) inspection was not requested.

7 LABELING RECOMMENDATIONS

Not applicable.

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/s/

SRIRAM SUBRAMANIAM
11/30/2015

HONG ZHAO
11/30/2015
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-50

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 11, 2015
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 050718/S-050
Product Name and Strength: Doxil (doxorubicin HCl liposome injection)
20 mg/10 mL (2mg/mL) and 50 mg/25 mL (2 mg/mL)
Submission Date: December 8, 2015
Applicant/Sponsor Name: Janssen Products, LLP
OSE RCM #: 2015-2099-1
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

DOP2 requested that we review the revised container labels and carton labeling for Doxil (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container labels and carton labeling for Doxil are acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Townsend, O. Label and Labeling Review for Doxil (NDA 050718). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 DEC 2. RCM No.: 2015-2099.

APPENDIX A. LABEL AND LABELING SUBMITTED ON DECEMBER 8, 2015

Container Labels

NDC 59676-960-01

DOXIL[®]
(doxorubicin HCl liposome injection)

20 mg in 10 mL
(2 mg/mL)

Single-Use Vial. Discard unused portion.

LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL

© Janssen 2001 10290201 **Rx ONLY**

FOR INTRAVENOUS INFUSION ONLY
Refrigerate, 2°-8°C (36°-46°F). Do Not Freeze.
See package insert for dosage information.
Janssen Products, LP
Horsham, PA 19044



An ALZA STEALTH[®] TECHNOLOGY PRODUCT



0100359676960010

LOT: EXP:

NDC 59676-960-02

DOXIL[®]
(doxorubicin HCl liposome injection)

50 mg in 25 mL
(2 mg/mL)

Single-Use Vial. Discard unused portion.

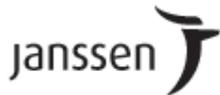
LIPOSOMAL FORMULATION - DO NOT SUBSTITUTE FOR DOXORUBICIN HCL

10290301

Janssen Products, LP
Horsham, PA 19044

FOR INTRAVENOUS INFUSION ONLY
Refrigerate, 2°-8°C (36°-46°F). Do Not Freeze.
See package insert for dosage information.
Rx ONLY

© Janssen 2001



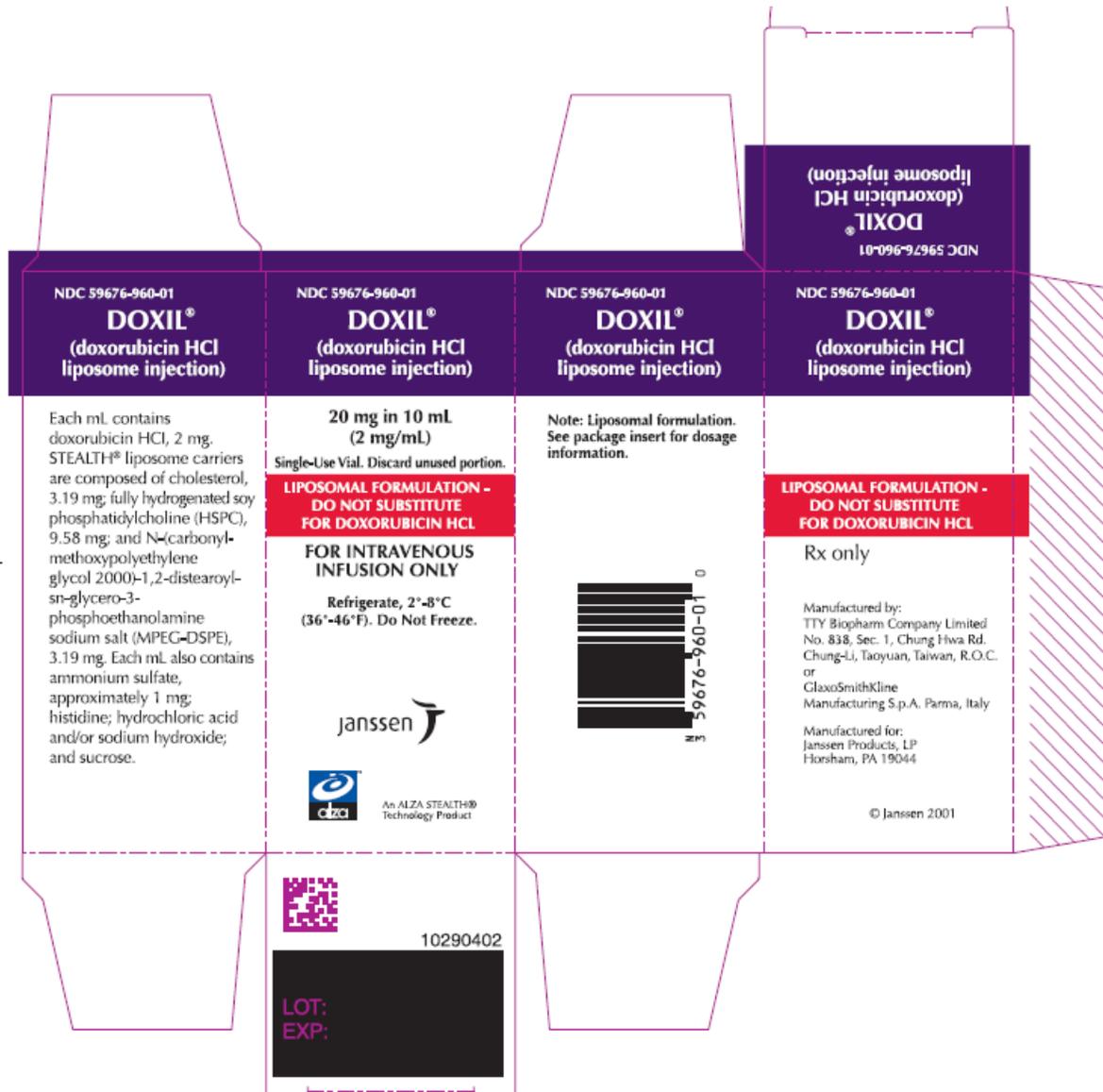
An ALZA STEALTH[®] TECHNOLOGY PRODUCT

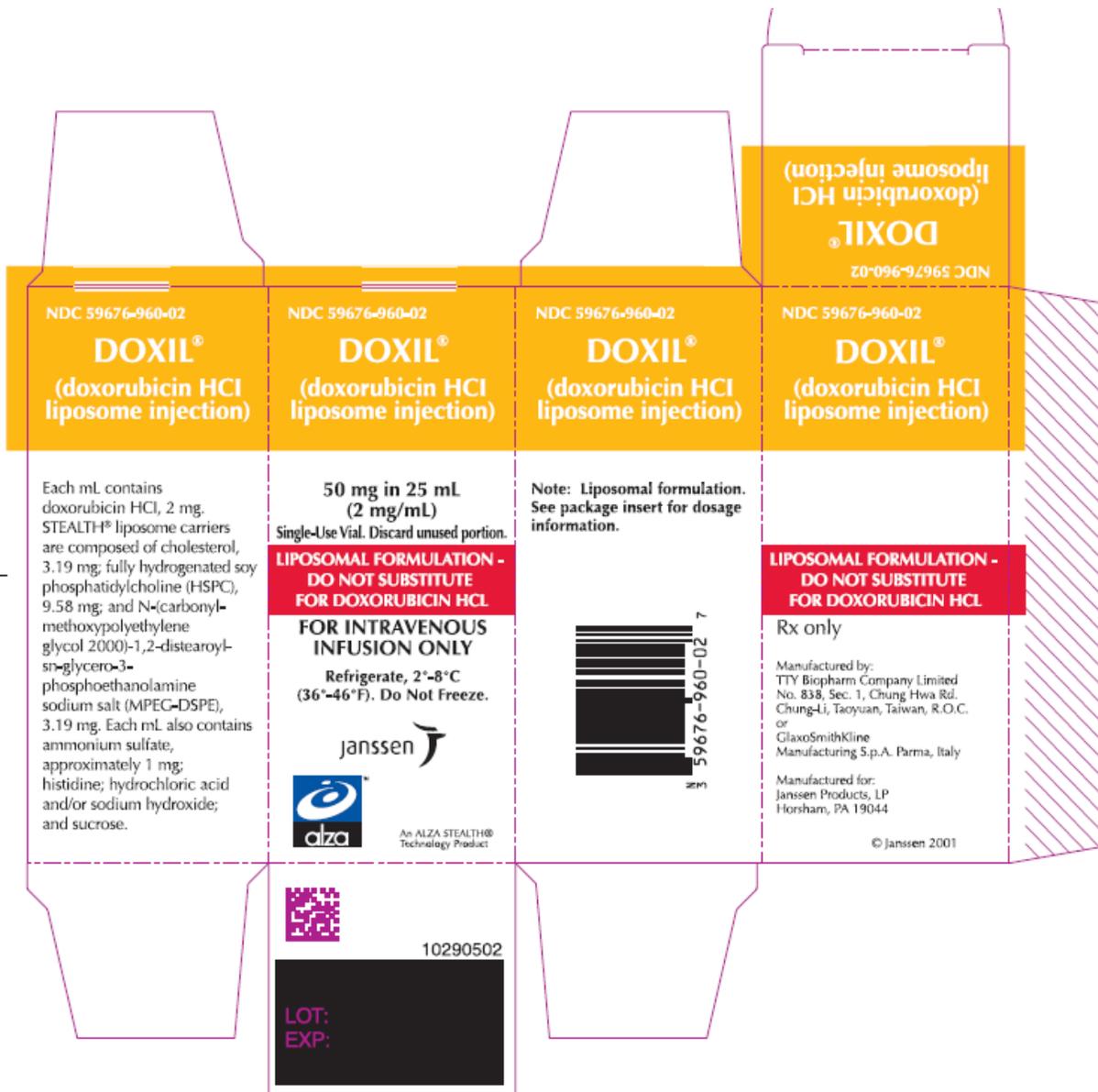


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LOT: EXP:

Carton Labeling





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/s/

OTTO L TOWNSEND
12/11/2015

CHI-MING TU
12/11/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: December 2, 2015
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 050718
Product Name and Strength: Doxil (doxorubicin HCl liposome injection)
20 mg/10 mL (2mg/mL) and 50 mg/25 mL (2 mg/mL)
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Janssen Products, LLP
Submission Date: September 1, 2015
OSE RCM #: 2015-2099
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This Prior Approval Supplement was submitted to request approval of GlaxoSmithKline Manufacturing, SpA, Parma, Italy (GSK Parma) as an additional drug manufacturing and primary packaging site for Doxil. As part of the supplement review, DOP2 asked DMEPA to assess the container labels, carton labeling, and Prescribing Information from a medication errors perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Approval of this Prior Approval Supplement would provide for an additional manufacturing site for Doxil. During initial review of the proposed container labels, DOP2 noted that Janssen proposes the deletion of TTY BioPharm Company Limited as the manufacturing site and had not included the GSK Parma site on the container labels. DOP2 submitted an information request to clarify this issue (see DARRTS Pending sNDA Information Request, dated November 24, 2015). In their response, dated November 25, 2015, Janssen stated that the size of the container label was too small to accommodate text for both manufacturing sites (TTY and GSK). They went on to cite 21 CFR 201.10(h)2(i) and stated that all required label information will be included in the carton labeling.

To satisfy the regulatory requirement that the name and place of business of the manufacturer, packer, or distributor be conspicuously displayed on the finished package form (21 CFR 201.1(a)), Janssen proposes listing “Janssen Products, LP” as the manufacturer (see Appendix G

for an illustration) on the container labels and adding more detailed manufacturer information about the GSK Parma site to carton labeling and Prescribing Information.

Janssen's proposal appears appropriate because the container label will bear the required elements, proprietary name, established name, an identifying lot or control number, and the name of the manufacturer. In addition, all other required information will be listed on carton labeling and the PI.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed container labels, carton labeling, and Prescribing Information acceptable from a medication errors perspective, but defer to the Office of Pharmaceutical (OPQ) or other applicable office on whether the Applicant's proposal to list both TTY Biopharm and GSK Pharma listed on the same carton labeling instead of a carton for TTY Biopharm and a separate carton for GSK Pharma is adequate.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Doxil that Janssen submitted on September 1, 2015.

Table 2. Relevant Product Information for Doxil	
Initial Approval Date	November 17, 1995
Active Ingredient	Doxorubicin Hydrochloride
Indication	Ovarian Cancer, AIDS-Related Kaposi's Sarcoma and Multiple Myeloma (in combination with bortezomib).
Route of Administration	Intravenous
Dosage Form	Liposome Injection
Strength	20 mg/10 mL (2 mg/mL) and 50 mg/25 mL (2 mg/mL)
Dose and Frequency	<u>Ovarian Cancer:</u> 50 mg/m ² intravenously every four weeks. <u>AIDS-Related Kaposi's Sarcoma:</u> 20 mg/m ² intravenously every three weeks. <u>Multiple Myeloma:</u> 30 mg/m ² intravenously on day 4 following bortezomib.
How Supplied	SINGLE-DOSE VIALS: 10 mL vial (20 mg/10 mL) and 30 mL vial (50 mg/25 mL) containing doxorubicin HCl at a concentration of 2 mg/mL.
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F). Avoid freezing.
Container Closure	Individually cartoned glass vials.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 30, 2015, we searched the L: drive and AIMS using the terms, “Doxil” and “doxorubicin” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two (2) previous reviews^{1 2}, and we confirmed that our previous recommendations were implemented or considered.

¹ Townsend, O. Label and Labeling Review for Doxil (NDA 050718). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 NOV 04. RCM No.: 2014-2032.

² Townsend, O. Label, Labeling, and Packaging Review for Doxil (NDA 050718). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 SEP 13. RCM No.: 2013-1713.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Doxil labels and labeling submitted by Janssen on September 1, 2015.

- Container label
- Carton labeling

G.2 Label and Labeling Images

(b) (4)



³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

(b) (4)



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/s/

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12/02/2015

CHI-MING TU
12/02/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 50-718/S-50

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 7, 2015

Application Number: NDA 050718/S-50

Product Name: Doxil

Sponsor/Applicant Name: Janssen Products LP

Subject: Clarification of Nonclinical Information for NDA 050718/S-50 Submission

FDA Participants : Whitney Helms, Nonclinical Team Leader; Shawna Weis, Nonclinical Reviewer; Anuja Patel, M.P.H., Senior Regulatory Health Project Manager, DOP 2/OHOP ; Idara Udoh, M.S., Senior Regulatory Health Project Manager, DOP 2/OHOP

Meeting Recorder : Idara Udoh, M.S., Senior Regulatory Health Project Manager, DOP 2/OHOP

Sponsor/Applicant Participants: Gerry Gendimenico, Senior Scientist, Preclinical Development; Srinivas (RAO) Mamidi, Director, Preclinical Development; Robyn Thomas, Associate Director, Global Regulatory Affairs; Ilona Scott, Director, Global Regulatory Affairs; Judy Shuster, Senior Director, Global Regulatory Affairs, CMC; and Ryan Mackenzie, Associate Director, Global Regulatory Affairs, CMC

FDA-Initiated ? Yes

BACKGROUND:

On October 2, 2015, Janssen Products LP (“Janssen”) submitted nonclinical data, under NDA 050718, via electronic mail (email) communication to be included with its supplemental application (S-50) currently under review. The supplemental application proposed to add a new manufacturing facility, GlaxoSmithKline (GSK) Manufacturing S.P.A., in Polo di Torriale, Italy.

FDA requested a teleconference with Janssen to determine whether the nonclinical data submitted in the supplement were new, or if they had been previously submitted to support an earlier manufacturing change, since many of the reports appeared to have similar or identical titles but different study numbers.

DISCUSSION:

Janssen confirmed that the nonclinical information provided in the October 2, 2015 email submissions contained different study numbers from those previously submitted to support the earlier approval of the TTY location, and that the new reports were submitted to support the approval of the GSK location. FDA inquired whether the reports contained anything new from a toxicological perspective, and what Janssen intended the data to be used for. Janssen stated that no new toxicological information was provided; the data were provided to satisfy EU expectations for demonstration of comparability between the GSK and BVL manufacturing sites.

FDA requested that Janssen submit a tabular summary of the reports included in S-50 and to indicate which reports were new, and which had been previously submitted to earlier supplements under this NDA.

Janssen inquired whether submission of the nonclinical information would impact the review time, and FDA confirmed that it would not.

The call ended.

ACTION ITEMS

Janssen will submit the nonclinical summary table to NDA 050718.

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/s/

IDARA UDOH
12/28/2015

**Initial Planning Meeting Minutes
September 24, 2015**

Product: DOXIL® (doxorubicin HCl liposome injection) for intravenous injection
sNDA: 50718/S-050
(CMC Prior Approval Supplement with Manufacturing Changes)
eCTD submission: SDN 181

Submission Date: September 1, 2015
Received Date: September 1, 2015
Sponsor: Janssen Products, LP

Purpose: The purpose of this prior approval supplement is to request approval of the following changes:

- Addition of a manufacturing site (GlaxoSmithKline Manufacturing S.P.A., in Polo di Torrile, Italy) for the manufacturing process of the drug product (long-term solution for the DOXIL drug shortages)
- Revisions to carton and container labels to include new manufacturer information

Currently Marketed Indications:

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

Assigned Review Team

Patricia Keegan, M.D., Director, DOP2
Monica Hughes, M.S., CPMS, DOP2
Idara Udoh, M.S., Senior Regulatory Health Project Manager
Anuja Patel, M.P.H., Senior Regulatory Health Project Manager
Marc Theoret, M.D., Clinical Team Leader (CDTL)
Meredith Chuk, M.D., Medical Officer (DOP 2)
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Sriram Subramaniam, Ph.D., Clinical Pharmacology Reviewer
Okpo Eradiri, Ph. D., Biopharmaceutics Reviewer (*in vitro review*)
Om Anand, Ph.D., Biopharmaceutics Reviewer (*in vitro review*)
Ramesh Raghavachari, OPQ Branch Chief
Zedong Dong, Ph.D., OPQ Reviewer
Olugbenga Okubadejo, Pharm.D., Regulatory Business Process Manager, OPQ

Regulatory Background:

Janssen's Long Term Plan on Drug Shortage:

(b) (4)		
CMC PAS Supplement 46	Received July 12, 2013	Supplement proposed adding TTY Biopharm site (b) (4)
	Complete Response issued November 12, 2013	(b) (4)
Resubmission CMC PAS Supplement 46	Received September 22, 2014	Approval of TTY manufacturing site (b) (4)
	Approval letter issued January 22, 2015	(b) (4)
Efficacy Supplement 48 (DHP Managed)	Received November 4, 2014	Provides updates to the PI based on the final study report for DOXIL Study MMY-3001.
	Approval letter issued April 16, 2015	
CBE-30 CMC Supplement 49	Received April 10, 2015; review ongoing.	Addition of (b) (4)

Agenda Items:

1. Review Status: **4 Months** (Action Date: January 1, 2016)

Discussion During Meeting:

- DOP2 plans to coordinate an action on or before December 15, 2015. If this does not occur, action to occur prior to PDUFA goal date.
- No filing letter needed for this supplement. Therefore the previously scheduled filing meeting can be cancelled.

2. Potential Consults/Collaborative Reviewers Needed:

Discussion During Meeting:

- Office of Compliance (OC) provided an update on the potential OAI status of the GSK Italy site, stating there were issues surrounding data integrity and aseptic manufacturing process. DOP2 inquired whether we can refuse to file this CMC supplement, and determined that theoretically it was possible since the Italy site may be OAI. OC stated that the inspection status is still ongoing, but DOP2 should not consider it a review issue.
- The final action (approval or complete response) may depend on the inspection status.
- No OSI consult is required for this supplement.
- OPQ RBPM (Olugbenga Okubadejo) will assist with the following :
 - Coordinate Inspection results and relay to DOP2
 - Coordinate CMC review of the Environmental Analysis: Request for Categorical Exclusion
 - Labeling review
 - Management of any Panorama Consults needed*

3. Miscellaneous Items or Issues:

- a. No other issues or concerns

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/s/

IDARA UDOH
12/22/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 4, 2015
From: Anuja Patel Senior Regulatory Health Project Manager, DOP 2
Subject: Informal Sponsor Teleconference
Application Number: NDA 50718/ Supplement 050
Product Name: Doxil
Applicant: Janssen Products, L.P.

TELECONFERENCE (10:00 AM – 10:15 AM, EST)

Janssen Products L.P. Attendees:

Ilona Scott, Director, Global Regulatory Affairs
Kim Jankowitz, Manager, Global Regulatory Affairs

FDA Attendees:

Idara Udoh, Senior Regulatory Health Project Manager
Anuja Patel, Senior Regulatory Health Project Manager
Monica Hughes, Chief, Project Management Staff

Background:

On September 1, 2015, Janssen submitted a Prior Approval Supplement (Supplement 050) under NDA 050718 for the addition of a manufacturing facility (GlaxoSmithKline). The submission contained revised labeling for the package insert and carton and immediate container (vials) for the 20 mg in 10 mL and 50 mg in 25 mL.

On November 24, 2015, FDA issued an information request to Janssen requesting clarification on the carton and container labeling submitted for Supplement 050. Janssen provided their responses on November 25, 2015.

Purpose:

The purpose of the teleconference was to obtain further clarification from Janssen on their November 25, 2015, responses.

Discussion During Teleconference:

FDA requested further clarification from Janssen as to whether they intended to have separate carton and container labeling for product manufactured at the TTY, Taiwan site and the proposed GSK Italy site. Janssen confirmed that Doxil manufacturing would occur at both sites and stated that they did not intend to have separate labeling but rather are proposing to include both the “manufactured by” TTY and GSK manufacturing information on the carton labeling. Janssen stated that due to limited space on the vials, only ^{(b) (4)} information would be included on the individual vials. Janssen further stated that internally they will be able to track which site the Doxil was manufactured at through batch and lot information.

FDA inquired whether Janssen had any concerns with including both “manufactured by” locations on the carton label; and, asked if they considered the potential impact of customs import regulations. Janssen stated that Doxil ^{(b) (4)}

[REDACTED]

FDA requested mock-up’s of all proposed carton and container labeling that Janssen intends to market in order for FDA to complete its review. FDA also requested that Janssen include a brief explanation of how Doxil shipment into the US will and final packaging will occur. Janssen stated that the requested information will be submitted to FDA as soon as possible.

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/s/

ANUJA PATEL
12/16/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 8, 2015
From: Idara Udoh –Regulatory Health Project Manager, DOP2/OHOP/CDER
Subject: NDA 050718/Prior Approval Supplement 050 – Janssen Products, L.P. – FDA Microbiology Information Request

Janssen Products, L.P.
Attention: Robyn Thomas, Associate Director, Global Regulatory Affairs
Janssen Research and Development, LLC
Welsh and McKean Roads
Spring House, PA 19477

Dear Ms. Thomas:

Please refer to your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DOXIL® (doxorubicin HCl liposome injection), for intravenous injection, single dose vial: 20 mg/10mL and 50 mg/ 25 mL.

We also refer to your Prior Approval Supplement (PAS), dated and received September 1, 2015, which proposes to add a new manufacturing facility, GlaxoSmithKline Manufacturing S.P.A., in Polo di Torrile, Italy.

We have the following microbiology deficiencies, in regard to your PAS:

(b) (4)

Please address all items listed above through a formal submission to your NDA 050718, by COB, December 14, 2015. Please send a courtesy copy of your submission via e-mail to me once your submission has been submitted.

Please note that your sNDA submission is currently under review and additional comments may be forthcoming.

If you have any questions, please call me at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

IDARA UDOH
12/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Idara Udoh, RPM/OHOP/DOP2 301-796-3074		
DATE December 1, 2015	IND NO.	NDA NO. NDA 050718/S-50	TYPE OF DOCUMENT sNDA	DATE OF DOCUMENT 9/1/2015
NAME OF DRUG Doxil (doxorubicin HCl liposome injection)		PRIORITY CONSIDERATION CMC supplement/PAS with manufacturing (4 months)	CLASSIFICATION OF DRUG Anthracycline antibiotic	DESIRED COMPLETION DATE December 11, 2015 Planned action date: December 15, 2015
NAME OF FIRM: Janssen Products, LP				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input checked="" type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Carton/container labeling revision				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
<p>Review of carton and container labeling for submission of supplement 50, which provides for new GSK manufacturing site in Polo di Torriale, Italy, for Doxil. It also includes revision to Package Insert (with the only change being the proposed addition of the GSK manufacturing site).</p> <p>Please note that assignments for this consult were made prior to upload in DARRTS. OSE/DMEPA Reviewer was invited to the planning meeting held on September 24, 2015 and to an internal meeting held on November 24, 2015.</p> <p>This consult is being uploaded so that DMEPA can link their review in DARRTS.</p>				
SIGNATURE OF REQUESTER Idara Udoh		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

IDARA UDOH
12/01/2015

Udoh, Idara

From: Udoh, Idara
Sent: Tuesday, November 24, 2015 5:03 PM
To: 'Thomas, Robyn [JRDUS]'
Cc: Patel, Anuja
Subject: FDA Information Request (Biopharmaceutics): NDA 050718-Prior Approval Supplement 050/Janssen Products, L.P./DOXIL/Addition of Italy GSK Site

Tracking:	Recipient	Read
	'Thomas, Robyn [JRDUS]'	
	Patel, Anuja	Read: 11/24/2015 5:04 PM

Good evening, Ms. Thomas. I hope this message finds you well.

FDA refers to your Prior Approval Supplement (PAS)-050, dated and received on September 1, 2015, under NDA050718, where you are proposing the addition of a GlaxoSmithKline manufacturing facility in Polo di Torrile, Italy.

We also refer to our September 29, 2015 and November 17, 2015 Clinical Pharmacology Information Requests; and acknowledge receipt of your responses to the Clinical Pharmacology Information Requests on October 2, 2015 and November 20, 2015, respectively. Lastly, we refer to our November 24, 2015 Information Request addressing the carton and container labeling, and requesting confirmation of Janssen's authorized points of contact to NDA 050718. Your PAS is currently under our review.

We have the following Information Request from our Biopharmaceutics Review Team:

- 1. For in-vitro release testing, mean data of batch # 4002 are provided in Table 3.2.P.5.4. However individual unit data could not be located in the submission dated September 01, 2015. Provide the comparative multipoint dissolution profile data (n=12) of batch # 4002 [Treatment B] and lot numbers DJBS300 and EDBS000 [Treatment A] used in Bioequivalence Study # DOXILNAP1004. In addition, explain the differences in in-vitro release profiles of batch # 4001[20 mg vs. 50 mg].**

Please provide a response to this Information Request by **COB, Friday, November 27, 2015**, in addition to a formal submission to NDA050718.

If you have any questions or concerns, please feel free to contact me.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

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/s/

IDARA UDOH
11/25/2015

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, November 24, 2015 4:35 PM
To: 'Thomas, Robyn [JRDUS]'
Cc: 'Iscott1@its.jnj.com'; Udoh, Idara; 'rmacken1@its.jnj.com'
Subject: FDA Information Request: DOXIL NDA 50-718 /Janssen/ Supplement 50

Importance: High

Hello Ms. Thomas,

We refer to the phone conversation today, November 24, 2015, between myself, Ms. Idara Udoh, and you in reference to your Prior Approval Supplement (PAS) (Supplement 050), dated and received on September 1, 2015, under NDA050718, where you are proposing the addition of a GlaxoSmithKline manufacturing facility in Polo di Torrile, Italy.

As mentioned during the phone call, we have the following request for clarification and information request in regards to your September 1, 2015 submission:

- 1. The labeling for the 20 mg and 50 mg vial and carton labeling submitted on September 1, 2015 lists TTY BioPharm Company Limited as the manufacturing site with a Janssen comment stating that “delete this text”. Please provide clarification as to why the TTY site is being deleted. Does Janssen intend to stop manufacturing product from TTY?**
- 2. Supplement 50 proposes to add GlaxoSmithKline manufacturing facility in Polo di Torrile, Italy. Submit revised carton and container labeling indicating the addition of GlaxoSmithKline manufacturing facility in Polo di Torrile, Italy.**

Finally, we refer to your November 24, 2015 email communication identifying Ilona Scott and Ryan MacKenzie (for CMC related matters) as additional authorized point of contacts for NDA 50718 while you are on vacation November 30, 2015 thru December 8, 2015. We have the following request in regards to your e-mail communication:

- 3. Please formally submit this information as a General Correspondence to your NDA, identifying the above mentioned contacts as authorized points of contacts for the IND and NDA and the dates for which they are authorized to speak.**

Your response to this information request is requested via e-mail to Idara Udoh, your Regulatory contact for Supplement 050, by Noon, EST November 25, 2015 followed with a formal submission to your NDA 50718/Supplement 050.

Please confirm receipt of this e-mail.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)

301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Thomas, Robyn [JRDUS] [<mailto:RThomas@its.jnj.com>]
Sent: Tuesday, November 24, 2015 3:04 PM
To: Patel, Anuja; Udoh, Idara; Okubadejo, Olugbenga (Gbenga)
Cc: Scott, Ilona [JANUS]; MacKenzie, Ryan [JRDUS]
Subject: DOXIL NDA 50-718 & IND 36,778: Janssen Regulatory contacts November 30 2015 - December 08 2015

Hello Anuja, Idara and Gbenga.

I will be out of the office on vacation November 30th – December 8th. If you should have any DOXIL related matters during my absence, please contact Ilona Scott at (908) 228-1830 (lscott1@its.jnj.com) or Ryan MacKenzie (for CMC related matters) at (215) 793-7215 (rmacken1@its.jnj.com).

Additionally, the Janssen offices will be closed November 26th and 27th in observance of the Thanksgiving Holiday.

Thank you and wishing you all a happy Holiday.

Robyn

Robyn Thomas

Janssen Research & Development, L.L.C.
Associate Director, Global Regulatory Affairs Established Products
Phone: (215) 793 7021
Email: rthomas@its.jnj.com

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/s/

ANUJA PATEL
11/24/2015

Udoh, Idara

From: Udoh, Idara
Sent: Tuesday, November 17, 2015 4:23 PM
To: 'Thomas, Robyn [JRDUS]'
Cc: Patel, Anuja
Subject: Additional FDA Information Request (Clinical Pharmacology): NDA 050718-Prior Approval Supplement 050/Janssen Products, L.P./DOXIL/Addition of Italy GSK Site

Tracking:	Recipient	Read
	'Thomas, Robyn [JRDUS]'	
	Patel, Anuja	Read: 11/17/2015 4:29 PM

Good afternoon, Ms. Thomas. I hope this message finds you well.

FDA refers to your Prior Approval Supplement (PAS)-050, dated and received on September 1, 2015, under NDA050718, where you are proposing the addition of a GlaxoSmithKline manufacturing facility in Polo di Torrile, Italy.

We also refer to our September 29, 2015 Clinical Pharmacology Information Request for SAS transport files; and acknowledge receipt of your response to the Clinical Pharmacology Information Request on October 2, 2015. Your PAS is currently under our review.

We have the following additional requests for information from our Clinical Pharmacology review team:

Regarding the encapsulated doxorubicin and total doxorubicin assays used in Study NAP1004, provide:

- 1. Data to demonstrate that the extraction process for the encapsulated doxorubicin assay is able to isolate liposome encapsulated doxorubicin from free doxorubicin in human plasma. It appears that the quality controls used for the validation of the encapsulated doxorubicin assay and during the study only included liposome encapsulated doxorubicin.**
- 2. Data to support the long-term stability of doxorubicin in human plasma. The reported stability data is limited to the stability of encapsulated doxorubicin in human plasma, as it appears that the quality controls used for the total doxorubicin assay only included liposome encapsulated doxorubicin. The study samples for total doxorubicin were first analyzed approximately 6 months after patient sample collection.**

Please provide a response to this Information Request by **COB, Friday, November 20, 2015**, in addition to a formal submission.

If you have any questions or concerns, please feel free to contact me.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365

Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idadara.udoh@fda.hhs.gov (email)

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/s/

IDARA UDOH
11/19/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 29, 2015
From: Idara Udoh – Senior Regulatory Health Project Manager, DOP2/OHOP/CDER
Subject: NDA 050718/Prior Approval Supplement 050 – Janssen Products, L.P. – FDA
Clinical Pharmacology Information Request

Janssen Products, L.P.
Attention: Robyn Thomas, Associate Director, Global Regulatory Affairs
Janssen Research and Development, LLC
Welsh and McKean Roads
Spring House, PA 19477

Dear Ms. Thomas:

Please refer to your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DOXIL® (doxorubicin HCl liposome injection), for intravenous injection, single dose vial: 20 mg/10mL and 50 mg/ 25 mL.

We also refer to your Prior Approval Supplement (PAS), dated and received September 1, 2015, which proposes to add a new manufacturing facility, GlaxoSmithKline Manufacturing S.P.A., in Polo di Torrile, Italy.

We have the following clinical pharmacology comments, in regard to your PAS:

1. Provide SAS transport files for the pharmacokinetic (PK) concentrations and parameters in the following format, and definition files. Provide separate SAS transport files for encapsulated, total, and free doxorubicin.

PK concentration: Subject, Period, Treatment Sequence, Treatment, Site, Concentrations 1, 2,.....,n

PK Parameters: Subject, Period, Treatment Sequence, Treatment, Site, AUCt, AUCinf, Cmax, Tmax, Kel, THALF.....

Please address item 1 above through a formal submission to your NDA 050718, by COB, October 2, 2015. Please send a courtesy copy of your submission via e-mail to me once your submission has been submitted.

Please note that your sNDA submission is currently under review and additional comments may be forthcoming.

NDA 050718 – Janssen Products, L.P.
FDA Clinical Pharmacology Information Request
Prior Approval Supplement 050

If you have any questions, please call me at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

IDARA UDOH
09/29/2015



NDA 050718/S-50

**ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT**

Janssen Products, L.P.
Attention: Robyn Thomas, Associate Director, Global Regulatory Affairs
Janssen Research and Development, LLC
Welsh and McKean Roads
Spring House, PA 19477

Dear Ms. Thomas:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 050718

SUPPLEMENT NUMBER: 050

PRODUCT NAME: DOXIL® (Doxorubicin HCl liposome injection), for intravenous injection, single dose vial: 20 mg/10mL and 50 mg/ 25 mL

DATE OF SUBMISSION: September 1, 2015

DATE OF RECEIPT: September 1, 2015

This supplemental application proposes to add a new manufacturing facility, GlaxoSmithKline Manufacturing S.P.A., in Polo di Torrile, Italy.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 31, 2015, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be January 1, 2016.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

IDARA UDOH
09/25/2015