Author's response to reviews

Title: Lipodox® (generic doxorubicin hydrochloride liposome injection): in vivo efficacy and bioequivalence versus Caelyx® (doxorubicin hydrochloride liposome injection) in human mammary carcinoma (MX-1) xenograft and syngeneic fibrosarcoma (WEHI 164) mouse models

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Version: 1 **Date:** 27 Feb 2017

Author's response to reviews:

Reviewer's comment Response

Reviewer 1

Error bars are missing or cannot be visualized

Figure has been redrawn including error bars

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Version: 2 Date: 27 February 2017

Author's response to reviews: see over

February 27, 2017

The Biomed Central Editorial Team

Object: MS: BCAN-D-16-02493R1 - Lipodox® (generic doxorubicin hydrochloride liposome injection): in vivo efficacy and bioequivalence versus Caelyx® (doxorubicin hydrochloride liposome injection) in human mammary carcinoma (MX-1) xenograft and syngeneic fibrosarcoma (WEHI 164) mouse models. Dr. Vinod Burade et al.

Thank you for consideration of our manuscript for publication in your journal.

We have reviewed the above manuscript according to your reviewer's comments.

Reviewer # 1

MINOR COMMENTS:

The manuscript is well written and provides in detailed efficacy, toxicity and plasma PK profile of Lipodox®. All experiments have been performed using proper controls and a thorough analysis of the results have been presented. The following needs authors clarification or editing:

1. Figure 1a. Error bars are missing or cannot be visualized.

- Error bars added to Figure 1a. Page 35.

2. Authors need to provide an explanation regarding different number of animals used in figure 1a between SPIL DXR HCL treated group (n=11) vs Reference DXR HCL (n=15)

- We have clarified and this information is included in the Study Design, Page 9, lines 224-226: "The aim was to have a minimum of 10 animals per group to get meaningful

conclusions after statistical evaluation. The animals were randomly assigned to different treatment groups (n=11 to n=15)." There were at least 10 animals in each group. There is no other specific reason for the different numbers (11 or 15) of animals per group.

Reviewer # 2

MINOR COMMENTS:

1. Title should be specific to MX-1 cells and/or WEHI 164 cells

- Title has been revised.

2. If SPIL DXR HCL liposome is already approved by FDA and it's already in clinic, then why this study?

- As the sponsor company, SPIL is obligated to publish the results of their preclinical and clinical studies supporting the comparative equivalence of their generic SPIL DXR HCL liposome with the reference product, Caelyx. (Clarification, no additions to manuscript)

3. Why authors only focused on efficacy and bioequivalence features for comparison? What about other pharmacological features, such as, pharmacokinetic and pharmacodynamics, stability, etc? These points' authors should explain thoroughly either in background or discussion section!!

- We have revised the Discussion section to provide more information on the additional studies conducted to demonstrate similarity between the SPIL DXR HCL liposome injection and Caelyx. Information has been added to the Discussion section, page 17, lines 440-448: "The present studies have been conducted in line with guidance proposed by the European Medicines Agency (EMA) [21] and form part of a program of studies designed to demonstrate similarity between the SPIL DXR HCI liposome injection and Caelyx® and Doxil®. The program included other preclinical studies in rodent models of breast cancer and ovarian cancer that assessed comparative plasma and tissue distribution, toxicity, and in vitro haemolytic potentiality; clinical studies in patients with breast or ovarian cancer or multiple myeloma to assess bioequivalence and safety; and physicochemical equivalence studies (structure, content and stability of liposomes in vitro and in vivo). These studies have now been completed, and it is anticipated that they will be published during 2017.

4. Manuscript required proof read, statements and conclusions should be specific to experiments and findings Eg. Title should be specific to MX-1 cells and/or WEHI 164 cells. Results using additional in vitro models should incorporated, if authors wish to state mammary carcinoma or syngeneic fibrosarcoma.

- The title has been amended to specify the use of MX-1 and WEHI 164–bearing mice models of mammary carcinoma and syngeneic fibrosarcoma, respectively. Please also see the amendments to the Discussion section concerning additional studies Page 17, lines 440–448: “The program included other preclinical studies in rodent models of breast cancer and ovarian cancer that assessed comparative plasma and tissue distribution, toxicity, and in vitro haemolytic potentiality; clinical studies in patients with breast or ovarian cancer or multiple myeloma to assess bioequivalence and safety; and physicochemical equivalence studies (structure, content and stability of liposomes in vitro and in vivo). These studies have now been completed, and it is anticipated that they will be publish