Assessing Whether Partial AUCs are Needed to Demonstrate Bioequivalence for Liposomal Doxorubicin

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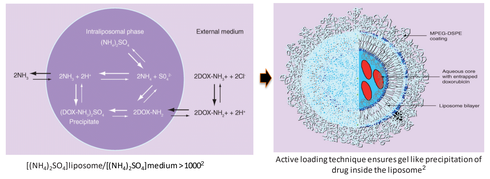
Introduction

- According to the Orange Book,[1] since the first liposome drug product, a PEGylated liposome formulation of doxorubicin HCl (Doxil®, NDA 050718), was approved by the U.S. FDA in 1995, two generic PEGylated liposome formulations of doxorubicin HCl were approved (ANDA 203263, Approved on Feb 04, 2013; and ANDA 208657, Approved on May 15, 2017).
- Liposomal doxorubicin is one of the leading approved nanoparticle products used in cancer therapy and has been shown to have significantly better cardiac safety profile and fewer occurrence of other adverse effects compared to non-liposomal conventional doxorubicin products.[2]
- Though the size of liposomal doxorubicin is about 100 nm, which is essential for liposome extravasation in tumor tissue, the payload of doxorubicin (DOX) inside the liposome is quite high (15,000 DOX molecules/vesicle) which is achieved via an active loading process, with an ammonium sulfate gradient established between liposome interior and exterior environment (Figure on the right).[2,3]

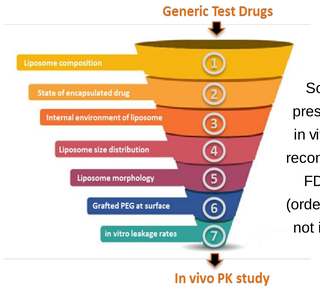


$[(NH_4)_2SO_4]$liposome/$[(NH_4)_2SO_4]$medium > 1000[2]

Active loading technique ensures gel like precipitation of drug inside the liposome[2]

This active loading accumulation of doxorubicin inside the liposome aqueous phase with most of the drug (>90%) present as a precipitate. The precipitate lacks osmotic effects and, thus, contributes to the doxorubicin stability inside the liposome. Precipitation also ensures negligible drug leakage in circulation but satisfactory drug release in targeting tissues.[2]

- FDA's product-specific guidance[4] (PSG) for PEGylated liposome formulation of doxorubicin HCl recommends both in vitro and in vivo studies. In addition to in vivo bioequivalence (BE) studies, the test product needs to show equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage rates comparable to the reference product. The main purpose of such rigorous in vitro studies recommendation is to reduce the chances of non-bioequivalent scenario in in vivo PK BE study.



Schematic presentation of in vitro studies recommended in FDA's PSG (order of study is not important).

- As per FDA's PSG recommendation,[4] for the in vivo PK study, the BE demonstration of test product to reference product is based on 90% confidence interval (CI) of C_{max} and AUC in two analytes, i.e., free doxorubicin and liposome-encapsulated doxorubicin in plasma. The European Medicines Agency (EMA)'s PSG for doxorubicin[5] additionally recommends partial AUCs (e.g., AUC_{0-48} and $AUC_{48-last}$) for liposome-encapsulated doxorubicin analytes, but not for free doxorubicin analytes.

Purpose

The purpose of this study was to determine if partial AUCs are needed as additional metrics to demonstrate BE based on in-house ANDA data and available exposure-response analysis for doxorubicin.

Methods

Individual patient data (concentration vs. time) of multiple in-house ANDA applications that included measurements of both free doxorubicin and liposome-encapsulated doxorubicin analytes were used for this study. R-program (version R-3.6.1) was used for data collection and plotting graphs. Phoenix software (version 7.0) was used to calculate point estimate (geometric least squares means ratio of test and reference) and 90% CI of C_{max}, AUC_{0-t} and pAUCs (including AUC_{0-24}, AUC_{0-48}, AUC_{0-72}, AUC_{0-96} and $AUC_{48-last}$) of log (natural) transformed data. The PK metric of $AUC_{48-last}$ was only assessed for liposome-encapsulated doxorubicin analyte as recommended by EMA's guidance. The test product was deemed BE to the reference product if the point estimate and 90% CI limit of the respective PK metrics fall within 80%-125% range. Residual variabilities of the respective PK metrics of both analytes for each ANDA were also assessed to find the PK metric (C_{max} vs AUC_{0-t} vs pAUCs) that has highest residual variabilities. Individual PK metric of both analytes were compared side-by-side [e.g., $C_{max(free\ dox)}$ vs $C_{max(encap\ dox)}$] to get an insight about the variability of these analytes. Literature data were studied to understand the exposure-response relationship of liposomal doxorubicin.

Results and Discussion

Assessing BE of PK metrics of in-house ANDA data

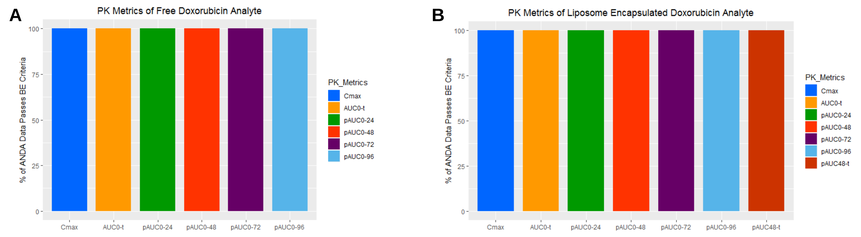
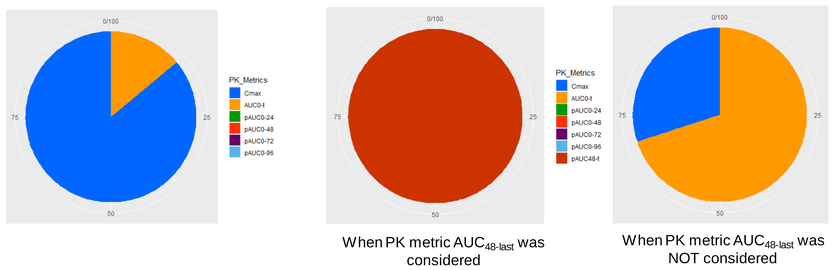


Figure 1: The percentage of ANDA data passes BE criteria. (A) PK metrics of free doxorubicin analyte (B) PK metrics of liposome encapsulated doxorubicin analyte

All the evaluated PK metrics of C_{max}, AUC_{0-t} and pAUCs (AUC_{0-24}, AUC_{0-48}, AUC_{0-72} and AUC_{0-96} for both analytes; $AUC_{48-last}$ for liposome-encapsulated doxorubicin analyte only) passed the BE criteria.

Finding the PK metric of each analyte that shows highest residual variability



When PK metric $AUC_{48-last}$ was considered

When PK metric $AUC_{48-last}$ was NOT considered

Figure 3: Percentage of PK metric of analyzed ANDA data showed highest residual variability. (A) Percentage of PK metric of analyzed ANDA data associated with free doxorubicin analyte (B) Percentage of PK metric of analyzed ANDA data associated with liposome encapsulated doxorubicin analyte.

For free doxorubicin analyte, C_{max} showed highest residual variability in ~ 85% ANDAs (ranges 26% - 61% among ANDAs) while AUC_{0-t} had highest residual variability for remaining ANDAs. On the other hand, $AUC_{48-last}$ of liposome-encapsulated doxorubicin analyte, showed highest residual variability in 100% ANDAs (ranges 13% - 25% among ANDAs). When $AUC_{48-last}$ was not considered, AUC_{0-t} of liposome-encapsulated doxorubicin analyte showed highest residual variability in ~70% ANDAs (ranges 10% - 26% among ANDAs) while C_{max} had highest residual variability for remaining ANDAs (ranges 7% - 15% among ANDAs).

Comparing residual variability of individual PK metrics between two analytes

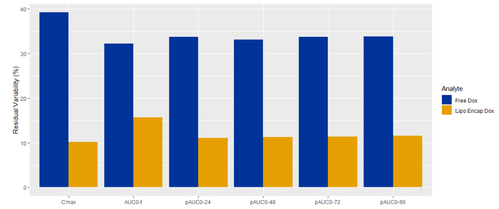


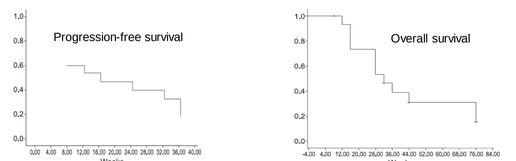
Figure 2: Comparison of mean residual variability of PK metric (of all ANDA data)

Residual variabilities of all PK metrics associated with free doxorubicin analyte were consistently higher than that of liposome-encapsulated doxorubicin analyte in all ANDA data which suggests that free doxorubicin analyte is more variable than liposome-encapsulated doxorubicin analyte.

Assessing potential exposure-response relationship of pAUCs

Efficacy data of liposomal doxorubicin from published literature and new drug application (NDA) suggest that the clinical efficacy of liposomal doxorubicin is evaluated by disease progression and/or overall patient survival after a few months from the treatment initiation.

Clinical efficacy (Kaplan-Meier plot) of liposomal doxorubicin in ovarian cancer patients[6]



Liposomal doxorubicin is for a chronic treatment. It dose not have a multiphasic in vivo PK profile. From the literature analysis, there is no established pharmacodynamic (PD) biomarker to corelate the PD effect with PK or partial exposure to support the clinical relevance of partial AUCs.

Conclusions

- All evaluated PK metrics including partial AUCs passed BE criteria based on in-house ANDA data which may indicate that the rigorous in vitro studies including comparable leakage/release rate recommended in FDA's PSG may have helped to ensure in vivo bioequivalence of these products.
  - Adding pAUC does not appear to enhance the discrimination in assessing formulation differences.
- As an analyte, free doxorubicin is more variable than liposome encapsulated doxorubicin analyte. While within free doxorubicin analyte, C_{max}, but not pAUCs, was found to have the highest residual variability in most ANDAs. Within liposome-encapsulated doxorubicin, $AUC_{48-last}$ showed the highest residual variability in submitted ANDAs.
- Based on analyses from this study and a lack of multiphasic in vivo PK profile and exposure-response relationship to support clinical relevance of partial AUCs for liposomal doxorubicin, including partial AUCs as additional metrics to demonstrate BE for liposomal doxorubicin product does not seem to be warranted.

Acknowledgments

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References

(1) Orange book (accessed on 10/26/2019) search on Doxorubicin (sub search: Liposomal) **(2)** Wenlei Jiang, Robert Lionberger & Lawrence Yu. In vitro and in vivo characterizations of PEGylated liposomal doxorubicin. Bioanalysis, 2011, 3(3), 333 **(3)** Upendra Bulbake, Sindhu Doppalapudi, Nagavendra Kommineni and Wahid Khan. Liposomal Formulations in Clinical Use. Pharmaceutics 2017, 9, 12 **(4)** FDA's product-specific guidance for doxorubicin hydrochloride liposome injection Recommended: Feb 2010, Revised: Sept 2018. www.accessdata.fda.gov /drugsatfda_docs/psg/Doxorubicin%20Hydrochloride_draft_Injection%20injec%20lipo_RLD%2050718_RC09-18.pdf **(5)** EMA's product-specific bioequivalence guidance for pegylated liposomal doxorubicin hydrochloride. Recommended: 13 December, 2018. www.ema.europa.eu/en/ documents/scientific-guideline/pegylated-liposomal-doxorubicin-hydrochloride-concentrate-solution-2-mg/ml-product-specific-bioequivalence-guidance_en.pdf **(6)** G. Gorumlu et al. 2008. Pegylated liposomal doxorubicin in heavily pretreated epithelial ovarian cancer patients. Journal of BUON 13: 349-352.

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