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Pegylated liposomal doxorubicin hydrochloride concentrate for solution 2 mg/ml product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	April 2018
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End of consultation (deadline for comments)	30 September 2018
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Keywords	***Bioequivalence, generics, pegylated liposomal doxorubicin hydrochloride***

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Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

Bioequivalence study design	**Single dose study:** Any dose (but no dose adjustments for toxicities during the study) in e.g. stable ovarian/breast cancer patients. **Background:** Dose proportional pharmacokinetics.
	cross-over
	Other critical aspects: The single dose study may need to be conducted with standardized light meals rather than in the fasting state due to patient's needs.
Analyte	☐ **total drug** ☒ **encapsulated drug** ☒ **unencapsulated drug** ☐ **doxorubicinol (metabolite)** **Other critical aspects:** Unencapsulated drug concentrations must be achieved by means of appropriate

	bioanalytical methods rather than by subtracting encapsulated from total drug.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, partial AUCs (e.g. AUC_{0-48h} and $AUC_{48-tlast}$) **Background/justification:** AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for encapsulated and unencapsulated drug. Partial AUCs for the encapsulated drug to ensure profile comparability.
	90% confidence interval acceptance limits: 80.00 – 125.00%
Additional information can be added if considered necessary	**To be noted**: Proving equivalent efficacy and safety of a liposomal formulation developed to be similar to an innovator product is considered a step-wise approach which in addition to the pharmacokinetic study also takes account of quality and non-clinical comparison, where appropriate.

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}, C_T, ss and partial AUC. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.