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Committee for Medicinal Products for Human Use (CHMP)

Exenatide powder and solvent for prolonged-release suspension for injection, 2 mg, and powder and solvent for prolonged-release suspension for injection in pre-filled pen, 2 mg product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party	June 2016
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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** *in case a BCS biowaiver is not feasible or applied*	**Single dose:** 2 mg, healthy volunteers **Multiple dose:** 2 mg, patients **Background:** Single dose and multiple dose studies required for prolonged release formulations with accumulation.
	cross-over or parallel
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**

Bioequivalence assessment	**Main pharmacokinetic variables:** **Single dose:** AUC_{0-t}, AUC_{0-inf}, $C_{max\ (initial\ burst)}$ and $C_{max\ (extended\ release\ phase)}$ **Multiple dose:** $AUC_{0-\tau}$, $C_{max,ss}$ and $C_{\tau,ss}$ **Background:** In the single dose study, $C_{max\ (initial\ burst)}$ and $C_{max\ (extended\ release\ phase)}$ should be analysed. The $C_{max\ (initial\ burst)}$ is important from a safety perspective.
	90% confidence interval: 80.00–125.00 % for all parameters except from $C_{max\ (initial\ burst)}$. For $C_{max\ (initial\ burst)}$ the upper limit should not exceed 125.00 %. **Background:** For the initial burst it is sufficient to demonstrate that plasma concentrations are not higher for the generic compared to the reference product.

* 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} $C_{\tau,ss}$, and partial AUC. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.

** For prolonged release formulations: If a single-dose study with the highest strength has shown that there is low risk of accumulation (i.e. $AUC\tau$ > 90 % of AUC_{inf}), the multiple-dose study may be waived. If low degree of accumulation is expected, the applicants might follow respective guideline recommendations.