Paracetamol oral use immediate release formulations product-specific bioequivalence guidance

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* This revision concerns defining what is meant by 'comparable' T_{max} as an additional main pharmacokinetic variable in the bioequivalence assessment section of the guideline.

Keywords	*Bioequivalence, generics, paracetamol*

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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)*

BCS Classification**	BCS Class: ☒ I ☐ III ☐ Neither of the two **Background:** Paracetamol is considered a high solubility compound with >85% absorption.
Bioequivalence study design _in case a BCS biowaiver is not feasible or applied_	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: Depends on the applied generic formulation; in principle any strength may be used. **Background:** Multiple product formulations are available; as paracetamol is highly soluble and shows linear pharmacokinetics, in principle any strength may be used.

	Number of studies: In general, one single dose study
	Other design aspects: Additional studies may be necessary depending on the formulation in accordance with the Guideline on the Investigation of Bioequivalence (for example orodispersible tablets)
Analyte	☒ **parent**　　　☐ **metabolite**　　　☐ **both**
	☒ **plasma/serum**　　　☐ **blood**　　　☐ **urine**
	Enantioselective analytical method:　　☐ **yes**　　☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** C_{max}, AUC_{0-t} and T_{max}
	90% confidence interval: 80.00–125.00% for C_{max} and AUC_{0-t}. Comparable median (≤ 20% difference, 80.00–125.00%) and range for T_{max}.

* 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}. If high intra-individual variability (CV_{intra} > 30%) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether in vivo studies seem to be mandatory (BCS class II and IV) or, on the contrary (BCS Class I and III), the Applicant may choose between two options: in vivo approach or in vitro approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85% within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).