EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2022
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Committee for Medicinal Products for Human Use (CHMP)

Paracetamol oral use immediate release formulations product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	April 2017
Adopted by CHMP for release for consultation	22 June 2017
Start of public consultation	28 July 2017
End of consultation (deadline for comments)	31 October 2017
Agreed by Pharmacokinetics Working Party (PKWP)	December 2017
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Start of public consultation	4 April 2022
End of consultation (deadline for comments)	31 July 2022
Agreed by Pharmacokinetics Working Party (PKWP)	
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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.

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12
13

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) 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).