EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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
Adopted by CHMP	25 January 2018
Date of coming into effect	1 August 2018
Draft Agreed by Pharmacokinetics Working Party (PKWP)	March 2022
Adopted by CHMP for release for consultation	25 March 2022
Start of public consultation	4 April 2022
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Draft revision agreed by Methodology Working Party (MWP)	3 April 2025
Adopted by CHMP	14 April 2025
Date of coming into effect	1 November 2025

* This revision addresses addition of partial AUC as a main pharmacokinetic variable in accordance with the ICH M13A 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 (MWP)*

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: Highest strength applied for, for a drug with linear pharmacokinetics. **Background:** Multiple product formulations are available.

	Number of studies: In general, one single dose study
	Other design aspects: Additional studies may be necessary depending on the formulation (e.g. orally disintegrating 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 either T_{max} or partial AUC
	90% confidence interval: 80.00–125.00% for C_{max}, AUC_{0-t}, (and partial AUC). 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, at this stage it is not possible to recommend 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).