



EUROPEAN MEDICINES AGENCY
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Committee for Medicinal Products for Human Use (CHMP)

Ibuprofen oral use immediate release formulations 200–800 mg product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	April 2017
Adopted by CHMP for release for consultation	20 July 2017
Start of public consultation	3 August 2017
End of consultation (deadline for comments)	31 October 2017
Agreed by Pharmacokinetics Working Party (PKWP)	April 2018
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Date of coming into effect	1 December 2018
Draft Agreed by Pharmacokinetics Working Party (PKWP)	March 2022
Adopted by CHMP for release for consultation	25 March 2022
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Agreed by Pharmacokinetics Working Party (PKWP) / Methodology Working Part (MWP)	11 April 2023
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* This revision addresses addition of partial AUC as a main pharmacokinetic variable in accordance with the ICH M13A guideline

Keywords	<i>Bioequivalence, generics, ibuprofen</i>
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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: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two Background: Ibuprofen may be considered a low solubility compound.
Bioequivalence study design <i>in case a BCS biowaiver is not feasible or applied</i>	single dose cross-over
	healthy volunteers
	<input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed
	Strength: The highest strength which is applied for should be studied. Background: Pharmacokinetics is linear between 200 mg and 800 mg.
	Number of studies: In general, one single dose study.

	Other design aspects: Additional studies may be necessary depending on the formulation (e.g. orodispersible tablets).
Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-t} , C _{max} and either T _{max} or partial AUC.
	90% confidence interval: 80.00–125.00% for AUC _{0-t} , C _{max} , (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, 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).