



1 20 July 2017
2 EMA/CHMP/356876/2017
3 Committee for Medicinal Products for Human Use

4 **Ibuprofen 200 - 800 mg oral use, immediate release**
5 **formulations product-specific bioequivalence guidance**
6 **Draft**

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

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Comments should be provided using this [template](#). The completed comments form should be sent to PKWPsecretariat@ema.europa.eu

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Keywords	<i>Bioequivalence, generics, ibuprofen</i>
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Ibuprofen 200 - 800 mg oral use, immediate release formulations product-specific bioequivalence guidance

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: <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 in accordance with the Guideline on the Investigation of Bioequivalence (for example 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 checked="" type="checkbox"/> yes <input type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: C_{max} , $AUC_{(0-t)}$ and T_{max} for S enantiomer. Background/justification: The enantiomers have different pharmacodynamics and pharmacokinetics and the rate of absorption has been shown to affect the ratio of enantiomers.
	90% confidence interval: 80.00 –125.00% for C_{max} and $AUC_{(0-t)}$. Comparable median 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 seems 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).

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