



1 25 March 2022  
2 EMA/CHMP/356876/2017 Rev.1\*  
3 Committee for Medicinal Products for Human Use (CHMP)

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

<b>Draft Agreed by Pharmacokinetics Working Party (PKWP)</b>	April 2017
<b>Adopted by CHMP for release for consultation</b>	20 July 2017
<b>Start of public consultation</b>	3 August 2017
<b>End of consultation (deadline for comments)</b>	31 October 2017
<b>Agreed by Pharmacokinetics Working Party (PKWP)</b>	April 2018
<b>Adopted by CHMP</b>	31 May 2018
<b>Date of coming into effect</b>	1 December 2018
<b>Draft Agreed by Pharmacokinetics Working Party (PKWP)</b>	March 2022
<b>Adopted by CHMP for release for consultation</b>	25 March 2022
<b>Start of public consultation</b>	4 April 2022
<b>End of consultation (deadline for comments)</b>	31 July 2022
<b>Agreed by Pharmacokinetics Working Party (PKWP)</b>	
<b>Adopted by CHMP</b>	
<b>Date of coming into effect</b>	

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8 \* This revision concerns defining what is meant by 'comparable'  $T_{max}$  as an additional main  
9 pharmacokinetic variable in the bioequivalence assessment section of the guideline.  
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Comments should be provided using this [template](#). The completed comments form should be sent to [PKWP@ema.europa.eu](mailto:PKWP@ema.europa.eu)

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<b>Keywords</b>	<b><i>Bioequivalence, generics, ibuprofen</i></b>
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13 Ibuprofen oral use immediate release formulations 200 – 800 mg product-specific  
 14 bioequivalence guidance  
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16 *Disclaimer:*

17 *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*  
 18 *marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.*

19 Requirements for bioequivalence demonstration (PKWP)\*

<b>BCS Classification**</b>	<b>BCS Class:</b> <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> <b>Neither of the two</b> <b>Background:</b> Ibuprofen may be considered a low solubility compound.
<b>Bioequivalence study design</b> <i>in case a BCS biowaiver is not feasible or applied</i>	<b>single dose</b> <b>cross-over</b>
	<b>healthy volunteers</b>
	<input checked="" type="checkbox"/> <b>fasting</b> <input type="checkbox"/> <b>fed</b> <input type="checkbox"/> <b>both</b> <input type="checkbox"/> <b>either fasting or fed</b>
	<b>Strength:</b> The highest strength which is applied for should be studied.
	<b>Background:</b> Pharmacokinetics is linear between 200 mg and 800 mg.
	<b>Number of studies:</b> In general one single dose study.
<b>Other design aspects:</b> Additional studies may be necessary depending on the formulation in accordance with the Guideline on the Investigation of Bioequivalence (for example orodispersible tablets).	

<b>Analyte</b>	<input checked="" type="checkbox"/> <b>parent</b> <input type="checkbox"/> <b>metabolite</b> <input type="checkbox"/> <b>both</b>
	<input checked="" type="checkbox"/> <b>plasma/serum</b> <input type="checkbox"/> <b>blood</b> <input type="checkbox"/> <b>urine</b>
	<b>Enantioselective analytical method:</b> <input type="checkbox"/> <b>yes</b> <input checked="" type="checkbox"/> <b>no</b>
<b>Bioequivalence assessment</b>	<b>Main pharmacokinetic variables:</b> AUC <sub>0-t</sub> , C <sub>max</sub> and T <sub>max</sub> .
	<b>90% confidence interval:</b> 80.00 – 125.00% for AUC <sub>0-t</sub> and C <sub>max</sub> . Comparable median (≤ 20% difference) and range for T <sub>max</sub> .

20 \* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to  
21 recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C<sub>max</sub>. If high intra-  
22 individual variability (CV<sub>intra</sub> > 30 %) is expected, the applicants might follow respective guideline recommendations.

23 \*\* 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  
24 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  
25 case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility  
26 experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being  
27 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  
28 unacceptable differences in the excipient composition).