



1 15 December 2016  
2 EMA/CHMP/805479/2016  
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Crizotinib hard capsules 200 mg and 250 mg product-**  
5 **specific bioequivalence guidance**  
6 **Draft**

Draft Agreed by Pharmacokinetics Working Party	October 2016
Adoption by CHMP for release for consultation	15 December 2016
Start of public consultation	22 December 2016
End of consultation (deadline for comments)	31 March 2017

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

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<b>Keywords</b>	<b><i>Bioequivalence, generics, crizotinib</i></b>
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11 Crizotinib hard capsules 200 mg and 250 mg product-specific bioequivalence  
12 guidance  
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14 Disclaimer:

15 *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*  
16 *marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.*

17 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> Crizotinib is considered a low solubility compound with limited absorption.
<b>BE 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> 250 mg <b>Background:</b> Highest strength to be used for a drug with linear pharmacokinetics with low solubility.

	<b>Number of studies:</b> one single dose study
<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>0-72<sub>r</sub></sub> and C <sub>max</sub>
	<b>90% confidence interval:</b> 80.00–125.00%

18 \* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to  
19 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-  
20 individual variability (CV<sub>intra</sub> > 30%) is expected, the applicants might follow respective guideline recommendations.

21 \*\* 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  
22 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  
23 case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility  
24 experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being  
25 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  
26 unacceptable differences in the excipient composition).