



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Sirolimus coated tablets 0.5, 1 and 2 mg, oral solution 1 mg/ml product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party (PKWP)	October 2013
Adoption by CHMP for release for consultation	24 October 2013
Start of public consultation	15 November 2013
End of consultation (deadline for comments)	15 February 2014
Agreed by Pharmacokinetics Working Party	29 April 2015
Adoption by CHMP	21 May 2015
Date of coming into effect	1 December 2015
Draft revision agreed by Methodology Working Party	29 April 2025
Adoption by CHMP	12 May 2025
Start of public consultation	10 July 2025
End of consultation (deadline for comments)	31 October 2025

*This revision addresses the requirements for a fasting study only and not both a fasting and fed study for the oral solution in accordance with the ICH M13A guideline.

Comments should be provided using this [EUSurvey](#). For any technical issues, please contact the [EUSurvey Support](#)

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Keywords	<i>Bioequivalence, generics, sirolimus</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 (PKWP)

BCS Classification	BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two Background: Sirolimus 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 checked="" type="checkbox"/> both <input type="checkbox"/> either fasting or fed Tablets: Sirolimus tablets are considered a “high risk product”. Since the specific formulation (e.g. manufacture, excipients) of the tablets is known to be critical to the performance of the formulation, it

	<p>cannot be assumed that the impact of food will be the same regardless of formulation. Therefore, both fasted and fed state comparisons of test to reference formulations are required.</p> <p>A waiver for this fed study may be applicable if the products are manufactured using the same technology and if excipients that might affect bioavailability are qualitatively the same and quantitatively similar between test and reference product.</p> <p>Oral solution: A fasting study is sufficient.</p> <hr/> <p>Strength: Tablets: 2 mg and 0.5 mg</p> <p style="padding-left: 40px;">Oral solution: 1 mg/ml used at 2 mg dose (corresponding to highest tablet strength)</p> <p>Background:</p> <p>Tablets: highest strength to be used for a drug with linear pharmacokinetics. The 0.5 mg tablets are not strictly bioequivalent with the higher strengths in terms of C_{max}.</p> <p>Oral solution: a bioequivalence study for the solution will be necessary unless the composition is qualitatively the same and quantitatively similar to the originator. If there is a quantitative difference in solubility enhancers, a bioequivalence study will be necessary if the differences cannot be justified by other data.</p> <hr/> <p>Number of studies</p> <p>For tablets: Four studies: single dose fasting and fed at 2 mg and single dose fasting and fed at 0.5 mg. The fed study for the 0.5 mg strength can be waived if the 0.5 mg and 2 mg tablets are dose-proportional.</p> <p>For oral solution: One single dose fasting study.</p>
Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input type="checkbox"/> plasma/serum <input checked="" 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} and C _{max}
	90% confidence interval: 80.00 – 125.00% for C _{max} and 90.00 - 111.11% for AUC _{0-t} Background: sirolimus is a narrow therapeutic index drug.