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3 Committee for Medicinal Products for Human Use (CHMP)

4 Sirolimus Product-Specific Bioequivalence Guidance

5 Draft

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Start of public consultation	15 November 2013
End of consultation (deadline for comments)	15 February 2014

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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	***Bioequivalence, generics, sirolimus***

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Sirolimus 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:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Sirolimus may be considered a low solubility compound.
BE Study design	**single dose** **cross-over**
	healthy volunteers
	☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed**

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	Due to specific formulation characteristics. High-fat meal.
	Strength: Tablets: 5 mg and 0.5 mg Oral solution: 1 mg/ml **Background:** For tablets dose proportionality between 2 mg and 5 mg doses. 0.5 mg tablets are not strictly bioequivalent with the higher strengths in terms of Cmax. A BE 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 BE study will be necessary if the differences cannot be justified by other data.
	Number of studies: four two-way cross-over single dose studies for the tablets (or two four-ways cross over single dose studies) and two two-ways cross over single dose studies for the oral solution (or one four-ways cross-over single dose study).
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☐ **plasma** ☒ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, Cmax
	90% confidence interval: 80.00– 125.00 for Cmax and 90.00-111.00 for AUC_{0-t} **Background:** Sirolimus is a narrow therapeutic index drug. Cmax appears not to be critical for efficacy/safety.

* As drug variability has not been reviewed, this guidance is not applicable to highly variables drugs.

** The BCS classification should be confirmed by the Applicant at time of submission based on available data (solubility experiments, literature, etc.). If a drug substance has been classified as BCS class II or IV, no further solubility investigations are needed.