1 April 2016
EMA/CHMP/159744/2016
Committee for Medicinal Products for Human Use (CHMP)

Tacrolimus granules for oral suspension 0.2 and 1 mg product-specific bioequivalence guidance*

Draft agreed by Pharmacokinetics Working Party	April 2015
Adoption by CHMP for release for consultation	24 September 2015
Start of public consultation	1 October 2015
End of consultation (deadline for comments)	1 January 2016
Agreed by Pharmacokinetics Working Party	23 February 2016
Adoption by CHMP	1 April 2016
Date for coming into effect	1 November 2016

*This guideline was previously published as part of a “compilation of individual product-specific guidance on demonstration of bioequivalence Rev.3 EMA/CHMP/736403/2014”

Keywords	***Bioequivalence, generics, tacrolimus***

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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:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** tacrolimus may be considered a low solubility compound.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 1 mg **Background:** highest strength to be used for a drug with linear pharmacokinetics and low solubility. Higher doses may be needed (multiple 1 mg doses) in case of poor bioanalytical methods.

	Number of studies: one single dose study
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☐ **plasma/serum** ☒ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h} and C_{max}
	90% confidence interval: 80.00 – 125.00% for C_{max} and 90.00 - 111.11% for AUC_{0-72h} **Background:** tacrolimus is a narrow therapeutic index drug.

* 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.