14 April 2025
EMA/CHMP/315234/2014 Rev.3*
Committee for Medicinal Products for Human Use (CHMP)

Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg 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 for coming into effect	1 December 2015
Draft agreed by Pharmacokinetics Working Party (PKWP)	June 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of public consultation	2 August 2017
End of consultation (deadline for comments)	31 October 2017
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Adopted by CHMP for release for consultation	25 March 2022
Start of public consultation	4 April 2022
End of consultation (deadline for comments)	31 July 2022
Agreed by Pharmacokinetics Working Party (PKWP) / Methodology Working Party (MWP)	11 April 2023
Adopted by CHMP	26 April 2023
Date of coming into effect	1 January 2024
Draft revision agreed by Methodology Working Party (MWP)	3 April 2025
Adopted by CHMP	14 April 2025
Date of coming into effect	1 November 2025

* This revision classified tadalafil as a high-risk product and adds partial AUC as a main pharmacokinetic variable in accordance with the ICH M13A guideline

Keywords	***Bioequivalence, generics, tadalafil***

Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg 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 (MWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Tadalafil is 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** **Background:** Tadalafil is considered a "high-risk product". Since the specific formulation (excipients) of the tablet is known to be critical to the performance of the formulation in fed conditions, it 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.

	A waiver for this fed study may be applicable if it can be shown that 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.
	Strength: 20 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics.
	Number of studies: Two single dose studies (20 mg fasted and 20 mg fed)
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, C_{max} and T_{max} or partial AUC
	90% confidence interval: 80.00–125.00% for AUC_{0-72h} $C_{max,}$ (and partial AUC). Comparable median (≤ 20% difference, 80.00–125.00%) and range for $T_{max.}$

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, at this stage it is not possible to recommend 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.

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