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Committee for Medicinal Products for Human Use (CHMP)

Semaglutide, 0.25, 0.5, 1 and 2 mg solution for injection in pre-filled pen, 0.25, 0.5, 1, 1.7 and 2.4 mg solution for injection in pre-filled pen and 0.25, 0.5, 1, 1.7 and 2.4 mg FlexTouch solution for injection in pre-filled pen product-specific bioequivalence guidance

Draft Agreed by Methodology Working Party (MWP)	29 April 2026
Adopted by CHMP for release for consultation	11 May 2026
Start of public consultation	14 July 2026
End of consultation (deadline for comments)	31 October 2026

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	***Bioequivalence, generics, semaglutide***

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Semaglutide 0.25, 0.5, 1 and 2 mg solution for injection in pre-filled pen
Semaglutide, 0.25, 0.5, 1, 1.7 and 2.4 mg solution for injection in pre-filled pen and Semaglutide, 0.25, 0.5, 1, 1.7 and 2.4 mg FlexTouch solution for injection in pre-filled pen

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)*

Bioequivalence study design *in case a biowaiver is not feasible or applied*	**single dose** **cross-over** Prior to conduct of a BE study, semaglutide substance sameness should be demonstrated.
	healthy volunteers
	☐ **fasting** ☐ **fed** ☐ **both** ☒ **either fasting or fed**
	Strength available: 0.5mg/0.37ml, 0.5mg/0.74 ml or 0.5 mg/0.5 ml

	A single dose study at the 0.5 mg dose level (at the same concentration level for test and reference) should be applied. The outcome of this study may be extrapolated to the other strengths and formulations (with or without preservative). **Background:** Despite the fact that the different strengths for the innovator formulation are not dose-proportional, and the excipients of the multiple and single dose formulations differ, PK is known not to be affected by these differences.
	Number of studies: One single dose study, either using the formulation with or without preservative **Background:** Even though the excipients of the multiple and single dose formulations differ with respect to preservative, these products are interchangeable.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and C_{max}
	90% confidence interval: 80.00– 125.00%
Waiver of PK bioequivalence study	The described in-vitro comparison should always be conducted, regardless of whether a comparative PK study is intended or has been conducted or a waiver is applied for. A comparative PK study can be waived if the formulation is qualitatively the same and quantitatively similar to the reference product and comparability has been demonstrated in vitro using a range of orthogonal techniques. The choice of the techniques should be justified by the applicant. Analytical methods typically used to demonstrate comparability include but are not limited to:

	• Primary structure: peptide sequence by Mass Spectrometry (usually LC-MS/MS) and enantiomeric purity by chiral GC-MS. • Secondary and tertiary structure: FTIR spectroscopy, FT-Raman spectroscopy, far and near UV Circular Dichroism (CD), intrinsic fluorescence spectroscopy, UV spectrometry and 2D NMR. • Oligomer formation: SV-AUC, SEC-UV HPLC, SEC-MALS, DOSY and DLS • Peptide aggregation/fibril formation: near-UV circular dichroism, TEM, intrinsic fluorescence spectroscopy, NMR, SEC-HPLC, SEC-MALS, SV-AUC, DLS and thioflavin T assay • Comparability of the oligomerisation should be demonstrated and the formation of fibrils should be minimised. The levels of fibrillation should be determined by appropriate analytical techniques and compared with the reference product, also at end of shelf-life. Kinetic measurements of fibril formation under mechanical stress treatment should be performed. This treatment should ideally be designed in a way that it mimics possible stress conditions that the product could be exposed to during storage, transport, and handling by patients. The method should be sufficiently discriminatory to detect different levels of fibril formation before a plateau is reached. A positive control should be included. • In vitro pharmacology: cellular assays, receptor binding • Physicochemical properties: pH, buffer capacity, osmolality, density At least 5 batches of the test and reference product should be included in the comparability studies. More batches may be needed in case of higher variability of the reference product results. The selection of the test- and reference batches, the studies, choice of statistical methods and acceptance criteria should be justified. The described in-vitro comparison should always be conducted. The potential impact of any differences in dosing-/administration device, including different needles, on the efficacy and safety should also be evaluated. If all comparisons comply, a waiver of a PK equivalence study is acceptable. If comparability cannot be concluded for the oligomerisations, a PK study should be conducted to evaluate the effect. If other comparisons do not comply, the proposed product should be reformulated.

	Where several strengths, concentrations, compositions, and volumes of the product are proposed, a bracketing approach may be applied if adequately justified. Bracketing cannot be applied over different compositions.

* 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.