Notes on the design of bioequivalence study: Nicotine Transdermal Patch

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines of submission of documentation for WHO prequalification. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-seventh Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited transdermal patches containing nicotine.

Pharmacokinetics of nicotine in transdermal patches

Following transdermal application, the skin rapidly absorbs nicotine.

For the patches labelled by the average amount of nicotine released over 16 hours, a linear relationship exists between released amount of nicotine (dose) and plasma levels of nicotine over the therapeutic dose range, 10-25 mg/16 hours. Plasma nicotine concentrations show dose proportionality for the three patch doses. The calculated peak plasma levels are 11 ng/mL for the 10 mg patch and 25 ng/mL for the 25 mg patch. Interpolation yields a peak plasma concentration of 16 ng/mL for the 15 mg patch. The maximum level of plasma concentration after administration is reached after approximately 9 hours (tmax). The plasma peak is in the afternoon/ evening when the risk of relapse is highest. The half-life approximately 3 hours. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound.

For the patches labelled by the average amount of nicotine released over 24 hours, the plasma concentrations of nicotine reach a plateau within 2-4 hours after initial application, with relatively constant plasma concentrations persisting for 24 hours or until the patch is removed. Approximately 68% of the nicotine released from the patch enters systemic circulation and the remainder of the released nicotine is lost via vaporisation from the edge of the patch. Plasma concentrations of nicotine are proportional to dose. With continuous daily application (worn for 24 hours), dose-dependent steady state plasma nicotine concentrations are achieved following the second application and are maintained throughout the day. The mean plasma steady state concentrations of nicotine are approximately 17 ng/ml for the 21 mg/day patch, 12 ng/ml for the 14 mg /day patch and 6 ng/ml for the 7 mg/day patch. For comparison, half-hourly smoking of cigarettes produces average plasma concentrations of approximately 44 ng/ml. The pronounced early peak in nicotine blood levels seen with inhalation of cigarette smoke is not observed with the transdermal patches. The half-life of nicotine ranges from 1 to 2 hours.

Guidance for the design of bioequivalence studies:

Taking into account the pharmacokinetic properties of nicotine in transdermal patches, the following guidance with regard to the study design should be taken into account:

Design: A single-dose cross-over design is recommended.

Dose: As the EoI includes 5 – 25 mg/16 h and 7 – 21 mg/24 h, the bioequivalence study should be conducted with the highest strength. The other strengths may be waived if the conditions for an additional strength biowaiver are fulfilled: same excipients and manufacturing process, proportional areas and similar dissolution profiles.

Fasting/fed: N/A.

Subjects: Healthy adult subjects should be recruited. It is not necessary to include patients in the bioequivalence study.

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. The data for the parent compound should be used to assess bioequivalence of nicotine transdermal patches.

Sample size: Information currently available in the literature suggest that the intra-subject variability is 10% for C_{max} and $AUC_{0\text{-}t}$ (DOI: 10.1002/cpdd.431). However, other parameters like C_{τ} (i.e. $C_{16\,h}$ or $C_{24\,h}$) are expected to exhibit a higher variability. A pilot study may be required to estimate of the intra-subject variability of all the primary PK parameters for a proper sample size calculation.

Washout: Taking into account the elimination half-life of the nicotine in healthy volunteers is reported to be approximately 3 hours, a cross-over design with a wash out period of at least 2 days could be feasible.

Blood sampling: The blood sampling should be intensive around the expected t_{max} and cover more than 80% of $AUC_{0\text{-}inf}$. The treatment phase should last as indicated in the dosing instructions of the comparator product, i.e. 16 or 24 hours from administration of the test or comparator nicotine patch. Samples should be taken for 8 hours following the removal of the patch. For example, blood samples might be taken at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 17, 18, 20, and 24 hours after drug administration for the products applied for 16 h and pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 25, 26, 28, and 32 hours after drug administration for the products applied for 24 h.

Analytical considerations: Information currently available indicates that it is possible to measure nicotine in human plasma using LC-MS/MS analytical methodology with a LLOQ of 0.2 ng/ml. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the C_{max} in most profiles of each formulation (test or comparator). See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations.

Statistical considerations: The data for nicotine should meet the following bioequivalence standards in a single-dose cross-over design study:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}t}$ of the test to reference product should be within 80-125%
- The 90% confidence interval of the relative mean $AUC_{0\text{-}inf}$ of the test to reference product should be within 80-125%
- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80-125%.

- The 90% confidence interval of the relative mean $AUC_{0\text{-}12\ h}$ or $AUC_{0\text{-}16\ h}$ of the test to reference product should be within 80-125%, for the products applied for 16 and 24 h, respectively.
- The 90% confidence interval of the relative mean $AUC_{12\text{-}24\ h}$ or $AUC_{16\text{-}32\ h}$ of the test to reference product should be within 80-125%, for the products applied for 16 and 24 h, respectively.
- The 90% confidence interval of the relative mean C_τ (i.e. $C_{16\ h}$ or $C_{24\ h}$, respectively) of the test to reference product should be within 80-125%.

In addition to the conventional bioequivalence study, skin irritation, sensitisation, phototoxicity (see ICH S10 Guidance on photosafety evaluation of pharmaceuticals) and patch adhesion should be investigated. The test product should demonstrate a similar or lower degree of local irritation, phototoxicity, sensitisation, and similar or better adhesiveness to the skin as the comparator product. In order to ensure equivalence in terms of safety, comparative state-of-the-art studies are required to investigate:

- cutaneous tolerability, irritation and sensitisation
- the potential to produce phototoxic reactions
- adhesion characteristics (for details regarding comparative adhesion tests

unless otherwise justified by e.g., very similar quantitative and qualitative composition in excipients.

To evaluate patch adhesion, the influence of external factors (e.g., heat, sun cream) should be considered. Tests should be performed in individuals with similar skin conditions as the expected patients (e.g., elderly patients). The adhesion properties of the patch should not be altered by, e.g., over-taping and the test conditions should reflect the real conditions of use.