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Guideline on the requirements for demonstrating therapeutic equivalence for nasal products

Draft

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56 **Executive summary**

57 This guideline is intended as a complement to the “Guideline on the pharmaceutical quality of
58 inhalation and nasal products” (EMA/CHMP/QWP/49313/2005 rev. 1). It addresses the requirements
59 for demonstration of therapeutic equivalence (TE) between nasally administered products containing
60 the same active moiety(ies).

61 Demonstration of TE between locally acting nasal products is based on a stepwise approach, where TE
62 could be demonstrated *in vitro*, if all *in vitro* requirements are fulfilled (pharmaceutically equivalent) or
63 else preferably by means of pharmacokinetics (PK) if equivalent systemic exposure (as a surrogate
64 marker for safety) and equivalent local absorption/deposition (as a surrogate marker for efficacy) is
65 demonstrated in spite of some *in vitro* differences. It is generally difficult to demonstrate TE using
66 pharmacodynamic (PD) or clinical endpoints as these are seldom sensitive enough.

67 The guideline also addresses the requirements for demonstrating bioequivalence (BE) for systemically
68 acting nasal products containing the same active moiety(ies) via BE studies and describes when these
69 studies can be waived based on *in vitro* data.

70

71 **1. Introduction (background)**

72 The aim of this guideline is to detail the data requirements for demonstrating TE between nasal
73 medicinal products with local action in the nasal mucosa containing the same active moiety(ies). In
74 addition, data requirements for demonstrating BE for nasal medicinal products with systemic action
75 containing the same active moiety(ies) are covered together with criteria for biowaivers.

76 The guideline is intended to be used together with the guideline on the pharmaceutical quality of
77 inhalation and nasal medicinal products (EMA/CHMP/QWP/49313/2005 rev. 1) to cover aspects
78 related to demonstration of TE. Thereby, regarding locally acting formulations it is a sister guideline
79 to the Guideline on the requirements for demonstrating therapeutic equivalence between orally
80 inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)
81 (CPMP/EWP/4151/00 Rev. 2) which covers TE related aspects for OIP products. Regarding
82 systemically acting formulations, reference is made to guidelines for demonstration of BE (Guideline
83 on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and ICH M13A).

84

85 **2. Scope**

86 This document provides guidance on the requirements for demonstrating equivalence between nasal
87 formulations with the same active moiety(ies), including both single active substance products and
88 combination products. The guideline covers both medicinal products with local action in the nasal
89 mucosa (e.g. xylometazoline, fluticasone, azelastine) and with systemic action (e.g. naloxone,
90 desmopressin, fentanyl, ketamine, zolmitriptan).

91 The guideline focuses on abridged applications, but the principles described may be applicable for all
92 other applications that are based on demonstration of TE compared to a reference product, such as
93 line extensions, variation submissions or during product development. Also, in the case that there is a
94 need to confirm similarity to a product for which literature data is available (e.g., well-established use
95 applications), the same principles apply.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles, part I and II of the Annex I to Directive 2001/83/EC and other pertinent elements outlined in the EU and the International Council for Harmonisation (ICH) guidelines, especially those on:

- CPMP/EWP/239/95: Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents;
- EMEA/CHMP/QWP/49313/2005 rev. 1: Guideline on the pharmaceutical quality of inhalation and nasal products;
- EMA/CHMP/QWP/BWP/259165/2019: Guideline on quality documentation for medicinal products when used with a medical device;
- CPMP/EWP/QWP/1401/98 Rev.1/Corr**: Guideline on the investigation of bioequivalence;
- ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms

4. General considerations

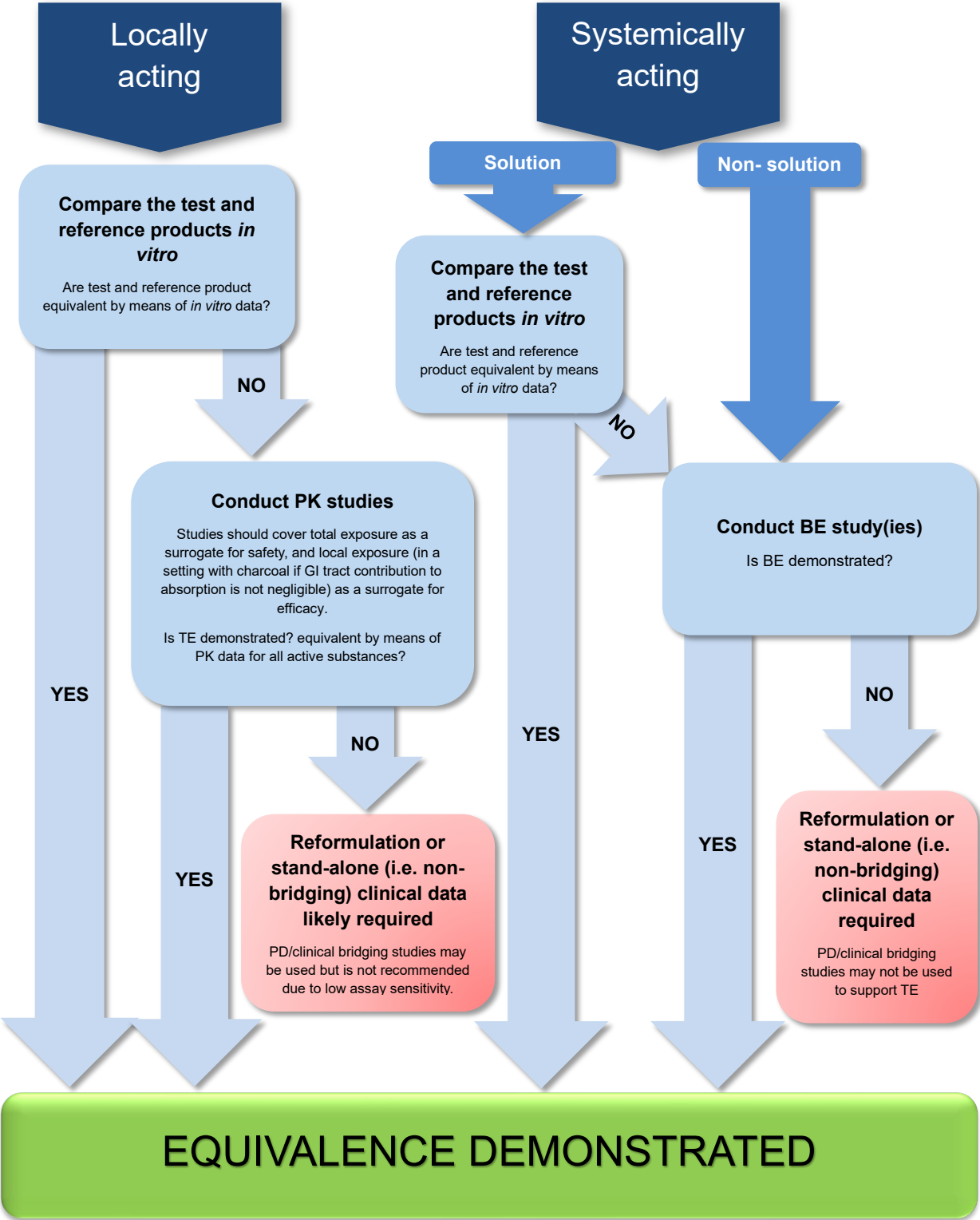
TE implies that the efficacy and safety profile of the test and reference products are sufficiently comparable so that clinically relevant differences between products can be reliably excluded. The expression is applicable to either *in vitro* or *in vivo* data collection.

The demonstration of TE between nasally administered locally acting products is based on a stepwise approach. *In vitro* data is to be provided (see Section 5) with a set of requirements to be fulfilled to allow a conclusion on TE. If similarity cannot be demonstrated *in vitro*, PK data may be used to support TE for locally acting medicinal products (see section 6). Demonstration of TE based on PD data may be an option, but it is not recommended as it is deemed difficult to ensure assay sensitivity (see Section 7).

For nasal medicinal products with systemic action containing the same active moiety(ies), demonstration of bioequivalence of the test product to the reference product is required, generally via the conduct of an *in vivo* BE study. However, for solutions, a waiver based on *in vitro* data is possible if the criteria in section 5 described for demonstration of TE are fulfilled. Use of PD or clinical data is not acceptable in case BE cannot be confirmed.

A schematic overview of the concept is presented in Figure 1.

129 *Figure 1 Flow chart – demonstration of equivalence between nasally administered products*



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136 **5. In vitro comparison**

137 The characterisation of the *in vitro* properties is the first step in the evaluation and demonstration of TE
138 between the test and reference products. *In vitro* criteria, as specified below, should be studied and, if
139 not all criteria are fulfilled, progression to *in vivo* studies is needed. For systemically acting products, *in*
140 *vivo* BE studies may be waived only for solutions and in case all criteria for demonstration of TE as
141 described below are fulfilled.

142 The *in vitro* characterisation and comparison are essential and should always be performed irrespective
143 of whether it has already been decided to conduct a PK study. The *in vitro* comparability exercise
144 should be performed and evaluated as predefined in a study protocol, which should include similarity
145 conditions, methods of comparison and acceptance criteria. Test procedures for the *in vitro* comparison
146 should be state-of-the-art and demonstrated to be suitable for the intended use. In cases where TE is
147 demonstrated based solely on *in vitro* data, at least three consecutive batches of the test product and
148 three batches of the reference product should be tested with a minimum of ten units of each batch. If
149 there is a high variability observed in a critical quality attribute (CQA), a larger number of batches
150 and/or more units per batch needs to be tested. To limit variability and maximize reproducibility, it is
151 advised to use automated actuation for testing spray device related parameters. Test product batches
152 should be representative of the product to be marketed and the manufacturing process – i.e. batches
153 at or near production scale. Alternatively, pilot scale batches, at least 1/10 production scale may be
154 used for characterisation and comparative purposes, if there are no changes in the manufacturing
155 process and equipment, however evidence should be provided that scale-up does not affect product
156 quality. The batches of the reference product used in the *in vitro* equivalence comparison should be
157 representative of the product on the market including consideration of different ages. In case *in vitro*
158 comparison is only supportive for TE, and *in vivo* study(ies) are required, a smaller data set is
159 considered sufficient, e.g., three batches and five units of test respectively reference product.

160 For a nasal medicinal product, claiming TE to a reference medicinal product, the package of studies
161 required depends on the pharmaceutical dosage form. The CQAs that may have an impact on the
162 efficacy and safety of the drug product, and consequently need to be compared, should be defined and
163 justified. Also, the attributes not considered critical (and therefore do not need to be compared) should
164 be discussed and justified. Parameters specified in Table 5.1 below should be considered, but other
165 parameters may also be relevant to use depending on the specific medicinal product characteristics.

166 TE is sufficiently demonstrated if the test product fulfils all relevant *in vitro* criteria as compared to the
167 reference product.

168 **Table 5.1.** *In vitro* parameters for demonstration of TE between test and reference nasal products.

<i>In vitro</i> parameter for demonstration of TE	Nasal spray		Nasal drops		Nasal powder
	Solution	Suspension	Solution	Suspension	
i. Qualitative and quantitative composition, and pharmaceutical form	Yes	Yes	Yes	Yes	Yes
ii. Handling of the device	Yes	Yes	Yes	Yes	Yes
iii. Particle size distribution of active substance	No	Yes	No	Yes	Yes
iv. Other physical characteristics of the active substance	No	Yes	No	Yes	Yes
v. Delivered dose	Yes	Yes	Yes	Yes	Yes
vi. Physicochemical properties of the formulation	Yes	Yes	Yes	Yes	Yes
vii. Droplet/particle size distribution of the product	Yes	Yes	No	No	Yes

viii. Spray pattern and plume geometry	Yes	Yes	No	No	Yes
ix. Mass in droplets/particles smaller than 10 µm	Yes	Yes	No	No	Yes

169

170 i. Qualitative and quantitative composition, and pharmaceutical form

171 The test product should contain the same active substance(s) as the reference product (i.e., same salt,
172 ester, hydrate or solvate). The excipients should preferably be qualitatively the same and quantitatively
173 similar. In case of any qualitative and/or quantitative difference, it must be adequately justified that
174 this difference does not influence the relevant CQAs and/or any aspect of product performance,
175 including residence time, absorption, safety and local tolerability.

176 The pharmaceutical dosage form should be the same (e.g., nasal spray, nasal drops, nasal powder)
177 with the same dispersion state of the active substance (e.g., solution, suspension).

178 ii. Handling of the device

179 The handling of the devices for the test and reference products in order to release the required amount
180 of the active substance should be similar.

181 iii. Particle size distribution of the active substance

182 If the active substance is in the solid state, the particle size distribution should be similar. If next to the
183 active substance, other substances in the solid state are part of the formulation, then a method should
184 be used that is able to discriminate between active substance particles and other particles. D_{10} , D_{50} ,
185 D_{90} and span $((D_{90}-D_{10})/D_{50})$ should be evaluated. In case of a normal distribution curve, comparison
186 of D_{50} and span would be sufficient. If aggregates/agglomerates are present, the study should also be
187 conducted on the product after actuation. To conclude on similarity the 90% confidence interval (CI)
188 for the geometric mean ratio of the test and reference products should be contained within the
189 acceptance criteria of $\pm 15\%$, assuming log-normal distribution of data (85-118%).

190 iv. Other physical characteristics of the active substance

191 If the active substance is in the solid state (powder, suspension), any difference e.g., in crystalline
192 structure and/or polymorphic form should not influence the performance of the product. If applicable,
193 the percentage of amorphous material in crystalline active substance and the rugosity of the particles
194 surface should be compared.

195 v. Delivered dose

196 The mean delivered dose should be similar. For solutions, delivered mass may be sufficient for
197 comparison. For the method of evaluation of similarity, see point iii.

198 vi. Physicochemical properties of the formulation

199 Depending on the pharmaceutical form, different physicochemical properties may be critical and
200 relevant to compare. For example, viscosity enhancers may be included to prolong the residence time
201 in the nasal cavity. For a suspension, wetting agents may be used to reduce surface tension and
202 thereby enhancing particle dispersion. Key parameters to be considered for evaluation and comparison
203 may be rheological properties (e.g., thixotropy, viscosity), surface tension, pH, density, osmolality and
204 buffer capacity. The physicochemical properties should be thoroughly discussed and justified.

205 For quantitative quality physicochemical characteristics, the 90% CI for the geometric mean ratio of
206 the test and reference products should be contained within the acceptance criteria of $\pm 10\%$, assuming
207 log-normal distribution of data (90-111%). In case the reference product variability is higher than

10%, the acceptance range might be widened up to $\pm 20\%$ (80-125%) depending on the reference product variability, using scaled-average-equivalence according to $[U, L] = \exp [\pm k \cdot sR]$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 1.056 and sR is the standard deviation of the log-transformed values of the reference product parameters. Table 5.2 gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Table 5.2. Acceptance limits depending on reference product coefficient of variation (CV).

CV	Acceptance range	
10.0	$\pm 10\%$	90-111%
12.5	$\pm 12.3\%$	87.7-114%
15.0	$\pm 14.6\%$	85.4-117%
17.5	$\pm 16.8\%$	83.2-120%
20.0	$\pm 18.9\%$	81.1-123%
21.365	$\pm 20\%$	80-125%

Alternatively, for quantitative quality physicochemical characteristics not related to strength, a CQA-range (based on the underlying distribution for the reference product) may be proposed, using the principle that all reference product batches on the market represent acceptable quality. For physicochemical CQAs, demonstrating similarity using the overlap of the test distribution with this reference range may be a more appropriate approach than using a mean with a fixed percentage variation as the range of acceptance. Applicants are recommended to apply for scientific advice from a competent authority and seek endorsement of their strategy if this is their approach of choice.

vii. Droplet/particle size distribution of the product

For a nasal spray, the droplet size distribution, and for nasal powders, the particle size distribution of the product, should be compared using a non-aerodynamic method, for example, laser diffraction. D_{10} , D_{50} , D_{90} and span $((D_{90}-D_{10})/D_{50})$ should be evaluated separately and tested at two different, justified distances from the laser beam (e.g., between 2 and 7 cm), and at least 3 cm apart. In case of a normal distribution curve, comparison of D_{50} and span would be sufficient. For the method of evaluation of similarity, see point iii.

viii. Spray pattern and plume geometry

Spray pattern and plume geometry describes characteristics of the emitted spray plume in terms of size and shape. The spray device properties such as valve, pump and actuator may have a significant impact on the spray pattern. The spray pattern should be determined using a single actuation and is normally tested at two distances (e.g., between 3 and 7 cm) at least 3 cm apart. D_{min} , D_{max} , ovality ratio (D_{max}/D_{min}) and area should be evaluated for the spray pattern measurements. Plume angle and plume width should be evaluated for the plume geometry measurements. The analysis of the plume geometry should be performed during the fully developed phase of the spray and preferably when the spray is still in contact with the tip.

For all parameters, a statistical evaluation should be performed. The 90% CI for the geometric mean ratio of the test and reference products should be contained within the acceptance criteria of $\pm 20\%$, assuming log-normal distribution of data (80-125%).

ix. Mass of droplets/particles smaller than 10 μm

Small droplets/particles (less than 10 µm) are more likely to be swallowed or inhaled and thereby deposited in the gastrointestinal (GI) tract or the lungs rather than in the nasal cavity. Therefore, the mass of active substance in droplets/particles smaller than 10 µm is considered a CQA for a nasal spray/powder and should be compared. A cascade impactor, or an abbreviated impactor with a cut-off plate insert for 10 µm, configured for nasal use, is recommended. For solutions, laser diffraction may be used. For the test product, the mass of active substance in droplets/particles smaller than 10 µm, or for solutions the fraction of droplets smaller than 10 µm, should not be more than +10% compared to the reference product. The 90% CI for the geometric mean ratio of the test and reference products should not be above +10% (one sided), assuming log-normal distribution of data (not larger than 111%).

6. Pharmacokinetics

6.1. Locally acting drugs

For locally acting medicinal products, if TE has not been demonstrated based on *in vitro* data as discussed in section 5, TE may be demonstrated using *in vivo* PK studies as described below. See Section 6.1.2 for general recommendations regarding the PK study (study design, study population, test and reference products, dose or strength to be tested, sampling schedule considerations).

It may however be necessary to administer more than one dose due to low plasma concentrations and analytical limitations, provided that participant-safety is adequately ensured and justified.

The same batches should be used for the efficacy and safety PK studies, whenever feasible.

6.1.1. Equivalence regarding systemic safety

i. Study design

In order to investigate systemic safety, the total systemic exposure for the test and reference product should be compared in a PK study as outlined in Section 6.2.

ii. Primary PK parameters and acceptance criteria

To support safety, it is sufficient to demonstrate that the systemic exposure is not higher for the test product than for the reference product, i.e., the upper limit of the 90% CI for the ratio of the test and reference product for $AUC_{(0-t)}$ and C_{max} should not exceed the upper BE acceptance limit of 125.00%. For C_{max} the recommendations in the Guideline on the investigation of BE regarding widening acceptance criteria for C_{max} based on high intra-individual variability can be followed.

iii. Additional considerations

Safety assessments including monitoring of adverse events should be included in the PK study. For additional considerations on local tolerability, refer to section 6.3.

6.1.2. Equivalence regarding efficacy

i. Study design

In case the contribution from the GI tract to the total systemic exposure following nasal administration is negligible (<5%) a PK study without charcoal blockade can be used for both efficacy and safety

comparisons. A low oral absolute bioavailability per se is, however, not synonymous with a negligible systemic contribution from GI absorption, since the contribution from the GI tract depends on the fraction of the dose being deposited in the nose and being swallowed, respectively, as well as on the fraction absorbed into the systemic circulation from each site. For investigation of efficacy, a PK study with activated charcoal should thus be performed, unless it can be justified that the contribution from the GI tract to the total systemic bioavailability following nasal administration is negligible (<5%).

It should be noted that the contribution from the GI tract is generally larger for nasally administered locally acting products than for orally inhaled products due to larger fraction of the dose being swallowed. Therefore, it is not possible to claim negligible contribution from the GI tract following nasal administration based on conclusions on negligible GI tract contribution following oral inhalation.

It is acknowledged that systemic exposure in a study with activated charcoal may not fully reflect local nasal availability (and nasal efficacy), e.g. since absorption could partly occur via the lung from small particles/droplets. However, the site of action and main site of absorption will be the nasal mucosa and similar PK exposure is expected to imply comparable behaviour of the two formulations. Since use of PK is more sensitive than a clinical endpoint study to detect differences between test and reference product, this approach is recommended to demonstrate TE regarding efficacy.

The charcoal blockade efficiency in terms of binding, charcoal dose and frequency of administration needs to be demonstrated (e.g., by *in vitro* binding studies and using a method that has been shown to be effective in the literature).

In case the study with activated charcoal would not demonstrate measurable absorption, a PK study would not be relevant in order to conclude on TE regarding efficacy.

If systemic exposure is known or expected to be non-measurable, PK data would not provide relevant information. In such cases, it is recommended to seek scientific advice to discuss possible alternative ways to demonstrate TE.

ii. Primary PK parameters and acceptance criteria

TE with regard to efficacy can be concluded if the 90% CI for the ratio of the test and reference products is contained within the acceptance interval of 80.00-125.00 for $AUC_{(0-t)}$ and C_{max} in the study with activated charcoal blockade. A widening of the acceptance criteria for C_{max} based on high intra-individual variability in line with the recommendations in the Guideline on the investigation of bioequivalence, may be possible. Any deviations from these acceptance criteria must be thoroughly justified and can never be accepted for results below the lower limit of the acceptance range or when data on safety is generated from a study using different test and/or reference batches.

6.2. Systemically acting drugs

For medicinal products intended for systemic action, demonstration of BE of the test product to the reference product is required, generally via the conduct of an *in vivo* BE study. However, for solutions, a waiver based on *in vitro* data is possible if the criteria in section 4 are fulfilled.

The guidance below is mainly applied for cases where both test and reference products are nasally administered formulations. The same general principles may apply also in case the reference product has a different route of administration (e.g. oral or intramuscular). However, in those cases there may be a need for additional data relevant for the new route of administration compared to the approved route.

i. Study design

Regarding study design considerations, primary PK parameters and acceptance criteria etc, reference could, for most aspects, be made to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms. However, it should be kept in mind that the latter GL is mainly dedicated for drugs absorbed by the gastro-intestinal tract, while absorption is expected to occur mainly at the nasal mucosa for systemically acting nasally administered drugs. Therefore, some items in relation to the particularity of the oral route may not be relevant here (e.g. a potential need for both a fasted and a fed study).

An open (bioanalytical laboratory blinded) randomized single-dose cross-over study is recommended and deemed to be appropriate in most cases. However, alternative designs, such as replicate crossover, parallel group or repeated-dose administration, could be accepted if justified as described in the BE guidelines referred to above.

ii. Study population

To reduce variability, BE studies should be conducted in healthy volunteers. The outcome of the investigations in healthy volunteers could be extrapolated to patients for which the drug is intended. If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy subjects, the study may instead be conducted in a targeted patient population under suitable precautions and supervision. Healthy volunteers should be understood here as subjects with normal general health conditions but also with no chronic or transient nasal affections.

If the product is self-administered by subjects, it is critical that all subjects included are properly trained to administer the product correctly in line with the product information and also to confirm during the study that subjects administer the product correctly. Also, in case of administration by study staff, correct administration should be confirmed. If administration is not correctly performed, subjects should be excluded. Decision on exclusion should be made before bioanalysis.

iii. Investigational test and reference products

The batch of the reference product should be representative of the commercial batches available on the market. How the representative batch(es) is chosen should be fully justified. Characterisation of several batches of the reference product should be performed. A minimum of five batches may be sufficient if suitably justified. However, if the reference product shows great variability or quality changes over storage, a larger number of batches is needed. The delivered dose of the reference batch(es) chosen for the *in vivo* study(ies) should be as close as possible to the calculated median of the observed reference product batches. A deviation within $\pm 15\%$ is reasonable.

The test product should be representative of the product to be marketed. Production scale batches are preferred but pilot scale batches may be used, if there are no changes in the manufacturing process and if it is demonstrated that scale-up does not affect product quality.

iv. Dose or strength to be tested

The dose to be administered should follow the recommendations of the reference product as presented in the product information.

If two or more strengths are available, it may be sufficient to include only one strength in the BE study. The following requirements must be met:

- a) The different strengths of the test product are manufactured by the same manufacturing process.
- b) The different strengths of the test product have the same qualitative and similar quantitative composition. For example, the lower strength is achieved by a formulation with lower concentration without any changes in actuator, metering valve or pump.
- c) For solutions, the droplet size distribution should be similar for the test product strengths. For suspensions and powders, the droplet size and the particle size distribution should be similar for the test product strengths. For similarity criteria, see section 5.

v. Sampling schedule considerations

It is critical that the sampling schedule is planned so that $C_{\max}$ can be reliably estimated and that it can be avoided that $C_{\max}$ is observed in the first sample post-dose. The sampling schedule should cover the plasma concentration - time curve long enough to provide a reliable estimate of the extent of exposure, which is achieved if $AUC_{(0-t)}$ covers at least 80% of $AUC_{(0-\infty)}$.

If justified, a suitably truncated AUC can be used instead of $AUC_{(0-t)}$ for drugs with long terminal elimination half-life. When such an approach is claimed, the decision for sampling cutoff time should be defined prospectively in the study protocol and take into account the local residence time of the drug before being cleared from the nasal mucosa. It should be noted that the truncation of AUC at 72 hours mentioned in ICH M13A is based on GI transit time. However, in most cases, this sampling time would likely be sufficient also for nasally administered products.

vi. Primary PK parameters and acceptance criteria

The $C_{\max}$ and $AUC_{(0-t)}$ should be evaluated. BE can be concluded if the 90% CI for the ratio of the test and reference products is contained within the acceptance interval of 80.00-125.00 for $AUC_{(0-t)}$ and $C_{\max}$. Intraindividual variability may be an issue for drug administered by nasal route. For $C_{\max}$ the recommendations in the Guideline on the investigation of bioequivalence regarding widening of acceptance criteria for $C_{\max}$ based on high intra-individual variability can be followed.

For drugs where the early onset of action is clinically relevant, an additional primary PK parameter such as area under the concentration vs. time curve between two specific time points (pAUC) or $t_{\max}$ should be used to establish BE as recommended in ICH M13A.

7. Pharmacodynamic and clinical studies

7.1. Locally acting drugs

As the objective is to demonstrate TE with the reference product rather than efficacy and safety of the test product, PK endpoints are considered more sensitive to detect differences between test and reference product than PD or clinical endpoints. For locally acting medicinal products, if TE has not been demonstrated based on *in vitro* data (see section 5) or in an *in vivo* PK study (see section 6), it is generally recommended to reformulate the product.

However, if other approaches with PD or clinical endpoints are considered, the study design must be such that assay sensitivity is clearly shown at an acceptable level. Appropriate efficacy endpoints for TE may include objective measures of nasal congestion/nasal airway resistance and/or inflammation, depending on the drug's mechanism of action. Subjective endpoints may be included as co-primary or secondary endpoint, but use of only subjective endpoints is not acceptable. Safety assessments including monitoring of adverse events should always be included in the efficacy studies regardless of the design.

Regardless of the objective of the study, it is necessary to demonstrate that the sensitive part of the dose/response curve for the PD/clinical parameter under investigation has been studied. To allow estimating assay sensitivity, it is essential to include at least one non-zero dose level besides the dose level(s) primarily investigated.

As for the PK studies (see section 6.2.2), the same batch of reference product should be used for safety and efficacy PD studies, unless adequately justified, and should be representative of the product on the market (see section 6.1). When feasible, it is of value to have access to PK data from the PD studies.

It is recommended that the statistical analysis allows calculating relative potency. The relative potency of the test product to the reference product is defined as the dose of the test product that produces the same biological response as one unit of the dose of the reference product. This analysis should be conducted based on the approach by Finney (1964)¹ for the primary **efficacy** variable, unless otherwise justified. The acceptance criteria for the 90% CI of the relative potency should be prespecified and normally retained within 0.67 to 1.50. To support TE, it should be clearly shown that a certain strength of the test product is more similar to the same strength of the reference product than the closest adjacent differing higher or lower strength (anticipated to differ by a factor 2 irrespective of whether there is an approved such strength or not). Any other choice of statistical approach must be sensitive enough to ensure assay sensitivity at this level.

7.2. Systemically acting drugs

In line with the principles for generic development of oral formulations, for generic nasal products of systemically acting drugs, PD or clinical data are not acceptable in case of deviation from BE. If a waiver based on *in vitro* data, as discussed in section 5, is not applicable and BE has not been demonstrated in an *in vivo* BE study, it is generally recommended to reformulate the product, or a full stand-alone clinical data package would need to be provided to support a MAA instead of a BE approach.

7.3. Local tolerability

Local tolerability of nasal medicinal products is an important consideration as some drugs or formulations can irritate the nasal mucosa, leading to discomfort, sneezing, or nasal discharge. In general, local tolerability may be ascertained by knowledge of the active substance and the choice of well-established excipients.

¹ Finney DJ. Statistical methods in biological assay. London: 104:1057–61. Griffin, 1964

Equivalence with respect to quality (see section 5 above) provides assurance of safety and local tolerability if the excipients are qualitatively the same and quantitatively similar. However, if the excipients are not qualitatively the same or not quantitatively similar, impact on the local safety profile should be addressed in a local tolerability study in humans or thoroughly justified based on literature, including e.g., irritation, changes in nasal secretions (discharge) or breathing (congestion), and nasal mucosal appearance. Consideration should also be given to particular aspects of medicinal product use e.g., posology and duration of treatment.

8. Children and adolescents

In case of a new nasal delivery device, not previously approved for children but where the reference product has a paediatric indication, data on usability needs to be provided (see section 9). The characteristics of the delivery device may be such that the device is more difficult to use for a child than for an adult and, therefore, the child or their caregiver is less able to use the device correctly, or the child/caregiver may use the device differently from an adult. Such differences in the handling of the product by a child/caregiver may result in a different risk/benefit relationship in the child compared with that seen in the adult. In case it has been shown that the device can be correctly handled and emptied by children/caregivers and TE/BE has been demonstrated (see sections 5 and 6 above), the lowest approved age for the test product could be set at the same as the reference product without further data or justification.

9. Usability studies

For medicinal products for which the medical device and/or device part and the medicinal product form an integral product that is not reusable (hereafter called integral), a formal usability study (also named human factor study) may be required to demonstrate safe and effective use of the integral medicinal product by the intended user population as stated in the 'Guideline on quality documentation for medicinal products when used with a medical device' (EMA/CHMP/QWP/BWP/259165/2019), section 5.4.

For such studies, study participants should be recruited to include a number of distinct user groups including patients (adults, and where appropriate children and adolescents) and caregivers, within which both reference product-naïve and experienced users should be included. A minimum of 15 participants should be recruited in each distinct user group. Participants selection for these studies should ensure representativeness of the intended users population incorporating general population trends (e.g., left handedness, elderly, patient with manual coordination difficulties, such as arthritic patients). The study protocol should direct participants in simulating the use of the new nasal delivery device to deliver doses as per normal use using an empty or placebo device, unless a different study setting is justified. The exercise should include the unpacking of a new device from the patient pack, simulated delivery of the first dose, as well as the intended storage of the device. Participants should be asked to simulate the delivery of further doses to assess the user interface with the device throughout its life. Areas of focus should allow ensuring that the user understands key features of the device. Clear acceptance criteria should be pre-specified together with an accompanying rationale in the protocol. The outcome of this summative usability study should be reported in the form of a usability report that should include details such as the intended use, observed risks, and study results as well as its corresponding appendices, including the study protocol.

10. Definitions

Abridged application	Application (generic, hybrid, biosimilar) submitted under Articles 10(1), 10(3) and 10(4) of Directive 2001/83/EC
Active moiety	The molecule or ion responsible for the physiological or pharmacological action of the drug substance
Assay sensitivity	Ability of a clinical trial to distinguish an effective treatment from a less effective treatment or ineffective treatment.
Delivered dose	The quantity of drug substance that is available to the user, ex-device in one spray or actuation.
Dose/Single dose	Amount of drug administered on a single occasion. One dose may consist of several actuations.
Metered dose	The quantity of drug substance contained in the delivery device metering chamber.
Reference product	A product against which therapeutic equivalence is claimed/assessed.
Relative potency	The relative potency of the test product to the reference product is defined as the dose of the test product that produces the same biological response as one unit of the dose of the reference product (i.e., comparative outcomes for different doses).
Single dose study	Study involving a single administration of each dose level under investigation.
Strength/dose	Strength refers to the amount of active substance metered or delivered in a single actuation (e.g., 125 microgram per actuation of a nasal spray). Dose, by contrast, refers to the total amount of active substance administered on one occasion. For example, one actuation in each nostril (e.g., 2 x 125 microgram).
Therapeutic equivalence	The performance of the test and reference products is sufficiently comparable (within the acceptance criteria outlined in this guideline) to ensure negligible impact on efficacy or safety. For systemically acting formulations, the term bioequivalence is normally used, but in this guideline, therapeutic equivalence may refer also to systemically acting formulations.

11. List of abbreviations

AUC	Area Under the Curve
BE	Bioequivalence
CI	Confidence Interval
C _{max}	Peak concentration
D ₁₀ , D ₅₀ , D ₉₀	Droplet/particle diameter at which 10%, 50% or 90% are smaller
D _{min} , D _{max}	Minimum or maximum diameter of the spray plume area
GI	Gastrointestinal
ICH	International Conference on Harmonisation
PD	Pharmacodynamic
PK	Pharmacokinetic
TE	Therapeutic equivalence
t _{max}	Time to peak concentration