CBG MEB | MEDICINES EVALUATION BOARD

Therapeutic equivalence of nasal products

Comparison of quality attributes

GOOD MEDICINES USED BETTER

Peter Caspers - BioBridges Conference 25/26 September Prague

Disclaimer

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- Analytical methods

Draft Guideline therapeutic equivalence of nasal drug products

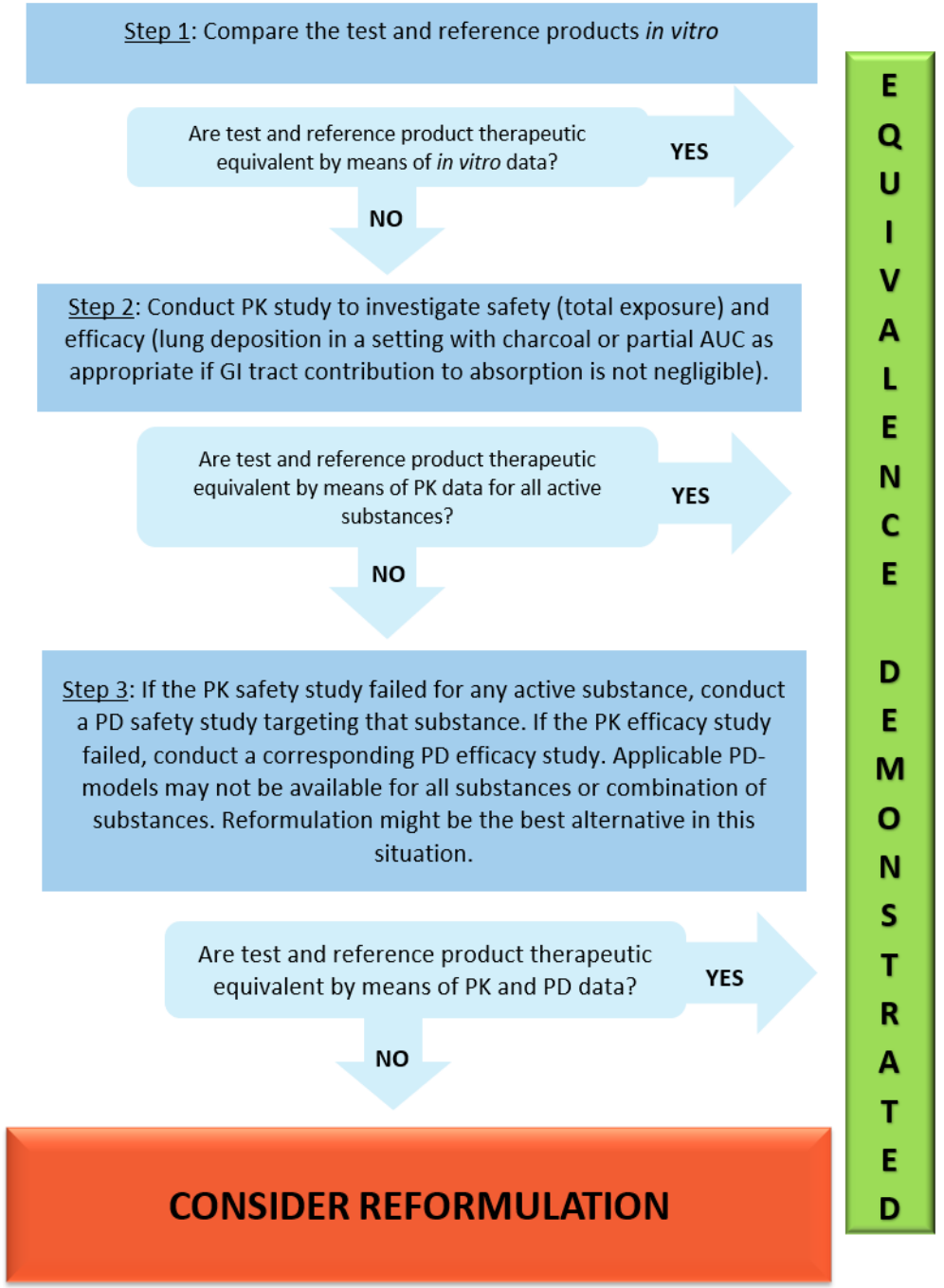
- Requirements for the development, manufacture, and control of nasal drug products is described in the Guideline on the pharmaceutical **quality** of inhalation and nasal products
- However, different to **inhalation** products, there is no specific guideline that deals with how to demonstrate therapeutic equivalence (TE) for **nasal** drug product.
- Sparse information is included in the Quality guideline
- As there is a clear need for more detailed guidance, work has started (September 2025)

Locally applied, locally acting

- **Therapeutic equivalence** means that the efficacy and safety profile of the test and reference products is sufficiently comparable so that a clinically relevant difference between products can be reliably excluded.
- In the **clinical OIP Guideline**, a stepwise approach is described for inhalation products, with a list of in vitro criteria to be fulfilled and additional PK studies to be conducted in case not all in vitro criteria are fulfilled.
- In PK studies charcoal block is used, if needed, to exclude absorption in GI tract

Stepwise approach for **Orally Inhaled Products**

In general, clinical endpoint studies are not suitable to discriminate between equivalence and non-equivalence of two comparable LALA drug products. Unless variability in results is very low.



Locally applied, locally acting (cutaneous)

- A comparable approach is applied in the Guideline on quality and equivalence of **cutaneous products**

  - Local application in control
  - The amount/concentration in plasma that is due to absorption from the skin, reflects both safety and efficacy because the amount available to go into the circulation (plasma) is also available to reach the site of action (skin) *or*
  - If systemic exposure is similar, it is assumed that the exposure to and absorption through the skin is also similar

- It is anticipated that for nasal products an approach similar to that of OIP would be applicable.

Locally applied, locally acting (nasal)

- Deposition of nasal product is not so clear
- Where does it deposit?
  - Mainly in the nostril?
  - How much in the turbinates?
  - How much in the olfactory region?
  - How much in the lungs?

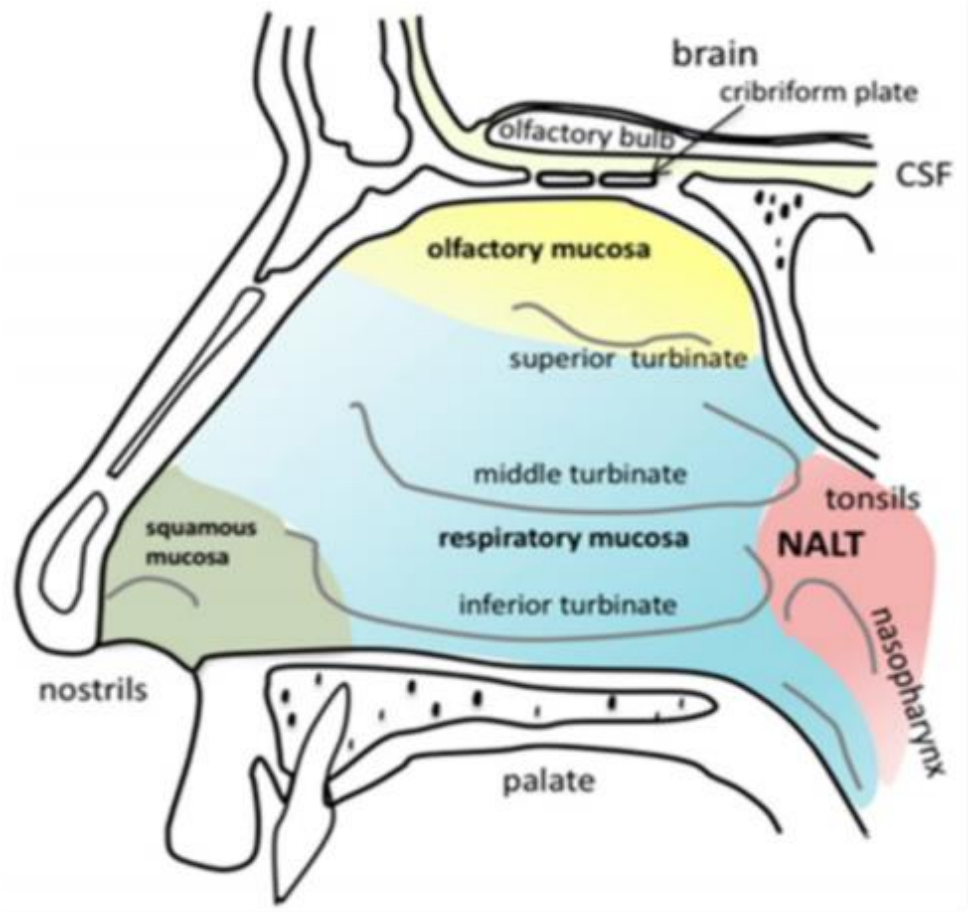
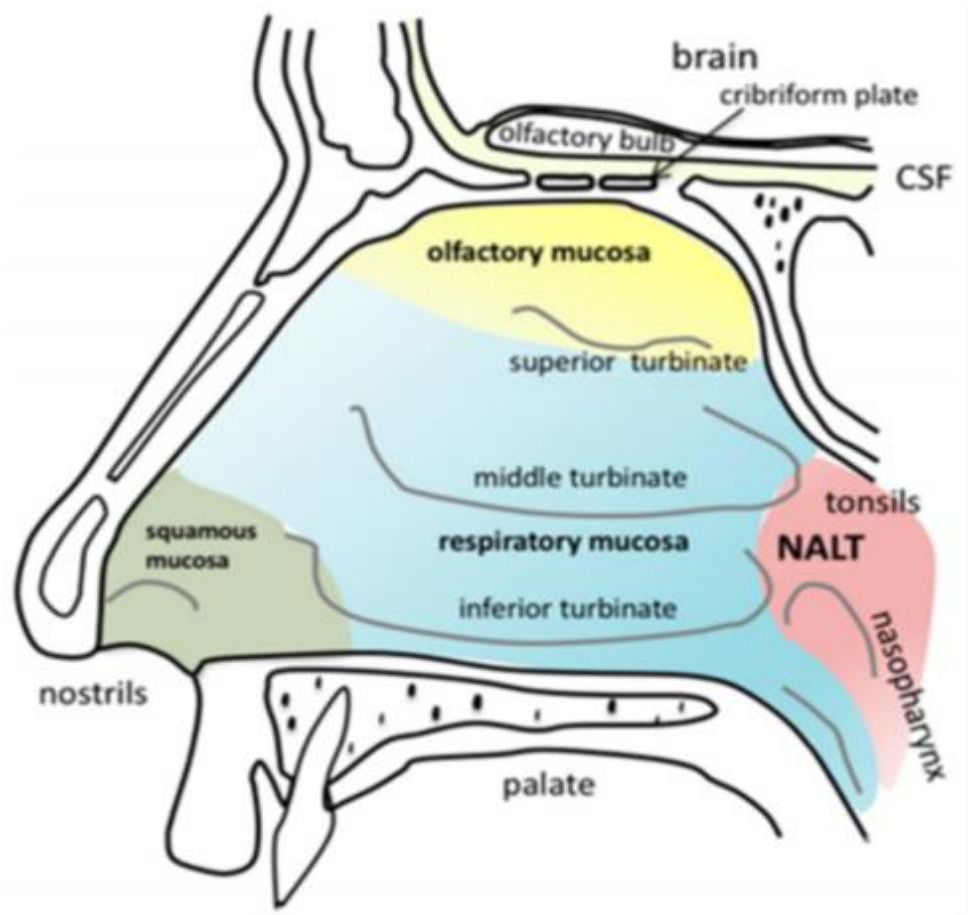


Figure from Salade et al [a]

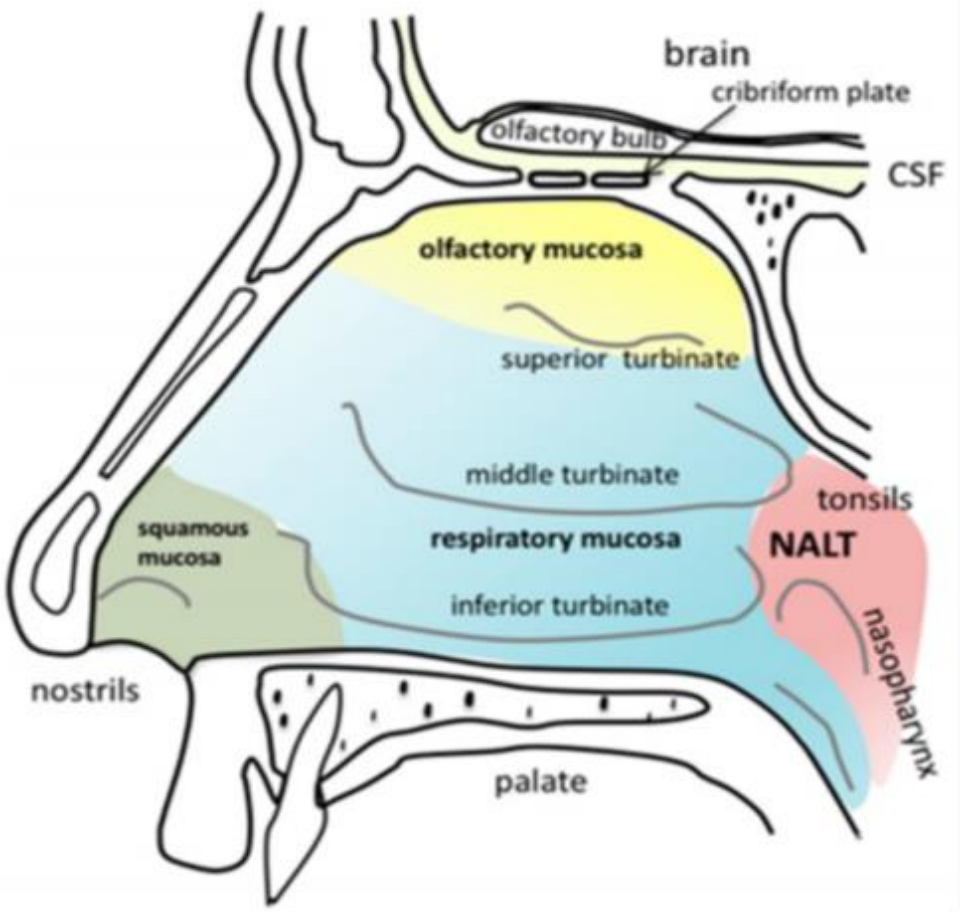
Locally applied, systemically acting (nasal)

- Nasal products are also applied for systemic use
  - Desmopressin
  - Sumatriptan nasal spray
  - Zolmitriptan nasal spray
  - Fentanyl nasal spray
  - Midazolam nasal spray
  - Adrenalin nasal spray (EURneffy)
  - Peptides



Locally applied, systemically acting (nasal)

- Systemic or local (?)
  - Vaccins
  - Nose to Brain (N2B): olfactory bulb
    - PK predictive for effect/safety?
    - Charcoal block of non-olfactory parts?



Stepwise approach for nasal products

1. In-vitro comparison
2. PK study
3. Clinical endpoint study?

- What is more discriminative?
- What is more predictive for the clinical situation?
- What is feasible?

Framework of in-vitro comparison – 10 steps

1) define and justify the critical quality attributes (CQAs) that may have an impact on the efficacy and safety of the drug product and consequently need to be compared
2) justify those attributes not considered critical and therefore do not need to be compared
3) *define and justify the **similarity condition** for each CQA*
4) define the marketed reference product, and characterise the reference product by testing all CQAs for a justified number of batches that together are representative of the variation observed in the reference product, also over storage
5) consider the observed variability in the reference product for each CQA

Similarity condition

- When is CQA considered similar to the reference product?

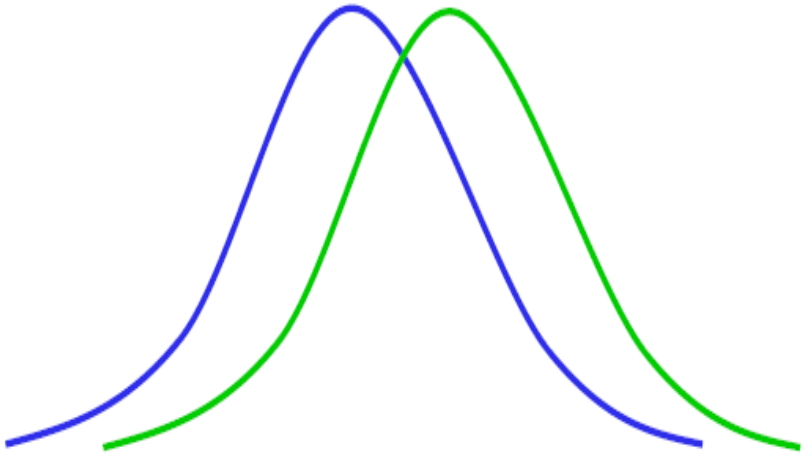


Figure 1

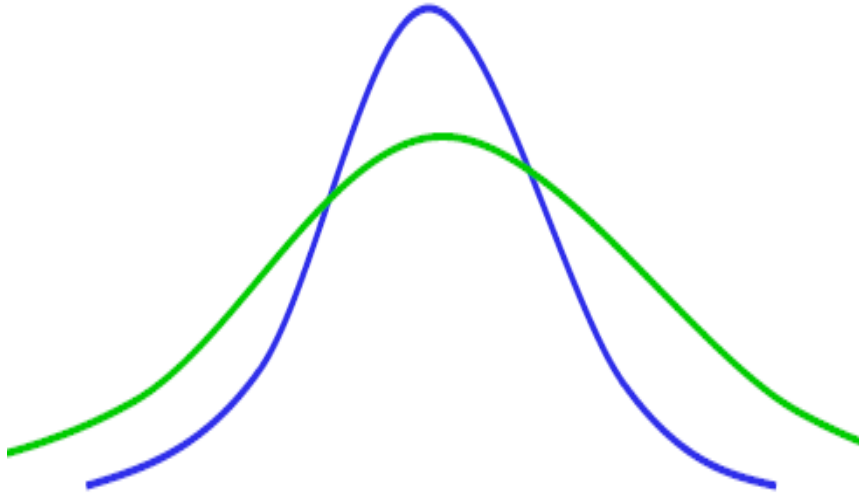


Figure 2

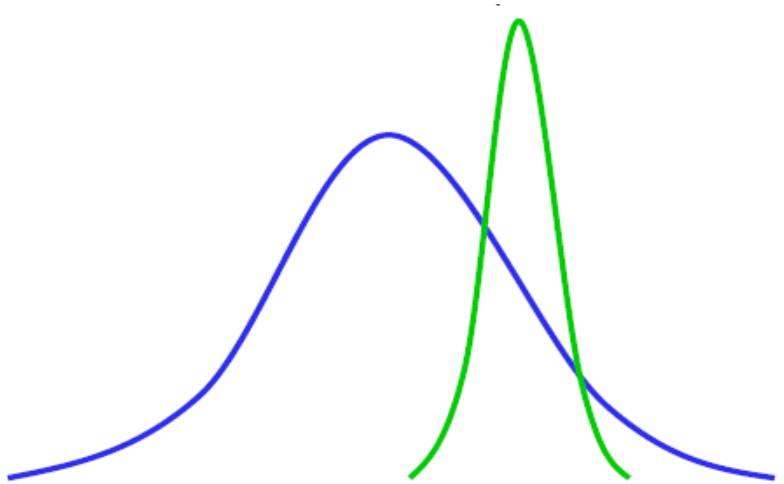


Figure 3

Similarity condition

- Composition
- Mean delivered dose (MDD)
- Uniformity of delivered dose (UDD)
- pH
- Viscosity
- Droplet size distribution – profile: D10, **D50**, D90, **span**
- Particle size distribution - agglomerates
- Mass in fraction < 10 µm (APSD)
- Priming / Re-priming

Similarity condition

- Composition : **excipients ± 5% ?**
- Mean delivered dose (MDD): **± 10% ABE ?**
- Uniformity of delivered dose (UDD) – **Compendial requirement ?**
- pH : **within range observed in reference product ?**
- Viscosity : **within range observed in reference product?**
- Droplet size distribution : profile: D10, **D50**, D90, **span** ?
- Particle size distribution - agglomerates : **± 10% ABE ?**
- Mass in fraction < 10 µm (APSD): **one sided, not more than?**
- Priming / Re-priming: **not more than for the reference product?**

Framework of in-vitro comparison – 10 steps

1) define and justify the Critical Quality Attributes (CQAs) that may have an impact on the efficacy and safety of the drug product and consequently need to be compared
2) justify those attributes not considered critical and therefore do not need to be compared
3) define and justify the similarity condition for each CQA
4) **define the marketed reference product**, and characterise the reference product by testing all CQAs for a justified number of batches that together are representative of the variation observed in the reference product, also over storage
5) consider the observed variability in the reference product for each CQA

Framework of in-vitro comparison – 10 steps

6) *Define and justify the statistical method of comparison and associated acceptance criteria for each CQA based on the attribute, the similarity condition, and observed variability in the reference product.*

Methods of comparison quality attributes

Historical	Does it look similar at face value?
OIP Guideline 2009 (LALA)	90% CI of ratio means TP/RP within 0.85 – 1.15 (ABE)
Gastro-intestinal tract 2019 (LALA)	In vitro similarity should be assessed with a ±10% acceptance range
OIP Guideline 2026 (LALA)	90% CI of ratio means TP/RP within 0.85 – 1.15 (ABE)
Cutaneous products 2025 (LALA)	90% CI of ratio means T/R within 0.9 –1.1 (ABE) or wider in case of large variability in reference product, or **range based on variability observed in RP**
FDA	Population Bioequivalence (PBE) 95% upper confidence bound for linearized criteria Hη must be ≤ 0, or Ratio of geometric mean within 0.90 – 1.10, or F2 > 50

ABE = Average Bioequivalence CI = Confidence interval TP = Test product RP = Reference product

Methods of comparison quality attributes

- Similarity related to maximum allowed differences between test and reference
  - Arithmetic or geometric approaches
  - Examples:
    - Ratio of geometric means using confidence intervals (ABE)
    - T-statistics
- Methods and criteria based on the range observed in the reference product
  - Absolute min-max range as criteria not suitable
  - Six sigma range not representative of the reference product on the market
  - Population Based equivalence?
  - Suggestions?

Framework of in-vitro comparison – 10 steps

6) Define and justify the statistical method of comparison and associated acceptance criteria for each CQA based on the attribute, the similarity condition, and observed variability in the reference product.
7) **Justify the selected number of test and reference batches to include in the comparison.**
8) Incorporate points 6 and 7 in a protocol together with the sampling and testing plan and the validated analytical methods. The protocol should be approved prior to use.
9) Test the reference- and test batches for the CQAs. The studies should preferably be conducted by side-by-side testing of products in the same analytical campaign.
10) Evaluate the results, draw conclusions and summarise in a separate, approved report.

Critical Quality Attributes of nasal drug products

Orally inhaled	Nasal product
Same form active substance	Same form active substance
Same pharmaceutical form	Same pharmaceutical form
Same morphological form active	Same morphological form active
Same composition (advised)	Same composition (advised)
Same handling, comparable device	Same handling, comparable device
Similar delivered dose	Similar delivered dose
Similar deposition: APSD (cascade impaction), at least four (groups of) stages, FPD and non-sized fraction	APSD - Mass in small droplets (< 10 µm) - Nasal cast studies
	Additional CQAs

Additional (critical) quality attributes

FDA / USP (fluticason nasal spray)	EU
Similar Droplet size distribution	Similar Droplet size distribution
Similar Particle size distribution (suspension) by MDRS or other method	Similar Particle size distribution (suspension)
Spray pattern	Spray pattern
Plume geometry	Plume geometry
Priming and repriming	**Rheological properties**
Dissolution	Surface tension, **pH**, density, osmolality, buffer capacity

Potential issues

- Plume velocity – or already covered by testing spray / plume at two distances
- pH – may have impact on the ionization of the active substance / absorption if pKa is close to pH
- Rheology / viscosity may have impact on the residence time in the nasal cavity
- PSD before (in bottle) and/or after actuation ?
- Dissolution – what additional information will this provide if Q1, Q2, and Q3 and PSD active substance are similar?
- Secondary or tertiary structure of large molecules (e.g. peptides)?
- Dimensions nozzle ?

Other options (critical) quality attributes

Length nozzle??

SmPC instructions – Method of Administration (4.2)

- Pharmaceutisch Weekblad (2017) 152:38 on incomplete inhalation instructions nasal sprays, evaluated in 31 SmPCs
- Large diversity in instructions
  - No instruction on position head (58%)
  - No instruction on direction nozzle(48%) - *not aimed at nasal septum*
  - No inhalation instruction (45%)
  - No exhale instruction (52%)
  - No instruction how deep the nozzle should be moved inside the nostril (100%)

Analytical methods

- DSD
  - Laser diffraction (LD) – range 30 nm to 3000 µm
- APSD – range 0.5 to 10 µm (depends on flow rate)
  - Different to LD, APSD can differentiate the solid active substance in the suspension or dry powder
  - Mass in droplets/ particles < 10 micrometer
  - Nasal cast studies
- PSD in the presence of excipient particles
  - Microscopy - USP Fluticasone Propionate Nasal Spray
  - Morphologically Directed Raman Spectroscopy (MDRS)

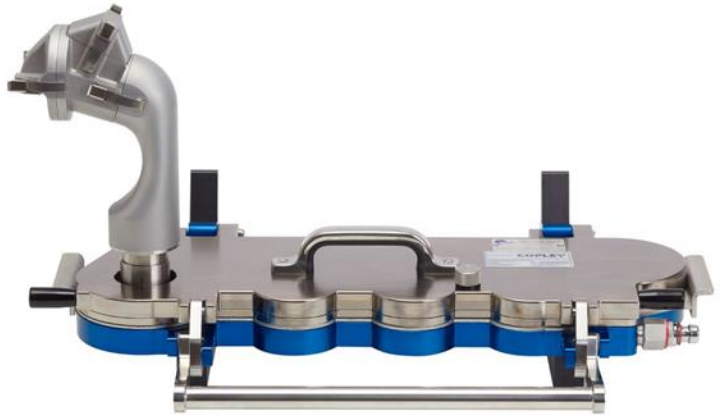
Aerodynamic Particle Size Distribution

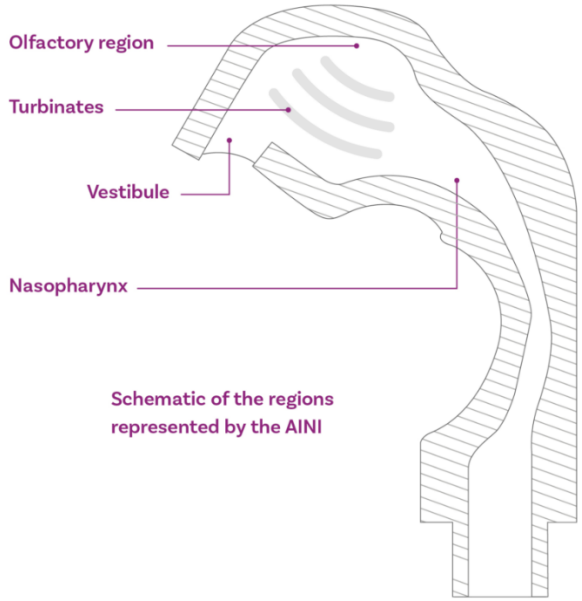
- Mass in droplets/ particles < 10 micrometer
  - Safety (fraction that may deposit in the lungs)
  - Evaluation required by EMA and FDA
  - No compendial method yet, work EDQM ongoing
  - Not suitable to compare the DSD or PSD of nasal sprays (20 to 200 µm)

Kiel Nasal Inlet with FSI

Aerodynamic Particle Size Distribution

- Nasal cast studies – in-vitro deposition
  - Deposition in the nose and lung
  - Permits differentiation between devices based on regional deposition
  - Mimics in vivo deposition (gamma scintigraphy data)
  - May be helpful for development of nasal products
  - Not (yet) demonstrated to be suitable to compare similarity of products





Alberta Idealised Nasal Inlet + NGI

PSD in the presence of excipient particles Microscopy

USP fluticasone propionate nasal spray

PARTICLE SIZE

Analysis: Remove the pump system after shaking the test bottle to ensure product uniformity. Transfer 1 drop of the Nasal Spray onto a clean microscope slide. Examine 10 random fields of view on the slide using 400× magnification. Drug substance particles are irregular in shape, whereas the excipient particles are elongated and angular. Record the number of individual drug substance particles that are less than 5 µm in diameter, greater than 5 µm but less than 15 µm in diameter, and greater than 15 µm in diameter. Calculate the percentage of each category by number.

Particle Size	Acceptance Criteria
<5 µm	NLT 98%
>5 µm – <15 µm	NMT 1.8%
>15 µm	NMT 0.2%

PSD in the presence of excipient particles

MDRS (Morphologically-Directed Raman Spectroscopy)

MDRS records the image and position of individual particles using an **automated, optical microscope** function for **particle size and morphology** analysis, and subsequently a **single point-and-shoot Raman spectrum measurement** at the center of the particle to obtain the chemical identity

Determination of average and RSD of D10, D50, D90, span, D_{mean}, D_{min} and D_{max}

In FDA PSBGLs proposed as alternate approach to the comparative PK and clinical endpoint study

Accepted in EU as method to determine active substance PSD in a suspension for the in-vitro comparison

PSD in the presence of excipient particles

MDRS (Morphologically-Directed Raman Spectroscopy)

Method development – to be conducted for each drug product

- A training set of 10,000 scanned particles of active and excipient(s)
- Morphology and Raman measurements are performed on each particle in the training set.
  - Morphology: circular equivalent diameter, aspect ratio, circularity, transparency, convexity, solidity
  - Raman: wavelength range, chemometrics, pre-processing
- Appropriate morphology filters are chosen to exclude most excipient particles – this safes Raman spectroscopy time during test
- Optimize filter cut-offs based on minimal number of particles to be measured but still allows representative, statistically meaningful active substance PSD results

PSD in the presence of excipient particles

MDRS (Morphologically-Directed Raman Spectroscopy)

Critical parameters

- Sample preparation (concentration, volume, settling time)
- Aggregates (exclude or not, stability issues)
- Stability of the samples
- Limit of detection: based on signal to noise ratio
- Diameter of the laser spot (~2 µm)
- Validation: accuracy, precision, and amount of particles included (filters)
  - use active substance raw material as validation samples for accuracy
  - max 3% difference in D10, D50, D90 and Dmean.
- Strict description of the development and test method

PSD in the presence of excipient particles

MDRS (Morphologically-Directed Raman Spectroscopy)

Limitations

- A separate method needs to be developed for each product
- Too much overlap of morphology of active and excipients problematic
- Inability to measure particles < 1 (optical) to 2 µm (Raman identification):
  - Laser diffraction may be suitable as orthogonal method for particles < 1 µm
    - Can show fraction sub 1 to be very small
    - in case of cellulose as only solid excipient, as the hygroscopic nature of cellulose means that these particles swell and agglomerate in an aqueous suspension it is unlikely that these contribute to the sub fraction1 µm particles

FDA Draft Guidance on Fluticasone Propionate

May 2023

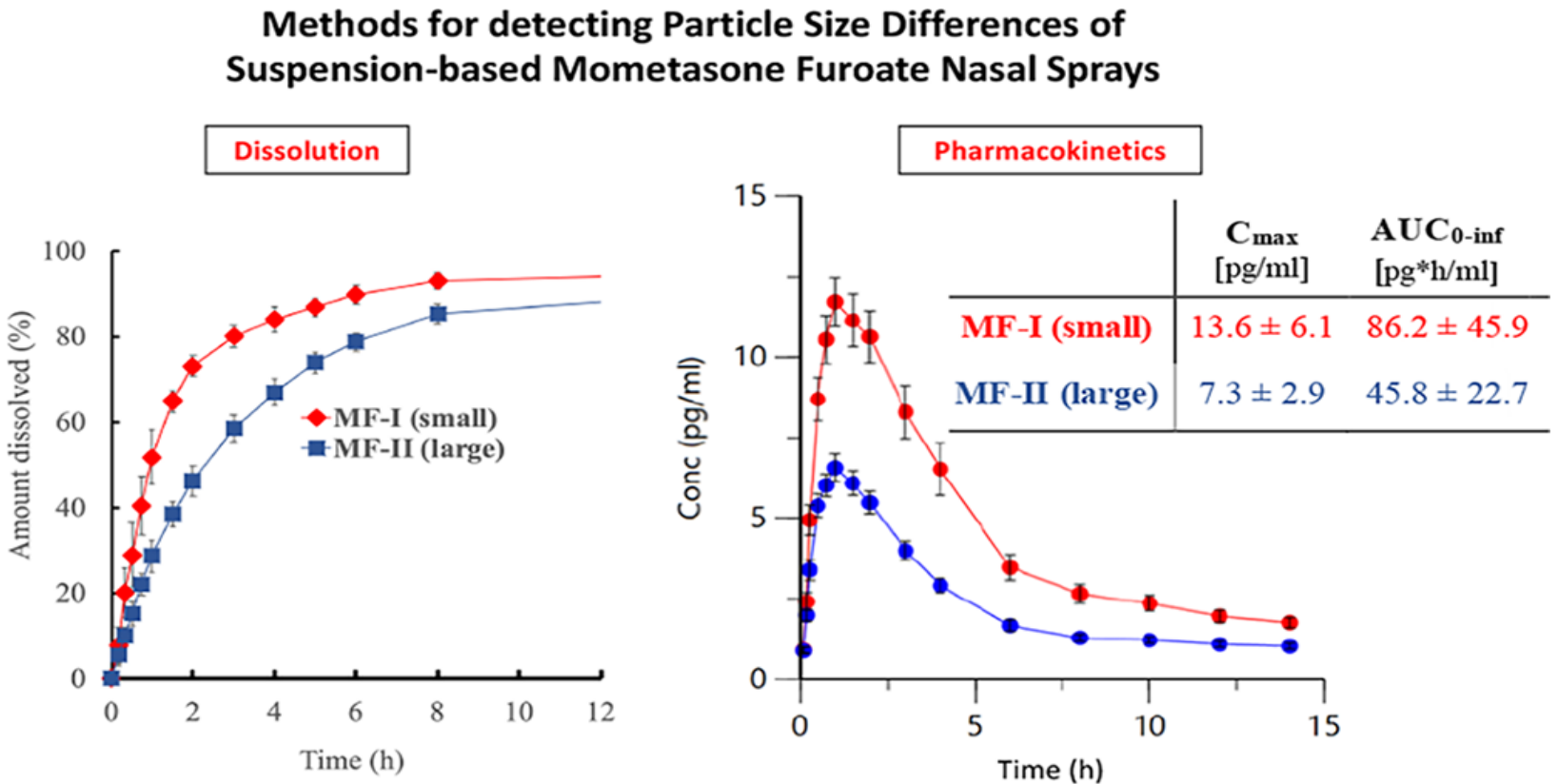
Type of study: Drug particle size distribution
Design: The emitted drug particle size distribution (PSD) should be determined using an optimized and validated analytical method (e.g., morphologically-directed Raman spectroscopy). The emitted drug PSD should be measured at the B lifestage of the product.
Additional comments: Samples for drug PSD measurement should be prepared to ensure that the drug is in its suspended state post-actuation. The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and measuring the size of the drug particles without any interference from the excipient particles that are also suspended in the formulation. Drug PSD and span should be reported. An orthogonal method may be required if the selected methodology is not sensitive to measure particles beyond a certain size range.
Equivalence based on: **PBE analysis of D50 and span.**

Stepwise approach - revisited

E. Amini. Sensitivity of Pharmacokinetics to Differences in the Particle Size Distribution for Formulations of Locally Acting Mometasone Furoate Suspension-Based Nasal Sprays. Mol. Pharmaceutics 2023, 20, 5690−5700

Batch MF-I	Batch MF-II
PSD raw material D50 = 1.33 µm	PSD raw material D50 = 3.43 µm
MDRS D10 = 2.25 D50 = 3.17 D90 = 4.59	MDRS D10 = 2.56 D50 = 5.50 D90 = 10.6

Nasonex (literature): D10 = 2.28
D50 = 3.20
D90 = 5.47



Stepwise approach - revisited

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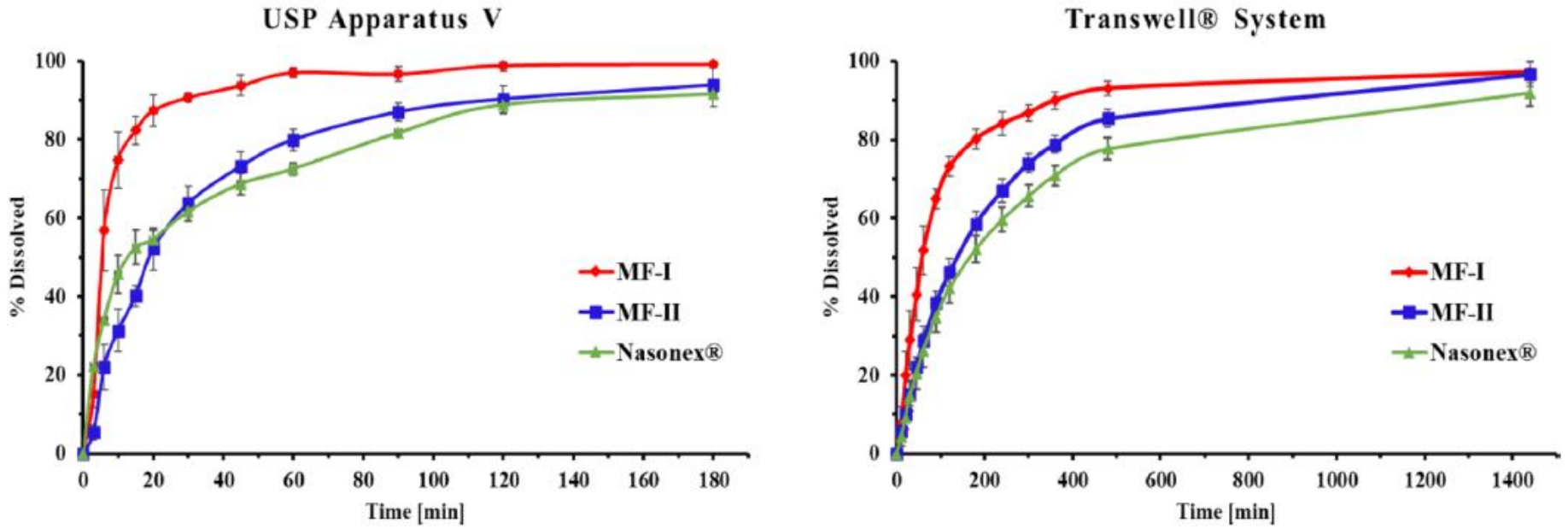


Figure 1. Dissolution profiles of MF-I, MF-II, and Nasonex in the USP apparatus V and in the Transwell system.

MDRS Nasonex corresponds with **MF-I**, but dissolution Nasonex corresponds with **MF-II**
Nasonex was not included in the PK study

Stepwise approach - revisited

L. Richards et al. The Evaluation of Equivalence of Mometasone Furoate Nasal Sprays via an In-Vitro Pathway using Dissolution, MDRS and Laser Diffraction Techniques. DDL 2024

Figure 1-
Dissolution Profiles Generated from two bioequivalent mometasone nasal sprays

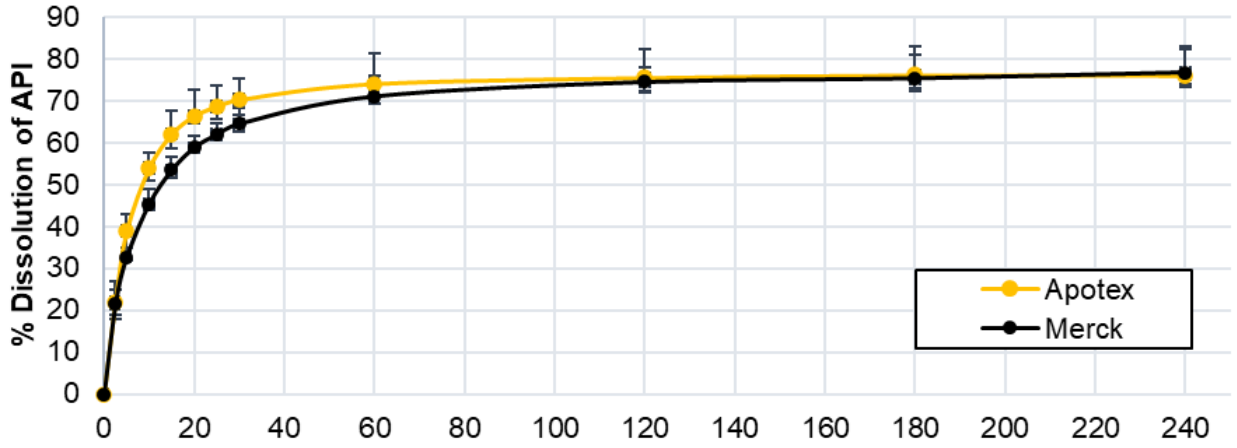
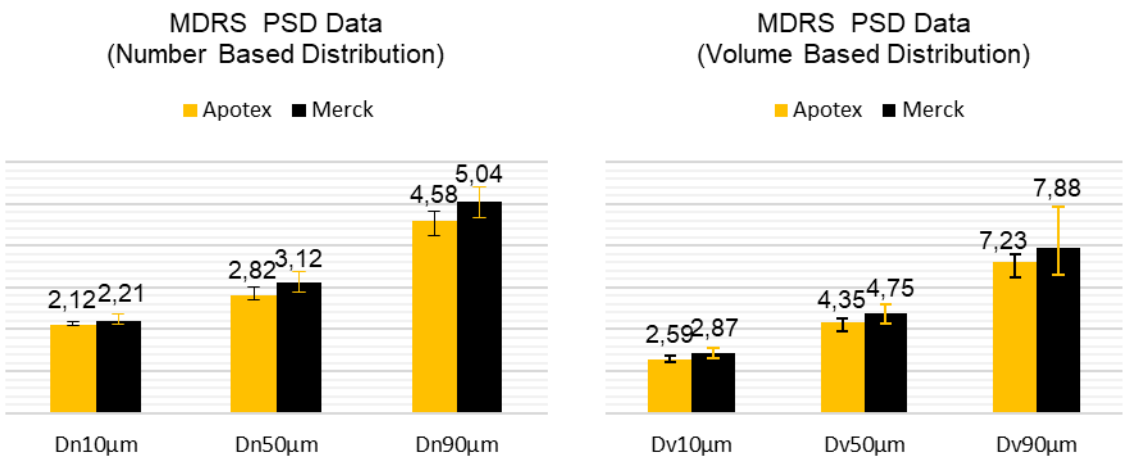


Figure 2-
Comparison MDRS PDS results



Stepwise approach - revisited

1. In-vitro comparison :
2. PK study
3. Clinical endpoint study?

- What is more discriminative?
- What is more predictive for the clinical situation?
- What is feasible?

Dissolution or MDRS

Take home messages

- Copy the formulation and device of the reference product
- Apply the 10 steps for in-vitro comparison of critical quality attributes
- In case of non-similarity in-vitro or in PK, adjust the product
- Copy the administration instruction of the reference product

Please ask critical questions that can be addressed in the drafting process.

Suggestions are welcomed.

Literature

a. L. Salade et al. How to characterize a nasal product. The state of the art of in vitro and ex vivo specific methods. Int J Pharm 561(2019)47-65.
b. Qing Liu et al. Scientific Considerations for the Review and Approval of First Generic Mometasone Furoate Nasal Suspension Spray in the United States from the Bioequivalence Perspective. The AAPS Journal (2019) 21:14.
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g. L. Richards et al. The Evaluation of Equivalence of Mometasone Furoate Nasal Sprays via an In-Vitro Pathway using Dissolution, MDRS and Laser Diffraction Techniques. DDL 2024.
h. Baltz et al. Advancing nasal formulation characterization: Considerations toward a robust and precise method to determine the mass fraction below 10µm in nasal products. Aerosol Science and Technology, 2024: 58:11, 1305-1317.