Prague

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DRAFT NASAL AND ORALLY INHALED PRODUCTS
EXAMPLE OF DISSOLUTION

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Training materials prepared by J-M. Cardot

INTRODUCTION

EMA NEWS 2024

NEW DRAFT GUIDELINE AND CONCEPT PAPERS

12 February 2024 EMA/CHMP/20607/2024
Guideline on the pharmaceutical quality of inhalation and nasal medicinal products

12 April 2024 EMA/CHMP/101453/2024 Draft guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)

15 July 2024 EMA/CHMP/315603/2024 Concept paper for the development of a guideline on the demonstration of therapeutic equivalence for nasal products

DIFFERENCIATION LOCAL VS SYSTEMIC EXAMPLE OF NASAL

The intention of administrating an active substance into the nose could be to apply local treatment in the nose (such as e.g., products containing decongestants to be used in case of common cold or anti-inflammatory medication in case of allergic rhinitis).

Another common use of nasal administration is as an alternative to injections to achieve rapid systemic exposure to an active substance following absorption through the nasal mucosa. The approach to take when demonstrating Therapeutic Equivalence (TE) will differ dependent on whether the product is intended for local or systemic treatment.

OIP/COPD DRAFT GUIDELINE, INTRODUCTION OF IVIVC

As discussed in section 6.3.2 iv, the development of an IVIVC may be useful to correct the results of the PK study to justified parts of the Aerodynamic Particle Size Distribution (APSD) of the typical marketed batch of the reference product and the corresponding typical test product batch according to the proposed specifications in the rare

occasions when it is difficult to find representative batches. Adjustment or normalization may be acceptable if an IVIVC has been established previously between the in vitro parameters and the PK parameters for systemic safety and lung deposition and has been pre-defined in the study protocol.

CONCEPT PAPER NASAL

Currently, abridged applications for locally active substances are supported by in vitro data on TE, sometimes, but not always, complemented by pharmacokinetic or clinical data. A number of in vitro parameters are to be considered:

- Qualitative and quantitative composition
- Actuation volume, single actuation content, or mass of single dose
- Droplet size distribution
- Mass of droplets smaller than 10 µm
- Particle size distribution and morphological form of active substance for suspensions
- Spray pattern / plume geometry
- Rheological properties (e.g., thixotropy, viscosity)
- Surface tension
- pH
- Density
- Osmolality
- Buffer capacity

If TE cannot be concluded by means of in vitro data, in vivo data would be warranted unless the product is reformulated to fit the in vitro criteria.

DRAFT GUIDELINE QUALITY

Covers for Inhalation products and Nasal products

- Active substance (CTD 3.2.S)
- Finished medicinal product (CTD 3.2.P)
- Description and composition of the finished medicinal product (CTD 3.2.P.1)
- Pharmaceutical development (CTD 3.2.P.2)
- Manufacture (CTD 3.2.P.3)
- Control of excipients (CTD 3.2.P.4)
- Control of the finished medicinal product (CTD 3.2.P.5)
- Container Closure System (CTD 3.2.P.7, 3.2.R)
- Stability (CTD 3.2.P.8)
- Therapeutic equivalence
- Product information
- Lifecycle management

DRAFT GUIDELINE

New marketing authorization applications, including abridged applications, variation : making changes to authorized medicinal products and during development of medicinal products used in clinical trials.

This guideline has been developed for medicinal products containing active substances of synthetic or semi-synthetic origin. However, the general principles described should also be considered for other inhalation and nasal medicinal products with active substances of other origins.

The guideline applies to medicinal products developed for administration of active substance(s) to the lungs, such as pressurized and non-pressurized metered-dose inhalers (MDI), dry powder inhalers (DPI), medicinal products for nebulization, as well as pressurized metered-dose nasal sprays, nasal powders and nasal liquids.

Liquid inhalation anesthetics and nasal ointments, creams and gels are excluded, however the general principles described in this guideline should be considered

DRAFT GUIDELINE

Summary tables on tests required for development and for finished products

SUMMARY TABLES OIP

Development

Pharmaceutical development study	Pressurised metered-dose inhalers (pMDI)	Dry powder inhalers (DPI)		Preparations for nebulisation		Non-pressurised metered-dose inhalers
		Device-metered	Pre-metered	Single-dose	Multi-dose	
(a) Physical characterisation	Yesa	Yes	Yes	Yesa	Yesa	Yesa
(b) Minimum fill justification	Yes	Yes	Yes	Yes	Yes	Yes
(c) Extractable volume	No	No	No	Yes	No	No
(d) Extractables / leachables	Yes	No	No	Yes	Yes	Yes
(e) Single-dose fine particle dose	Yes	Yes	Yes	No	No	Yes
(f) Aerodynamic particle / droplet size distribution	Yes	Yes	Yes	Yes	Yes	Yes
(g) Uniformity of delivered dose and fine particle dose through container life	Yes	Yes	Yes	No	No	Yes
(h) Uniformity of delivered dose and fine particle dose over patient flow rate range	No	Yes	Yes	No	No	No
(i) Aerodynamic particle size distribution with spacer use	Yes	No	No	No	No	No
(j) Actuator / mouthpiece deposition	Yes	Yes	Yes	No	No	Yes
(k) Delivery rate and total delivered dose	No	No	No	Yes	Yes	No
(l) Shaking requirements	Yesa	No	No	Yesa	Yesa	Yesa
(m,n) Initial & re- priming requirements	Yes	No	No	No	No	Yes
(o) Cleaning requirements	Yes	Yes	Yes	No	No	Yes
(p) Low temperature performance	Yes	No	No	No	No	No
(q) Performance after temperature cycling	Yes	No	No	No	No	Yes
(r) Effect of environmental moisture	Yes	Yes	Yes	No	No	No
(s) Robustness	Yes	Yes	Yes	No	No	Yes
(t) Delivery device development	Yes	Yes	Yes	Yes	Yes	Yes
(u) Preservative effectiveness / efficacy	No	No	No	Yesb	Yesb	Yesb
(v) Compatibility	No	No	No	Yes	Yes	No
(x) Spray pattern / plume geometry	Yes	No	No	No	No	Yes

Finished product

Finished medicinal product specification test	Pressurised metered-dose inhalers (pMDI)	Dry powder inhalers (DPI)		Preparations for nebulisation		Non-pressurised metered-dose inhalers
		Device-metered	Pre- metered	Single- dose	Multi- dose	
(a) Description	Yes	Yes	Yes	Yes	Yes	Yes
(b) Assay	Yes	Yes	Yes	Yes	Yes	Yes
(c) Moisture content	Yes	Yes	Yes	No	No	No
(d) Mean delivered dose	Yes	Yes	Yes	No	No	Yes
(e) Uniformity of delivered dose	Yes	Yes	Yes	No	No	Yes
(f) Content uniformity / uniformity of dosage units	No	No	No	Yes	No	No
(g) Fine particle dose	Yes	Yes	Yes	Yesa	Yesa	Yes
(h) Leak rate	Yes	No	No	No	No	No
(i) Microbial / microbiological limits	Yes	Yes	Yes	Yesb	Yes	Yes
(j) Sterility	No	No	No	Yesc	Yesc	No
(k) Leachables	Yes	No	No	Yes	Yes	Yes
(l) Preservative content	No	No	No	Yesb	Yesb	Yesb
(m) Number of deliveries per container	Yes	Yes	No	No	No	Yes

STATISTICAL APPROACH

Nothing is mentioned

Options

- ABE after Ln transformation and 90% interval ?
- Non transformed data and Fieller Theorem ?
- Limits ± 10% or ± 15% or ???

- How to deal if reference is more variable than test

- Complex particle/droplet size distribution analysis EMD?

DRAFT GUIDELINE DISSOLUTION

Interestingly dissolution is mentioned for inhalation products in draft guidelines

3.2.P.2.1.1-2 For the finished medicinal product, development and characterization studies based on dissolution testing can be provided as supportive information
Life cycle Mngt Any other change that affects the in vitro APSD or in vitro dissolution release characteristics of the finished product.
Guideline on the pharmaceutical quality of inhalation and nasal medicinal products

If the active substance is in the solid state (powder, suspension): any differences in crystalline structure and/or polymorphic form should not influence the performance of the product (e.g., aerosol particle behaviour, in vitro dissolution with relevant conditions).
Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)

DISSOLUTION TESTS FOR INHALATION AND NASAL PRODUCTS

DISSOLUTION FOR NASAL AND INHALATION PRODUCTS

Mentioned as research topics from early 80-90s

In the last decade many publications even from agencies for example (not limitative)

- 2017 Vincenzi (EMA) informed that dissolution was an ongoing discussion point in update of guideline
- 2022 Boc and Newman (FDA) indicated that dissolution tests were able to differentiate formulations with different API particle size and referenced Hochhaus G, et al.

DISSOLUTION

Various apparatus were proposed and used. For pure dissolution using Pharmacopeia apparatus, the most commonly cited are

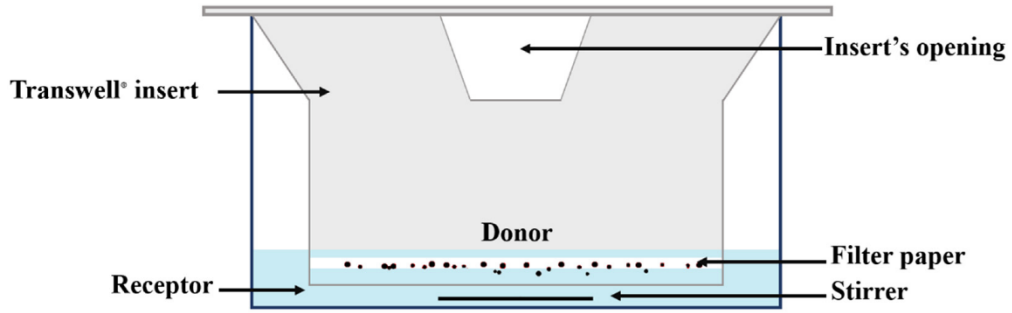
USP 4 Flow Through Cell
Like injectable suspension

USP 5 Paddle Over Disk
As described by Hochhaus

Both could respect sink conditions

DISSOLUTION

Transwell is also cited using an amorphus filter but that is not compendial, is not respecting sink conditions, filter selection is of importance



(From Animi 2021)

DISSOLUTION

Assuming that a dissolution method for OIP must be developed and validated like a normal dissolution method, and further 3 test vs 3 reference batches must be used for comparison

Main problems are to

- Set the system including the dissolution composition and volume
- Prepare the sample to be tested (shaking, dispensing, etc…), including the use of the actuator as it is a main component of the system
- Introduce the product using a well define way such as membrane as support
- Withdraw with filtration the sample
- Deal with the low doses and LLOQ
- Analyze the results

EXAMPLE

In order to simplify the reading : mass delivered and dose expressed in % of the claim

Data of RLD are presented

Dissolution were performed with USP 4 or USP 5 to stay with pharmacopeia described apparatus

Mass and dose delivered were compared

Data were analyzed as per the classical approach on dissolution

FIRST PROBLEM SAMPLE

The sample introduced could be measure as per the mass (and not the dose)

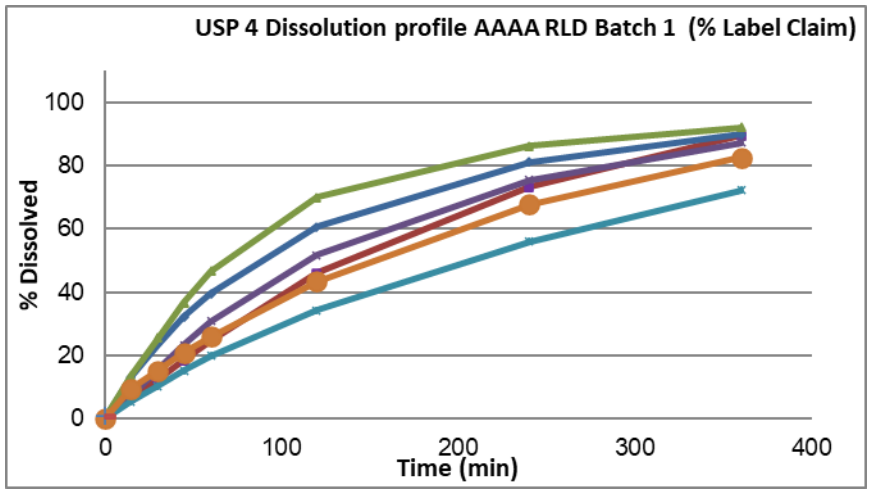
One or two actuations/puffs used.

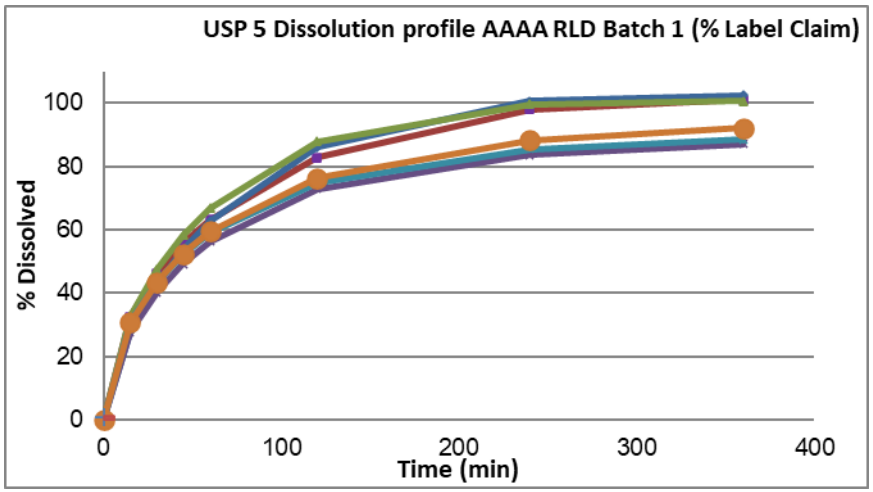
The mass introduced could help to adjust the results to the mass as the precision of actuation could be of ± 15% or even to ± 25% for some extreme values as per the EP

However that suppose that mass is correlated to the dose

DISSOLUTION USP 4 VS USP 5 RLD DRUG AAAA

Variability could be observed which depend of the batches, example test 1 drug AAAA

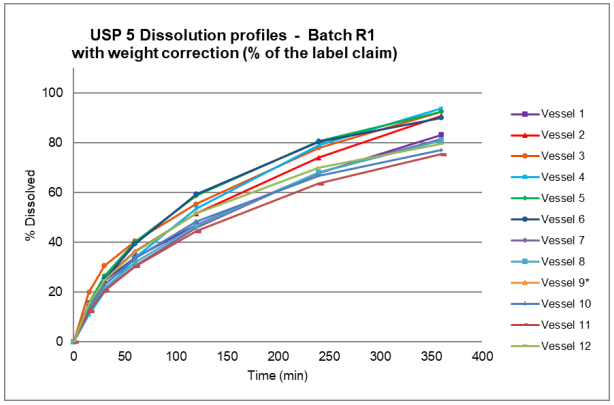


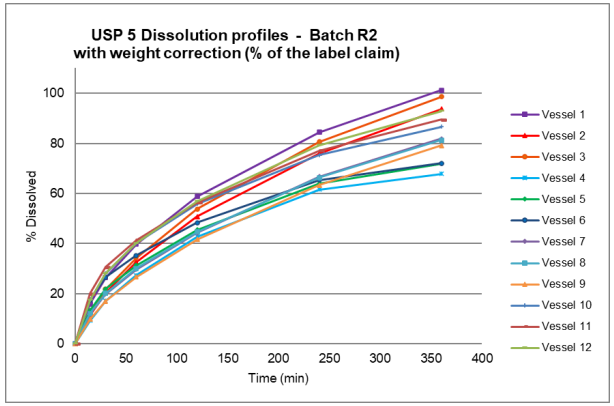


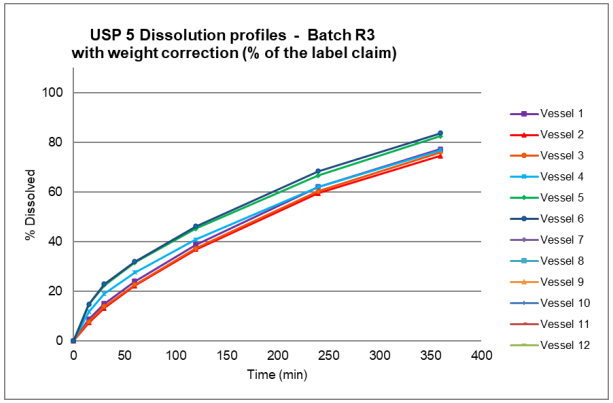
USP V exhibit a lower variability in the current example

Neither USP 4 nor USP 5 finished at 100% in present example

USP 5 VARIABILITY RLD BATCHES 1, 2, AND 3 DRUG BBBBB







Depending of the batches variability could be observed

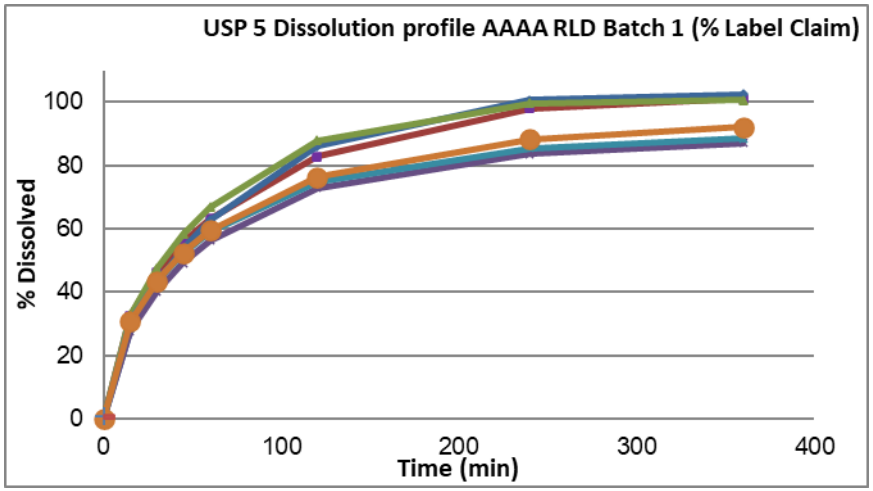
DOSE …

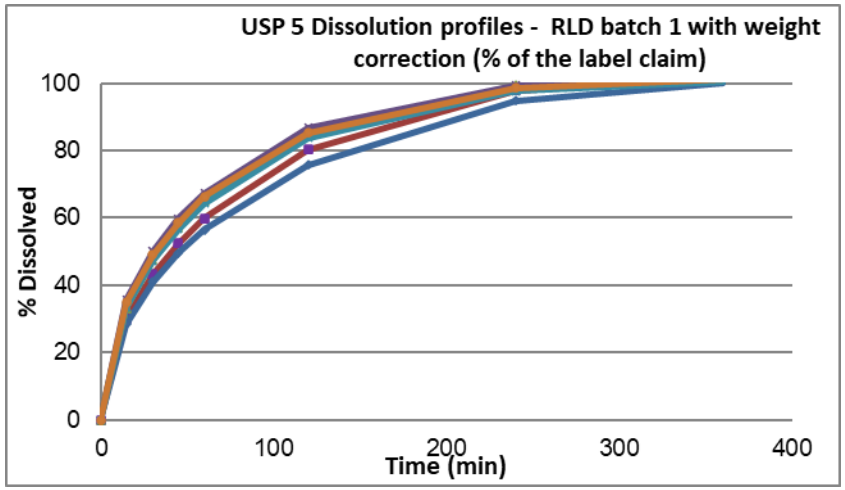
Draft Quality Guideline The amount of active substance in one actuation should be determined by calculating the mean of the delivered dose uniformity test results (see 4.2.5.5), with corrections as necessary to convert from “per dose” amounts to “per actuation” amounts. Limits of ±15% of the label claim should apply, as stated in accepted pharmacopeia (e.g. Ph. Eur. monograph “Preparations for inhalation”).

OIP / COPD draft guideline The target delivered dose should be similar (within ±15%).

CORRECTION BY THE MASS DELIVERED DRUG BBBB

It is possible to correct it by the mass delivered

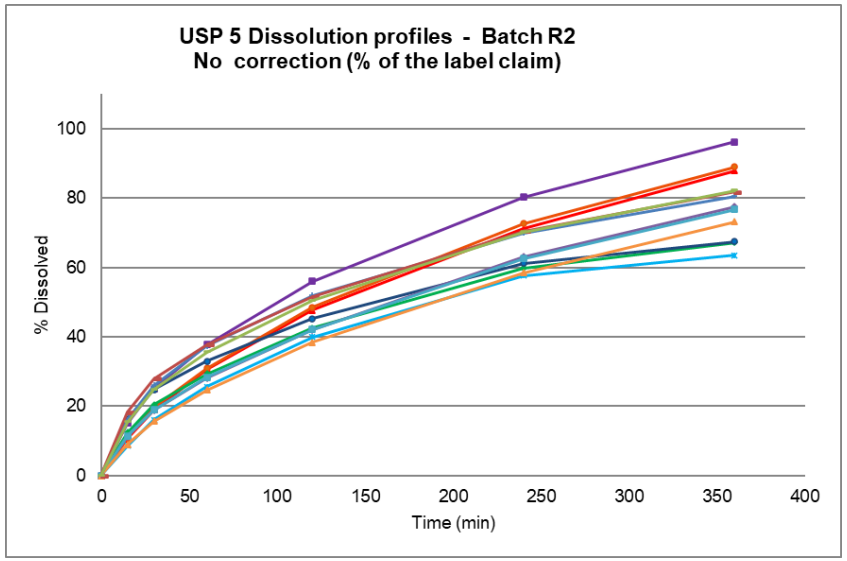


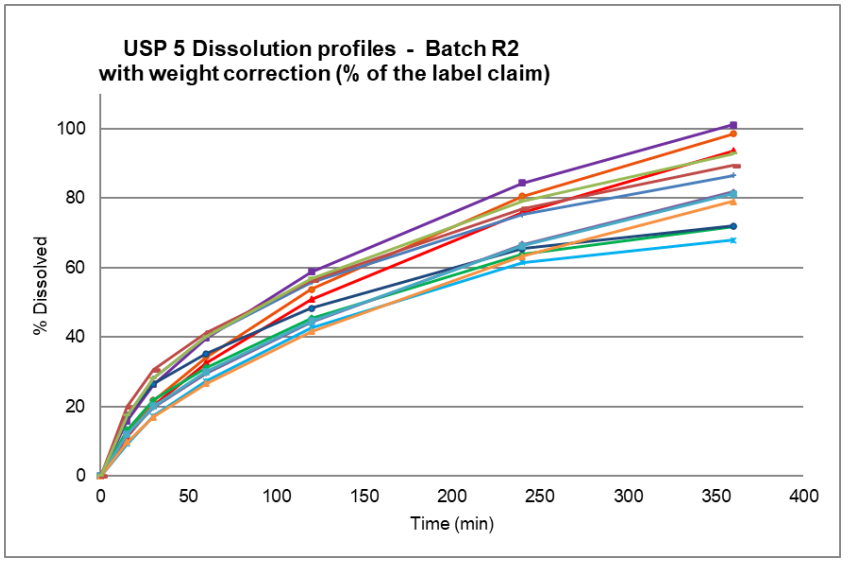


However mass does not mean dose … and then the correction would not be of interest

CORRECTION BY THE MASS DELIVERED DRUG CCCC

When mass and dose are not correlated





STUDY OF MASS DELIVERED VS DOSE DELIVERED RLD

Using the test as per pharmacopeia the results of mass and dose delivered are as follow for drug CCCCC.

			SAC Dose µg		SAC Mass mg	
Type	**Batch**	N	Mean	Std	Mean	Std
Ref	X1	10	89.14	6.57	102.73	1.09
	X2	10	100.74	5.91	100.74	1.99
	X3	10	92.19	13.69	101.73	2.17

It could be observed that the mass delivered is correct for all formulations/drug but dose delivered is or not linked with the mass delivered, that lead to problems in the way to analyze/ normalize the results even if the results are within the acceptable limits of pharmacopeia for both.

F2

The usual way to compare dissolution curves is F2.

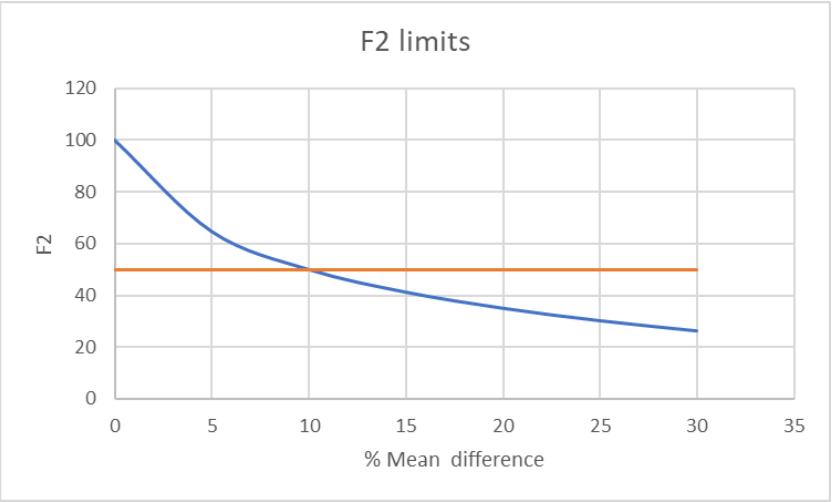
F2 is designed to detect a 10% difference between the test and the reference.

For solid oral dosage formulations the dose must be with ± 5%

For Inhaled and nasal dosage formulation the dose must be with ± 15%

Is F2 limits at 50 adapted ?

Using 2 times the limits of dose results to 30% difference and F2 = 26%



F2 AND ALTERNATIVE OF F2

If variability is high F2 could not be used and as variability is a key factor of bootstrap … the risk to fail is high highlighting the risk linked with variability between vessels.

US-FDA

EXAMPLE OF NASAL SPRAY

GUIDELINES

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation July 2002

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action April 2003

Almost 40 product specific guideline with around 50% revised in the last 2 years

COMMON BASIS

- Equivalence of in vitro performance
- Equivalence of systemic exposure
- Equivalence of local delivry via comparative clinical endpoint (CCEP)

However aknowledge that it is complicated for in vivo and mainly CCEP due to variability, improvement of new technique lead to alternative solutions if validated, described in product specific guideline such as

– Azelastine Hydrochloride and Fluticasone Propionate – Beclomethasone Dipropionate Monohydrate
– Budesonide – Ciclesonide – Fluticasone Propionate – Mometasone Furoate Monohydrate
– Mometasone Furoate and Olopatadine Hydrochloride – Triamcinolone Acetonide

PRODUCT SPECIFIC GUIDELINES EXAMPLE

Open to alternative such as Fluticasone Propionate Nasal Spray, Metered (June 2023) seems to be the reference for recommendations on design and equivalence criteria for the in vitro bioequivalence studies, and general recommendations on the conduct of the in vitro bioequivalence studies and data submission.

Two options: (1) eight in vitro bioequivalence studies, or (2) six in vitro bioequivalence studies, one in vivo bioequivalence study with pharmacokinetic endpoints, and one comparative clinical endpoint bioequivalence study

PRODUCT SPECIFIC GUIDELINES

In vitro:

- SAC, Droplet size distribution (D50, Span), Small particle, Spray Pattern, Priming repriming, Drug Particle Size distribution (Morphological Directed Raman Spectroscopy), comparison PBE (Budesonide Inhalation Suspension for more information),
- Plume geometry Ratio of the polled geo mean of T to that R for both plume angle and width, within 90-111% (no CI)
- Dissolution (Apparatus 2, Apparatus 5, or Transwell system) and comparison using F2

REMARKS

For MDRS minimum number of particle should be justified as well as the filter selection (cut off) for both API and excipients, and duration of exposure for Raman spectra

For dissolution sink condition are with USP 2 and 5, possibly non sink conditions with transwell (the selection of the filter is of importance and could play a role, paper is cited in Amini article)

STATISTICAL ANALYSIS

PBE (population bioequivalence) is presented at least for D50 and Span and was first described in Budesonide Inhalation Suspension guideline

Main difference vs ABE takes into account the variability of the reference to set limits

REMARK

In Statistical Approaches to Establishing Bioequivalence Guidance for Industry from December 2022 in section C-6 it is mentioned “EMD is a statistical metric that measures the discrepancy (distance) between distributions without a prior assumption of the distribution.

The EMD has been recommended in a profile comparison approach to assess equivalence of particle size distribution profile, where the profile exhibits complex distribution (i.e., multiple peaks) that cannot be accurately described by some conventional descriptors (e.g., the D50 and SPAN).”

CONCLUSION

DISSOLUTION

Dissolution is introduced in draft guideline for OIP and not for nasal product (up to now at least)

Dissolution for OIP or nasal is challenging for many reasons and currently no indication is given on the way to proceed

F2 test might not be the best test using the actual limits and no indication is given on the acceptance limits

AKNOWLEDGMENT

To P. SUPLIE and Substipharm for the fruitful discussions

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THANK YOU

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