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**Experience with OIP Equivalence Determinations in the Netherlands - Focus on *in-vitro* Aspects**

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## Disclaimer

**My views do not necessarily represent the views of the Medicines Evaluation Board in the Netherlands, the working parties or committees of the European Medicines Agency, or the working parties of the European Directorate for the Quality of Medicines and Healthcare Products.**

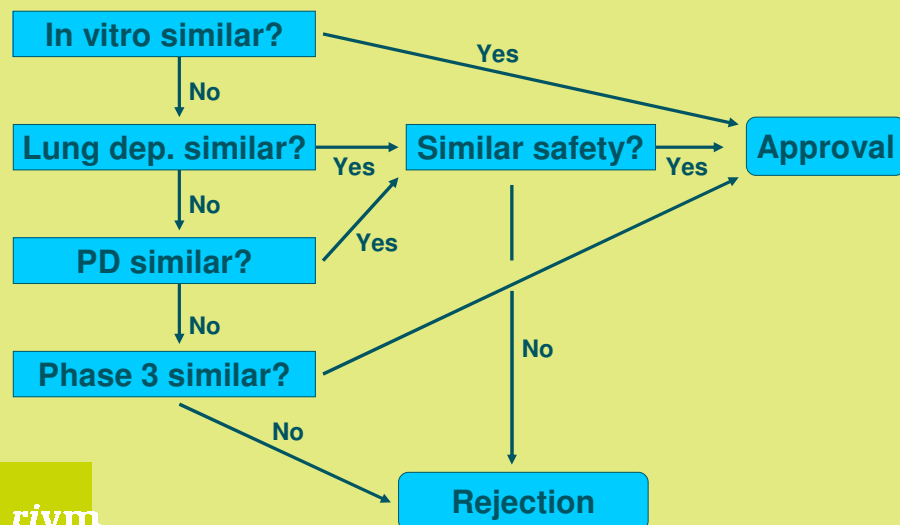
## EMA-CHMP guideline

Adopted by CHMP in January 2009:

'Requirements for Clinical Documentation for **Orally Inhaled Products (OIP)**, Including the Requirements for Demonstration of **Therapeutic Equivalence** Between Two Inhaled Products for Use in the Treatment of **Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults** and for Use in the Treatment of **Asthma in Children and Adolescents.**'

As revision of 'Points to consider on the requirements for clinical documentation for orally inhaled products (OIP).'

## Stepwise approach in EMA guideline



## First step in EMA guideline:

Comparative **impactor analysis** is allowed as surrogate for therapeutic equivalence when a set of criteria is fulfilled:

- Same **drug substance** (same salt, ester, hydrate, etc.)
- Identical **dosage form** (pMDI versus pMDI)
- In case of **drug in solid state**: differences in crystalline structure and/or polymorphic form have no influence on dissolution and aerosol particle behaviour
- In case of **different (amounts of) excipients**: differences have no influence on aerosol particle behaviour and patient inhalation behaviour

## Criteria (continued):

- In case of **different (amounts of) excipients**: no change in safety profile
- Target **delivered dose** is similar ( $\pm 15\%$ )
- Inhalation device: the same **resistance to airflow** ( $\pm 15\%$ ); applicable to DPI
- **Inhaled volume** for the required dose is similar ( $\pm 15\%$ )
- **Handling** of the device similar

So, a lot of comparative **in vitro tests** are needed to support the evidence of therapeutic equivalence; not only impactor analysis!!

## Drug in solid state

‘Differences in crystalline structure and/or polymorphic form have no influence on **dissolution** and **aerosol particle behaviour**’

→ **Dissolution**: no compendial test methods available. Dissolution in a set of solvents with a range of extreme characteristics (polar/non-polar, ionic/non-ionic, low/high viscosity, etc.)? Dissolution in fluid simulating micro-environment in (certain regions of) the lungs? Demonstrating absence of differences is easier.....

→ **Aerosol particle behaviour**: tested with impactor/impinger

## Excipients

‘In case of different (amounts of) excipients: differences have no influence on **aerosol particle behaviour** and **patient inhalation behaviour**’

→ **Aerosol particle behaviour**: tested with impactor/impinger

→ **Patient inhalation behaviour**: large difference in particle size of carrier may affect mouth/throat feel; ‘cold freon’ effect in case of propellants. Large differences in excipients will make comparative *in vitro* testing irrelevant for demonstrating equivalence.

## Comparative impactor analysis



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## Issues of frequent discussion

- ❖ Stage pooling
- ❖ Equivalence limits
- ❖ Spacers/holding chambers



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## Stage pooling

### How to justify stage pooling?

- ❖ This should be considered before starting the *in vitro* study! A **pre-established protocol** for *in vitro* equivalence testing should be prepared (like a clinical trial protocol).
- ❖ Safest route: no stage pooling.

**Problem:** sometimes very low amounts of drug on certain impactor stages; equivalence cannot be proven based on the currently suggested criteria ( $\pm 15\%$ ).

## Low amounts on stages, example

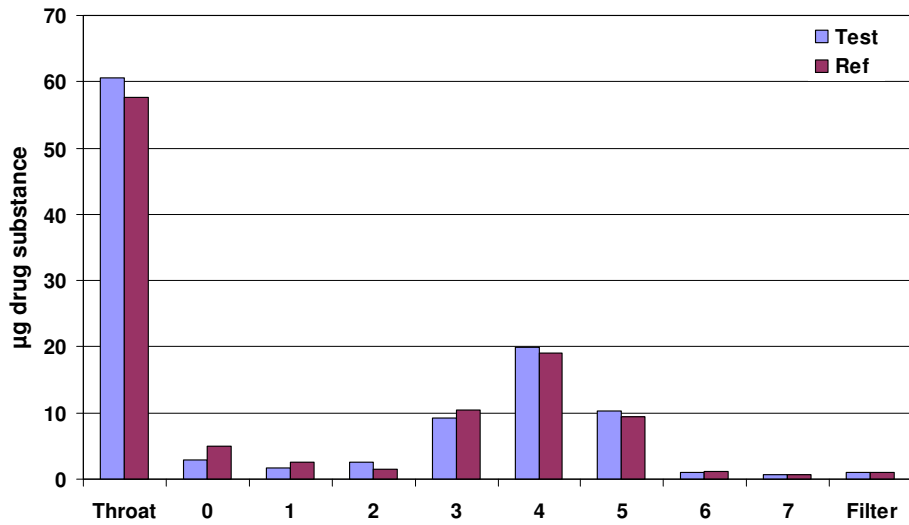
Stages	Test	Ref	$\Delta$	% of FPM*	Ratio	CI lower	CI upper
Throat	60,61	57,6	3,01	6,55	1,05	0,96	1,14
0	2,91	4,92	2,01	4,37	0,59	0,52	0,65
1	1,63	2,64	1,01	2,20	0,62	0,59	0,66
2	2,54	1,62	0,92	2,00	1,57	1,51	1,63
3	9,23	10,41	1,18	2,57	0,89	0,85	0,94
4	19,87	19,01	0,86	1,87	1,05	0,96	1,15
5	10,28	9,36	0,92	2,00	1,10	1,08	1,12
6	1,08	1,20	0,12	0,26	0,90	0,84	0,96
7	0,62	0,67	0,05	0,11	0,93	0,89	0,98
Filter	1,01	1,05	0,04	0,09	0,96	0,91	1,02
Delivered FPM	109,78	108,48			1,01	0,96	1,07
	46,26	45,96			1,01	0,94	1,08

\*Stages 1 up to Filter (cut-off point 5.9  $\mu\text{m}$ )

pMDI, ACI data, 28.3 l/min, amounts expressed as  $\mu\text{g}$

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## Will these products **not** be **equivalent** *in vivo*?

**Extremes** of observed differences in FPM range leading to conclusion 'equivalence **not proven**':

- stage 0: **2.01 µg** (=4.4% of FPM)
- stage 6: **0.12 µg** (=0.3% of FPM)

**Extremes** of observed differences in FPM range leading to conclusion 'equivalence **proven**':

- stage 3: **1.18 µg** (=2.6% of FPM)
- filter: **0.04 µg** (=0.1% of FPM)

## Do very **low amounts** of drug really matter?

**To illustrate:**

Parenteral drug product, or tablet intended to act in duodenum, with assay limits of 90-105%: a difference of 15% in drug dose entering the patient is apparently acceptable....

**To consider:**

If 6 batches of a reference product will be compared to 6 other batches of the same reference product: will they be equivalent????

## How to justify the **stage pooling**? (cont.)

- ❖ Stage pooling: distinction should be made between stages which will only reflect **safety** (fraction with a high likelihood to be swallowed) and **efficacy/safety** (fractions with a high likelihood to enter the lungs).

The problem is: how to provide evidence for this.....

## How to justify the **stage pooling**? (cont.)

Bronchodilator response of 3  $\mu\text{m}$  and 6  $\mu\text{m}$  salbutamol particles is larger than 1.5  $\mu\text{m}$  particles (Usmani et al., 2003 and 2005). Deposition efficiency of particles 0.1 – 1.0  $\mu\text{m}$  is low (Heyder, 2004). So:

- stages representing particles between 3  $\mu\text{m}$  and 6  $\mu\text{m}$  should not be grouped
- stages representing particles < 1  $\mu\text{m}$  may be grouped and
- throat has unknown/high cut-off: should not be pooled

## How to justify the **stage pooling?** (cont.)

A view on acceptable pooling: ACI, 28.3 l/min

Throat

Stage 0 + stage 1 (5.8 – 9.0  $\mu\text{m}$ )

Stage 2 (4.7-5.8  $\mu\text{m}$ )

Stage 3 (3.3-4.7  $\mu\text{m}$ )

Stage 4 + stage 5 (1.1-3.3  $\mu\text{m}$ )

Stage 6 + stage 7 + filter (< 1.1  $\mu\text{m}$ )

## Equivalence limits

## How to justify the **equivalence limits**?

- ❖ This should be considered before starting the *in vitro* study! A **pre-established protocol** for *in vitro* equivalence testing should be prepared (like a clinical trial protocol).
- ❖ Safest route: apply 15%! But is rather strict/prudent and not always feasible due to low drug amounts on specific impactor stages.

## How to justify the **equivalence limits**?

### Rationale behind $\pm 15\%$ :

- no IVIVCs available for most substances; rather conservative approach is chosen
- mean delivered dose is allowed to be  $\pm 15\%$  of the claimed delivered dose

## How to justify **wider equivalence limits** than 15%?

Frequently wider limits (than 15%) are proposed by applicants, but without appropriate justification.

E.g. the following aspects are **rarely discussed** by applicants, in order to justify the wider limits:

- ❖ therapeutic index
- ❖ steepness of dose-response curves (for efficacy and adverse drug reactions)
- ❖ analytical (im-)possibilities

## Aspects **rarely discussed** by applicants (cont.):

- ❖ supporting literature dedicated to IVIVCs or in another way relevant for justification
- ❖ discriminatory power of impingers / impactors
- ❖ application of different limits for various stages (or grouped stages): limit for adverse drug reaction may/will be different from efficacy limit
- ❖ application of an equivalence limit in microgram (instead of percentage)
- ❖ the relevance of impinger / impactor analysis at all

A more scientific approach would be welcome....

Is the **concept** of acceptance criteria expressed as **percentage** ( $\pm 15\%$ ) valid?

**Extremes** of observed differences in FPM range leading to conclusion 'equivalence **not proven**':

- stage 0: **2.01  $\mu\text{g}$**  (=4.4% of FPM)
- stage 6: **0.12  $\mu\text{g}$**  (=0.3% of FPM)

When stages with low amounts will be compared and need to comply with  $\pm 15\%$ : the chance that equivalence

will be proven based on *in vitro* data is very low.....

**Other approaches** could be (??):

- Calculate the absolute difference, including confidence interval, and apply limits for absolute difference based on expected influence on efficacy/safety.
- Calculate the difference expressed as percentage of the FPM, including confidence interval, and declare differences below 5% as clinically not relevant.
- Make use of 'the area under the curve' and other characteristics of the total *in vitro* deposition profile. Demonstrate similarity.

## Spacers/holding chambers

### What **kind of data** to be provided in case of a spacer/holding chamber?

Test product will follow the summary of product characteristics (SPC) of the reference product: if a spacer is included in the reference product SPC, the test product is likely to be used with the **same spacer**, according to the **same instructions**.

## What **kind of data** to be provided in case of a spacer/holding chamber? (cont.)

The same principles apply as for the comparative pMDI testing programme: start with *in-vitro* comparison. If equivalence cannot be demonstrated: *in-vivo* studies are required.

## What **kind of data** to be provided in case of a spacer/holding chamber? (cont.)

*In-vitro* study: spacer should be treated as prescribed by the spacer manufacturer (and applied by the patient), e.g. washed with soap solution/drip-drying, or no pre-treatment.

Setting up the test in a **clinically relevant** manner:

- Time delay between actuation/inhalation (e.g. 2 seconds)
- Tidal breathing (unless to be used in one breath)

## Experience in the Netherlands

### Common deficiencies

- ❖ No pre-established protocol
- ❖ Too limited number of batches (resulting in wide confidence intervals)
- ❖ Changes in acceptance criteria during procedure
- ❖ Air flow resistance not adequately compared
- ❖ No rationale for chosen air flow rate
- ❖ Only one flow rate tested in case of DPI
- ❖ No comparison of polymorphic forms/amorphous fractions drug substance (when in solid state)

## To summarize / key messages:

- ❖ **Comparative *in vitro* testing** in order to prove therapeutic equivalence is **more than** comparing impactor data.
- ❖ Discussion between industry/regulators and scientific evidence is needed on **wider equivalence limits** and on **stage grouping** when using impactors.
- ❖ Available **scientific knowledge** could/should be used more extensively.
- ❖ Additional scientific knowledge should be gathered on **other ways of defining acceptance criteria**.

Thank you for your attention!