



# Clinical development program for demonstrating therapeutic equivalence between inhaled products

(abridged application)

Dr. Michael Klein

AGAH Workshop „Beyond the Guidelines“

May 16, 2013

# EU Guideline Orally Inhaled Products

## Legal Basis

---

- Orally Inhaled Products (OIP) Guideline from Jan 2009 (CPMP/EWP/4151/00 Rev. 1)  
in conjunction with CHMP guidance
  - *EMA/CHMP/QWP/49313/2005corr: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products;*
  - *CPMP/EWP/239/95: Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents;*
  - *CPMP/180/95: Guideline for PMS Studies for Metered Dose Inhalers with New Propellants;*
  - *CPMP/EWP/240/95 Rev.1: Guideline on the Clinical Development of Fixed Combination Medicinal Products;*
  - *CPMP/III/5378/93-Final: Note for Guidance: Replacement of Chlorofluorocarbons (CFCs) in Metered Dose Inhalation Products;*
  - *CPMP/ICH/363/96: Note for Guidance on Statistical Principles for Clinical Trials;*
  - *CPMP/EWP/QWP/1401/98 Rev.1 Guidance on the Investigation of Bioequivalence;*
  - *CPMP/ICH/364/96 Note for Guidance on Choice of Control Group in Clinical Trials;*
  - *EMA/CPMP/EWP/2158/99 Guideline on the Choice of the Non-inferiority Margin*
-

# EU Guideline Orally Inhaled Products

## Scope (Abridged Application)

---

Existing CHMP documents which discuss the clinical requirements for the development of inhaled products - *Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma CPMP/EWP/2922/01* and *Points to Consider on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) CPMP/EWP/562/98* - discuss primarily the development of new active substances. This guideline is directed particularly at the requirements for demonstration of therapeutic equivalence between two inhaled products, in the context of abridged applications or variations / extensions to a marketing authorisation, used in the management and treatment of adult patients with asthma and/or COPD and children and adolescents with asthma.

---

# 3-step Approach for Therapeutic Equivalence

---

## *In-vitro*

### 1. Pharmaceutical equivalence

## *In-vivo*

### 2. Pulmonary deposition equivalence (PK study level and/or imaging studies)

Systemic total (AUC) + maximal (C<sub>max</sub>) exposure levels

- via lungs only: surrogate for efficacy
- via lungs + GI tract: surrogate for safety

### 3. Therapeutic equivalence (PD / clinical study level)

- efficacy
  - safety
-

# *In-vitro*: 1. Pharmaceutical Equivalence

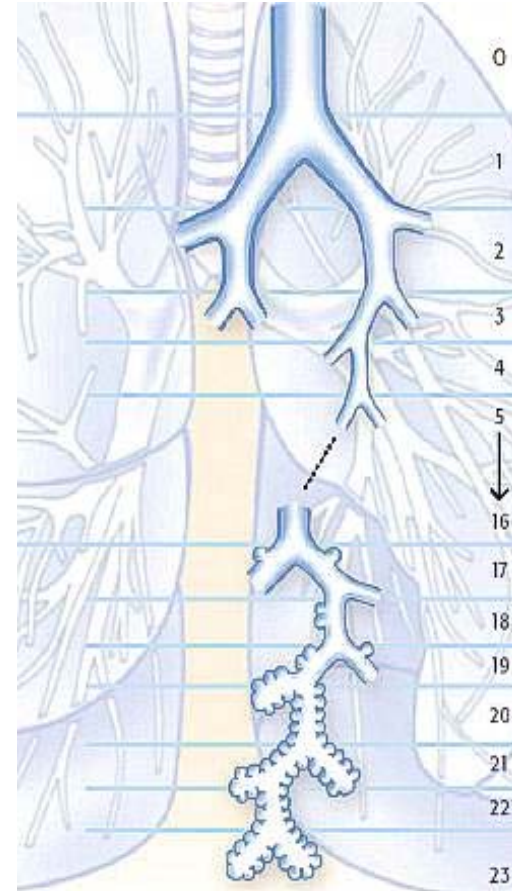
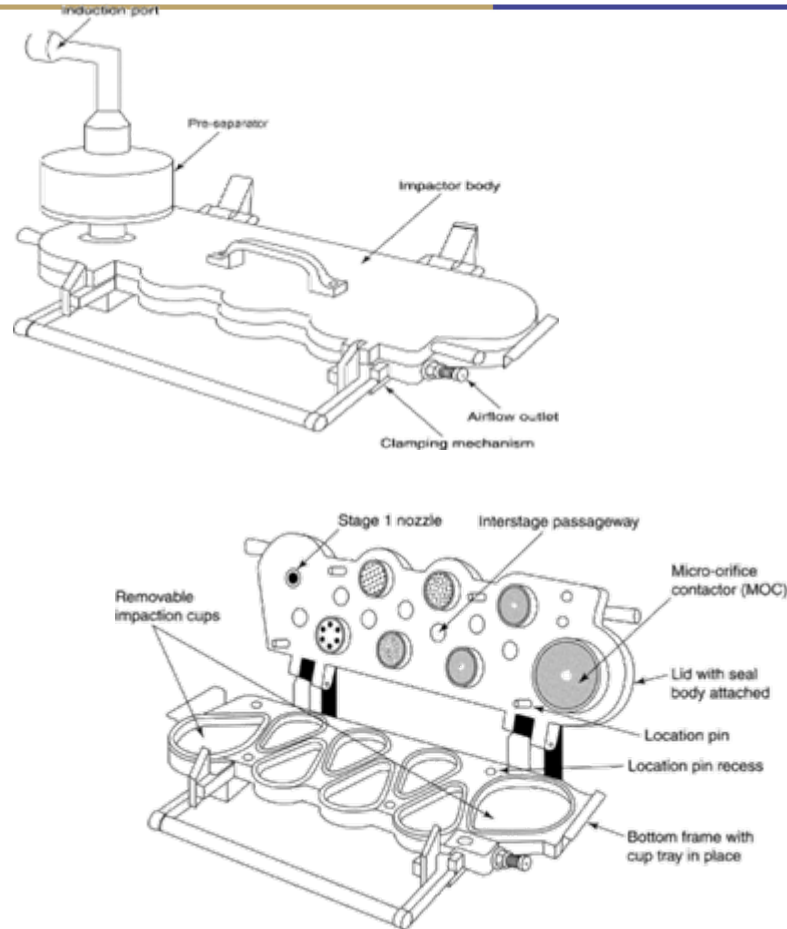
---

- Parameters for product characterisation
  - API characterisation & API used: same active substance (i.e. same salt etc.) and solid state (powder, suspension)
  - Qualitative and quantitative composition excipients and API
  - Pharmaceutical dosage form (e.g. pMDI etc.)
  - Target delivered dose
  - Impactor data/ APSD
  - Device handling
  - Inhaled volume, resistance
- Backbone for any develop. even if not equivalent!

***If non-equivalence concluded go to next level of in-vivo characterisation (PK / imaging study level)***

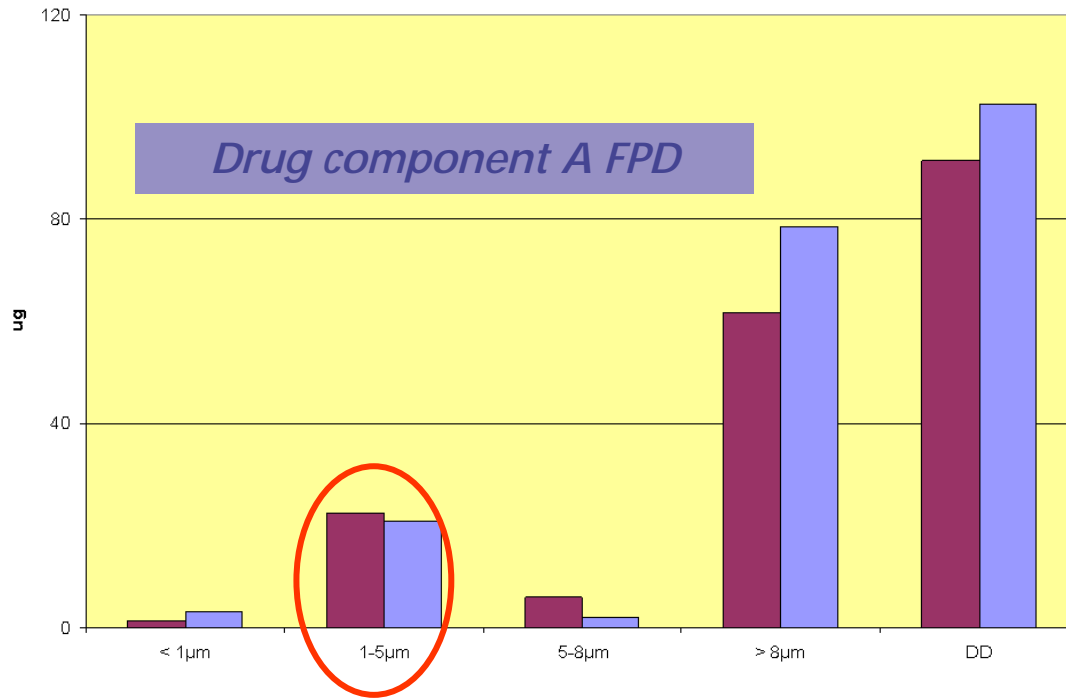
---

# In-vitro Testing/ Next Generation Impactor (NGI)



NGI: **In-vitro** Aerodynamic Particle Size Distribution testing

# test to reference comparison - In-vitro NGI data



■ y study batch  
■ x study batch


x delivers slightly less drug dose (~10% less) within the **respirable particle fraction size 1-5 µm**

= in-vitro **equivalence** particle fraction 1-5 µm

# *In-vivo*: 2. Pulmonary Deposition Equivalence

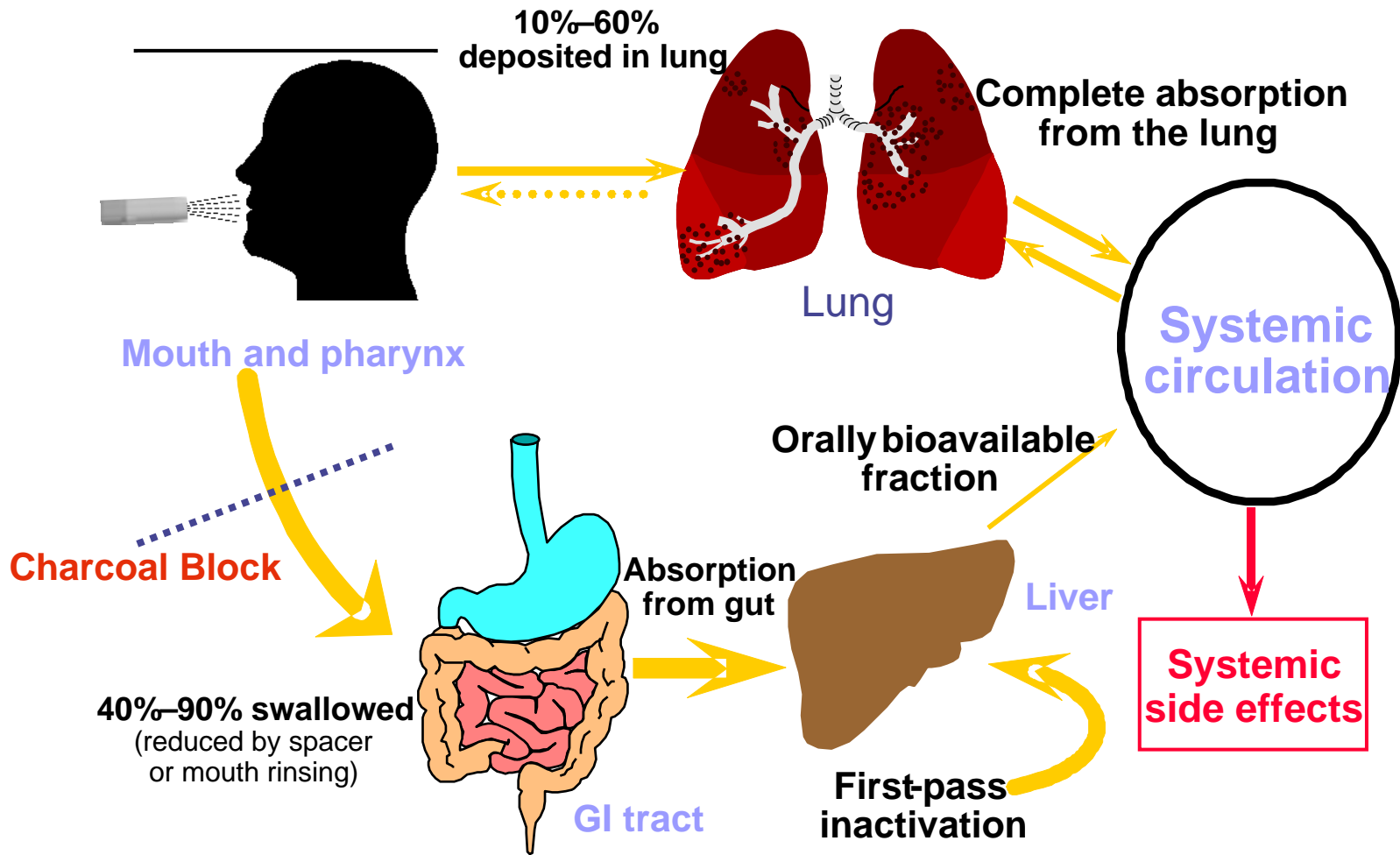
## PK Study and/or Imaging Study Level

---

- Investigate Bioequivalence in PK Studies 
    - Systemic exposure (AUC & Cmax) via lungs & GI tract  
→ *Surrogate for safety*
    - Systemic exposure (AUC & Cmax) via lungs only; concomitant intake of charcoal during inhalation blocks pathway via GI tract  
→ *Surrogate for efficacy & lung deposition*
  - PK Study Design Considerations
    - *Healthy volunteers / patients*, double blind, crossover
    - If negligible GI absorption PK only with concomitant charcoal
    - AUC & Cmax: 90% CI 0.80 -1,25
    - *if ICV >30% Cmax*: 90% CI scaled acc. to ref variability from replicate study design
    - *validated method charcoal block*
-

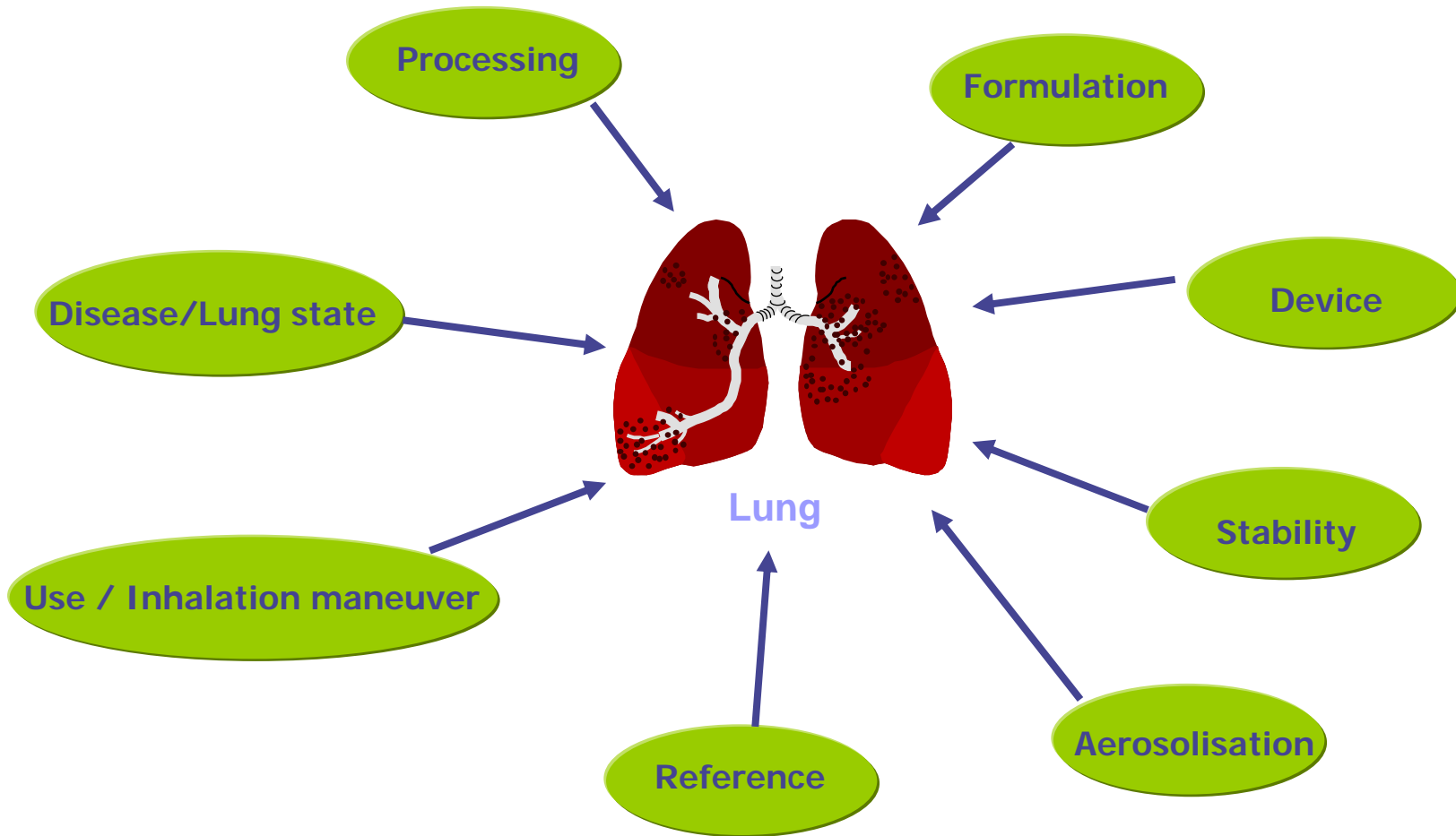


# Pathways Inhalation – With & Without Charcoal



# *In-vivo*: 2. Pulmonary Deposition Equivalence Factors Pulmonary Deposition

---



# In-vivo: 2. Pulmonary Deposition Equivalence

## PK study results

API B				
	Ratio	PE*	90 % CI**	
AUC0-Tlast	T/R	92	86 – 98	
	TC/RC	102	95 – 108	
Cmax	T/R	106	97 – 115	
	TC/RC	114	104 – 123	

API A				
	Ratio	PE*	90 % CI*	
AUC0-Last	T/R	80	74 – 87	Too low Efficacy?
	TC/RC	85	78 – 92	
Cmax	T/R	68	62 – 75	
	TC/RC	76	70 – 83	

API B				
	Ratio	PE*	90 % CI**	
AUC0-Tlast	T/R	92	86 – 98	
	TC/RC	102	95 – 108	
Cmax	T/R	106	97 – 115	
	TC/RC	114	104 – 123	

API A				
	Ratio	PE*	90 % CI*	
AUC0-Tlast	T/R	120	110 – 130	Too high Safety?
	TC/RC	120	110 – 130	
Cmax	T/R	120	110 – 130	
	TC/RC	120	110 – 130	

T or R = without charcoal  
 TC or RC = with charcoal

■ bioequivalence

\* PE = point estimate

\*\* CI = confidence interval 80 - 125



If non-equivalence go to next level  
 Therapeutic equivalence (PD / clinical studies  
 -*efficacy*  
 -*safety* } Dissanayake 2010 either or  
 (combination)!

# *In-vivo*: 3. Therapeutic equivalence

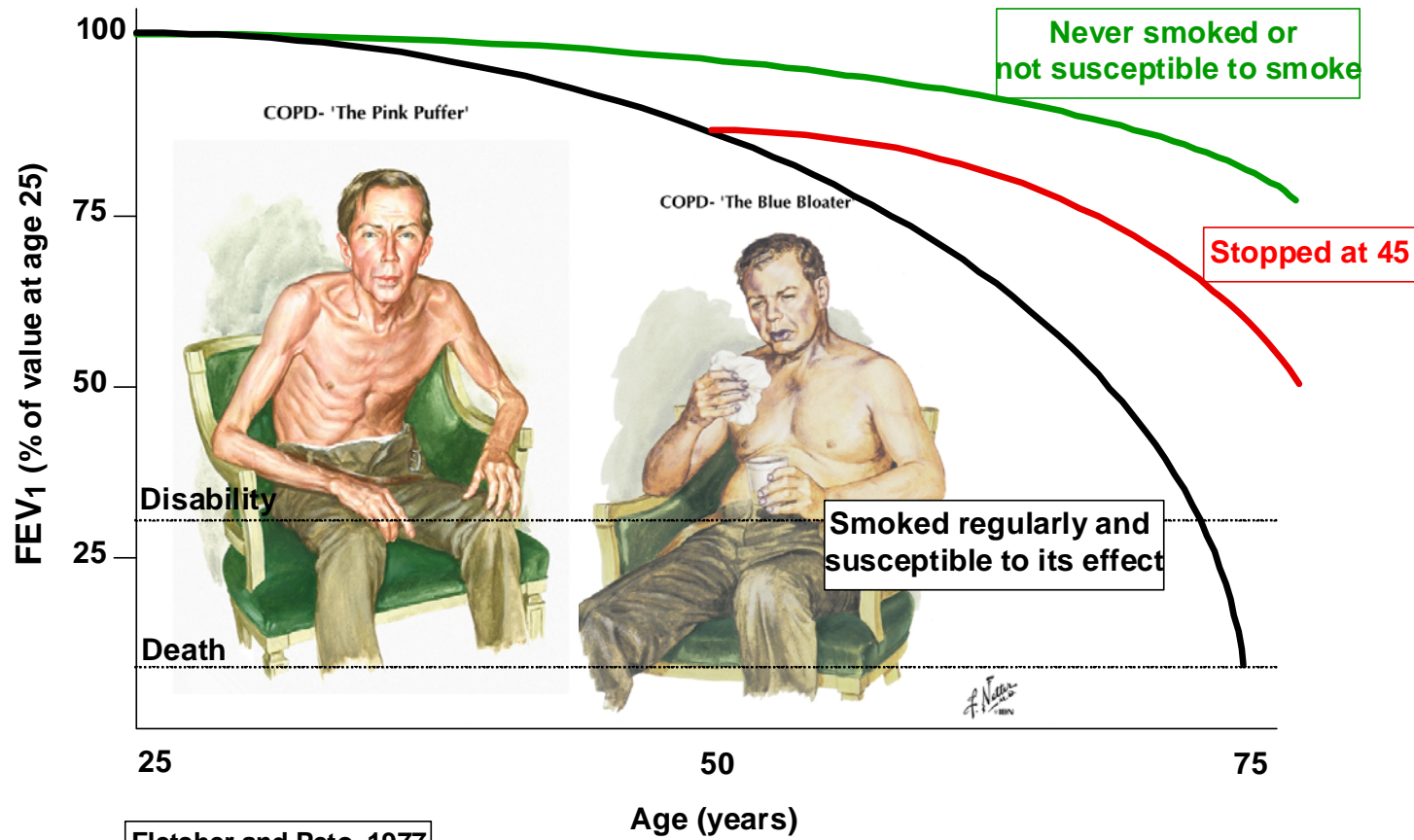
## PD / Clinical Study Level

---

### ***Developmental Frame***

- equivalence in efficacy & safety in well validated study designs
    - COPD may be covered as well if clinical equivalence shown in asthmatic adult program including comparable safety 
    - Cave: *in-vitro* product characterisation required under various flows clinically relevant for target populations to cover COPD & children etc 
    - Children: separate clinical development may be required and depending on device characteristics and clinical adult data
  - **Inspiratory flow studies in children, severe COPD & asthma**
    - Can different populations operate the proposed new device and generate a flow sufficient to use the device?
    - Needed also if *in-vitro* level 1 or *in-vivo* level 2 only
-

# Chronic Obstructive Pulmonary Disease (COPD)





Fletcher and Peto, 1977



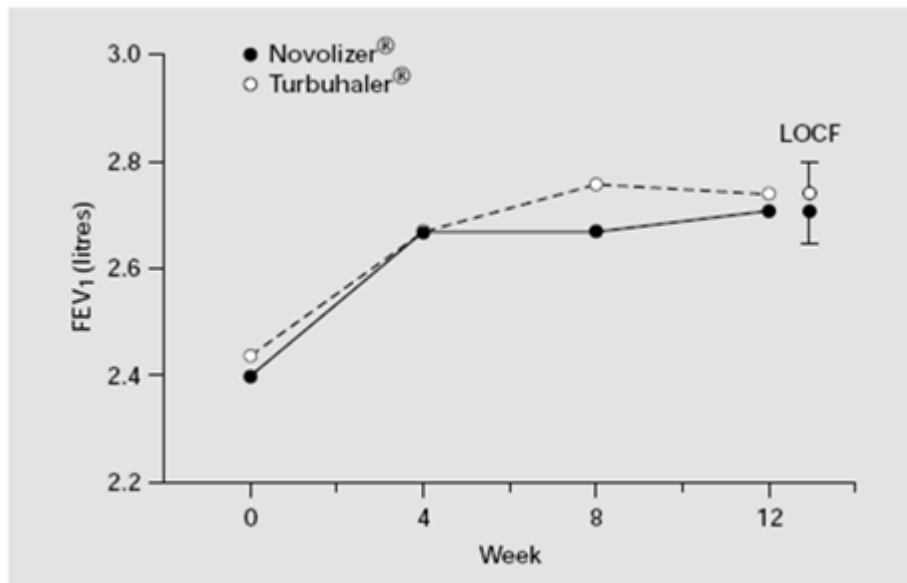
# *In-vivo*: 3. Therapeutic equivalence

## Design Considerations Efficacy Studies

- equivalence in efficacy (both APIs if combinational product)
  - study designs (for SABA/LABA/LAMA and ICS:)
    - bronchodilatation / improved airway function 
    - bronchoprotection 
  - in asthmatic patients with demonstrated reversibility
  - assay sensitivity
    - *superiority between two non-zero dose levels*
    - steep part of the dose response curve
  - 2 types of efficacy evaluation
    - relative dose potency: ratio of potency Test / Ref for 2 dose levels
    - Test / Ref comparison each dose (CI in predefined margins)
  - **less discriminative to product differences than PK studies**
  - pilot studies needed to work out assay sensitivity
-

# Bronchodilatation/ Improved Airway Function

- Stable but less / partially controlled (lung function & symptoms)
- LABA: FEV<sub>1</sub> AUC & change in FEV<sub>1</sub> after single dose
- ICS: FEV<sub>1</sub> or PEF after at least 8 weeks of treatment
- Assay sensitivity challenge (flat or at top of dose response)??
- Alternative concepts e.g. Ahrens & Gros stability & maintenance of initially achieved asthma control via oral CS



Chuchalin et al. 2002

# Bronchoprotection Studies

---

- Drug protection against bronchial challenge with provocation (methacholine, etc)
- Requires high degree of standardisation and patient selection
- Outcome: provocative dose / concentration needed for 20% fall in FEV1 at time of maximum effect ( $PD_{20}$  FEV1 or  $PC_{20}$  FEV1)
- Single dose (SABA / LABA / LAMA) or repetitive dose (ICS)
- Higher chance to show assay sensitivity vs. bronchodilation studies





# *In-vivo*: 3. Therapeutic equivalence

## PD / Clinical Study Level

---

### Safety

- **SABA / LABA / LAMA**
    - equivalence in safety PK or in safety PD variables of relevant cardiovascular (vital signs ECG, QTC), biochemical (potassium, glucose) & physiological parameters, as well as AE monitoring (incl. bronchospasm)
    - highest recommended dose with a second dose for assay sensitivity
      - second dose can be supra-therapeutic (dose response)
      - placebo
  - **ICS**
    - equivalence in safety PK or PD safety variable  
Change from baseline in 24-hr plasma cortisol AUC (Cmax) in steady state
    - highest recommended dose with lower dose for assay sensitivity
      - repetitive dosing does not allow for supra-therapeutic doses
    - cortisol very vulnerable parameter over study duration
    - safety margins: relative ratio/ comparison not acceptable?
-

# Therapeutic Equivalence in Children

---

- Extrapolation from adult data is challenging due to different handling or physiology in children (e.g. airway geometry, tidal volume, breathing patterns etc.)
  - Unless *in-vitro* equivalence is fully shown clinical development in children likely required to demonstrate equivalence for all component(s) in
    - efficacy via PD and/or efficacy studies  
(bronchodilatation / improved airway function or bronchoprotection)
    - safety via PD (cardiovascular (vital signs, ECG, QTC), biochemical (potassium, glucose) and physiological parameters, and cortisol & growth) and/or PK studies
    - *harmonization: PK vs. PD vs. efficacy studies?*
  - Consider assay sensitivity?! (maximum & lower dose?)
  - Studies in adolescents may be required
-