Global Bioequivalence Requirements for Orally Inhaled Drug Products (OIDPs)

Development of Inhalation Therapeutics
(Jointly by AAPS-BADG&PBSS)

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Orally Inhaled Drug Products (OIDPs)

- Metered Dose Inhalers (MDI)
- Dry Powder Inhalers (DPI)
- Nebulizer
- Inhalation Spray

OIDPs

MDI	• Propellant, suspended or dissolved drug, co-solvents or surfactants (optional) • Widely available for most inhaled medicine, requires good coordination
DPI	• Micron-sized drug particles deposited on carrier (e.g., lactose) surface or drug agglomerated with micronized anhydrous lactose • No propellant, does not require coordination of breathing in and pressing down, does need to breathe strong enough
Nebulizer	• Often drug solution or suspension in aqueous based formulations • Widely used in hospital and home setting
Inhalation Spray	• Aqueous based formulation with dissolved drug • No propellant, slower release over a longer duration compared with an MDI, may need some strength and coordination to assemble the inhaler

Bioequivalence (BE)

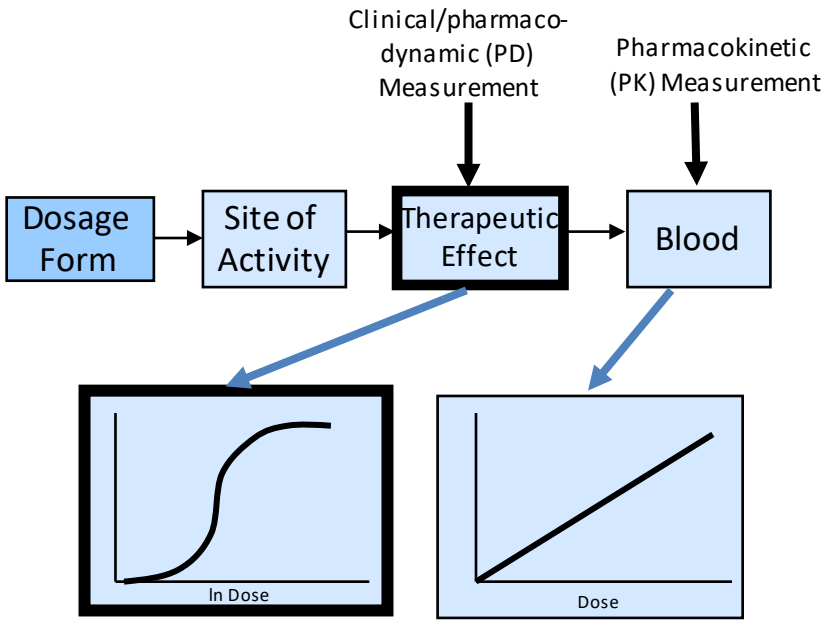
"The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study"

Code of Federal Regulations – Title 21 [21 CFR], Part 314.3

Challenges in Establishing Bioequivalence of Locally Acting Inhalation Products

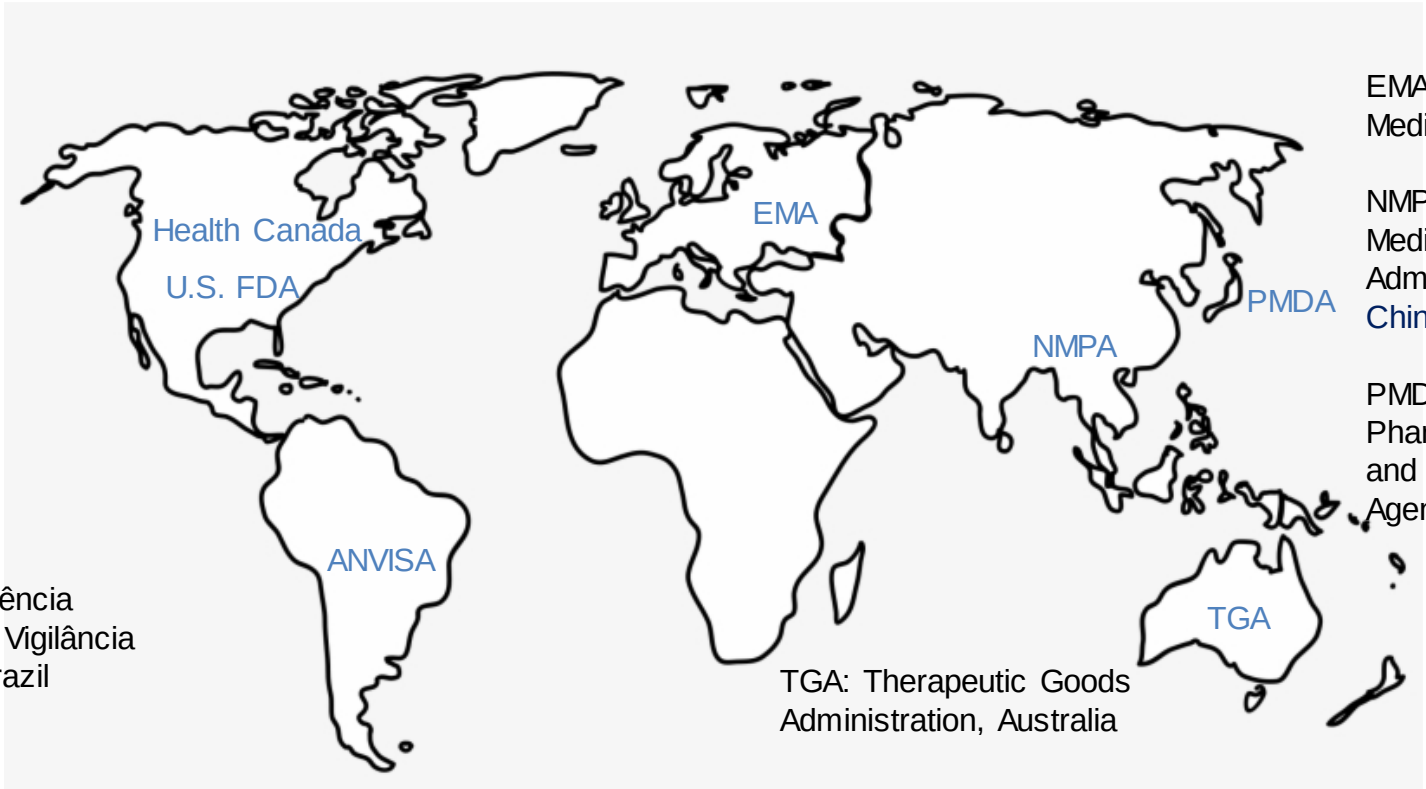
- Most OIDPs are locally acting drugs
- OIDPs are complex drug-device combination products whose performance depends on:

  -- formulation and delivery device interactions
  -- formulation and patient interactions
  -- patient and device interactions (e.g., user interface, patient's inhalation effort)



- Not intended to be absorbed into the bloodstream
- Delivered directly to sites of action (lung)

Example Regulatory Agencies



EMA: European Medicines Agency

NMPA: National Medical Products Administration, China

PMDA: Pharmaceuticals and Medical Devices Agency, Japan

ANVISA: Agência Nacional de Vigilância Sanitária, Brazil

TGA: Therapeutic Goods Administration, Australia

Clarification on Terminologies

- Pharmaceutical equivalence (PE)
- Bioequivalence (BE)
- Therapeutic equivalence (TE)

US FDA

TE = PE + BE
BE is applicable for both systemically and locally acting drugs.

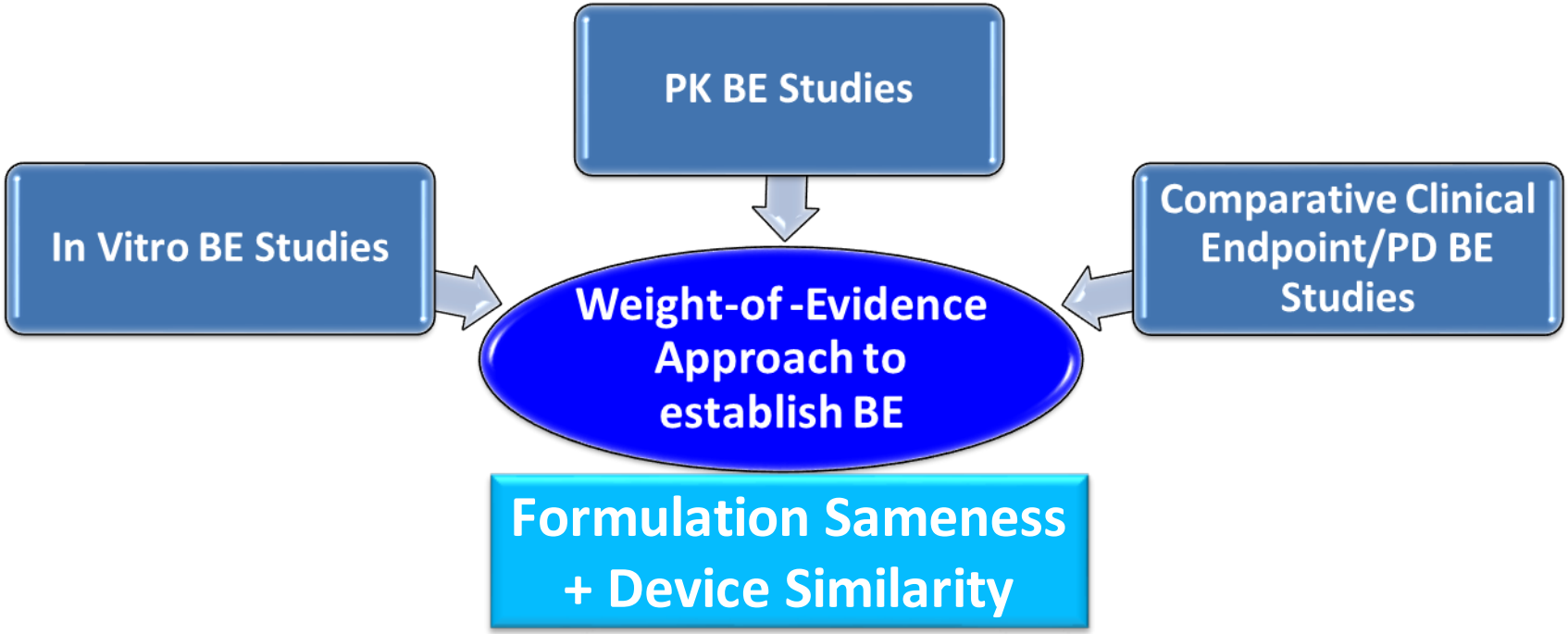
EMA

BE emphasizes primarily on the systemic exposure, i.e., PK study. For locally acting orally inhaled drug products, where PD, PK, and/or in vitro options are possible assessments, EMA guideline uses a term TE.

For the purpose of this presentation, we use the term BE for both systemically and locally acting drugs.

U.S. FDA Approach to Establish BE for OIDPs

For locally-acting MDIs and DPIs



PK: pharmacokinetic; PD: pharmacodynamic

Formulation Sameness

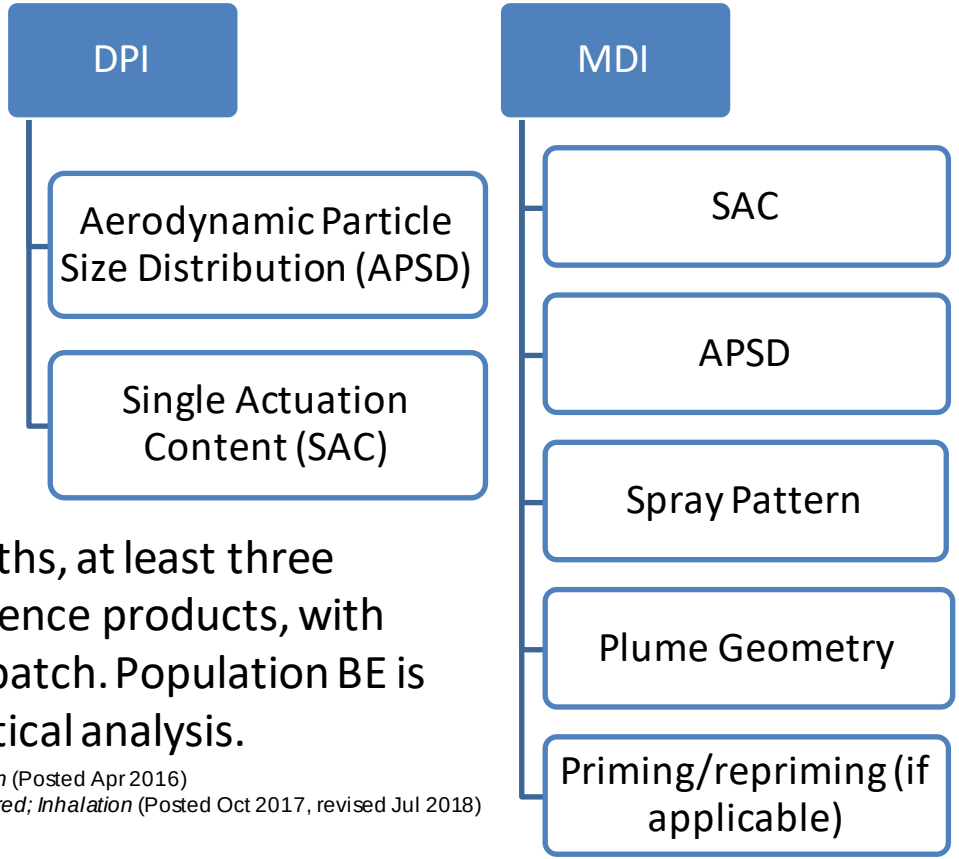
- Qualitative (Q1) sameness
  - Same inactive ingredient(s)
- Quantitative (Q2) sameness
  - Cannot exceed the levels used in other FDA-approved products administered by the same route of administration (i.e., inhalation)
  - Effect of Q2 difference on bioequivalence assessed by in vitro and in vivo BE studies
  - Submit pharmaceutical development data to support the selected test formulation

Device Similarity

- Same energy source for respiratory drug delivery
  - Passive vs. active
- Same metering principle
  - Pre-metered single unit-dose (e.g., HandiHaler, capsule),
  - Pre-metered multi-unit-dose (e.g., Diskus, blister strip), or
  - Device-metered multi-dose (e.g., Flexihaler, reservoir)
- Same number of doses
- Similar size and shape
- Comparable basic external operating procedure(s)
- Dose counter (if the reference listed drug (RLD) device has one)

FDA may accept certain design differences if they are adequately analyzed and scientifically justified. Refer to draft FDA Guidance: *Comparative Analysis and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017)

Equivalent In Vitro Performance



Conducted on **All** strengths, at least three batches of test and reference products, with no fewer than 10 units/batch. Population BE is recommended for statistical analysis.

PSGs for *Fluticasone Furorate. Powder; Inhalation* (Posted Apr 2016)
PSGs for *Fluticasone Propionate. Aerosoal, metered; Inhalation* (Posted Oct 2017, revised Jul 2018)

Equivalent Systemic Exposure

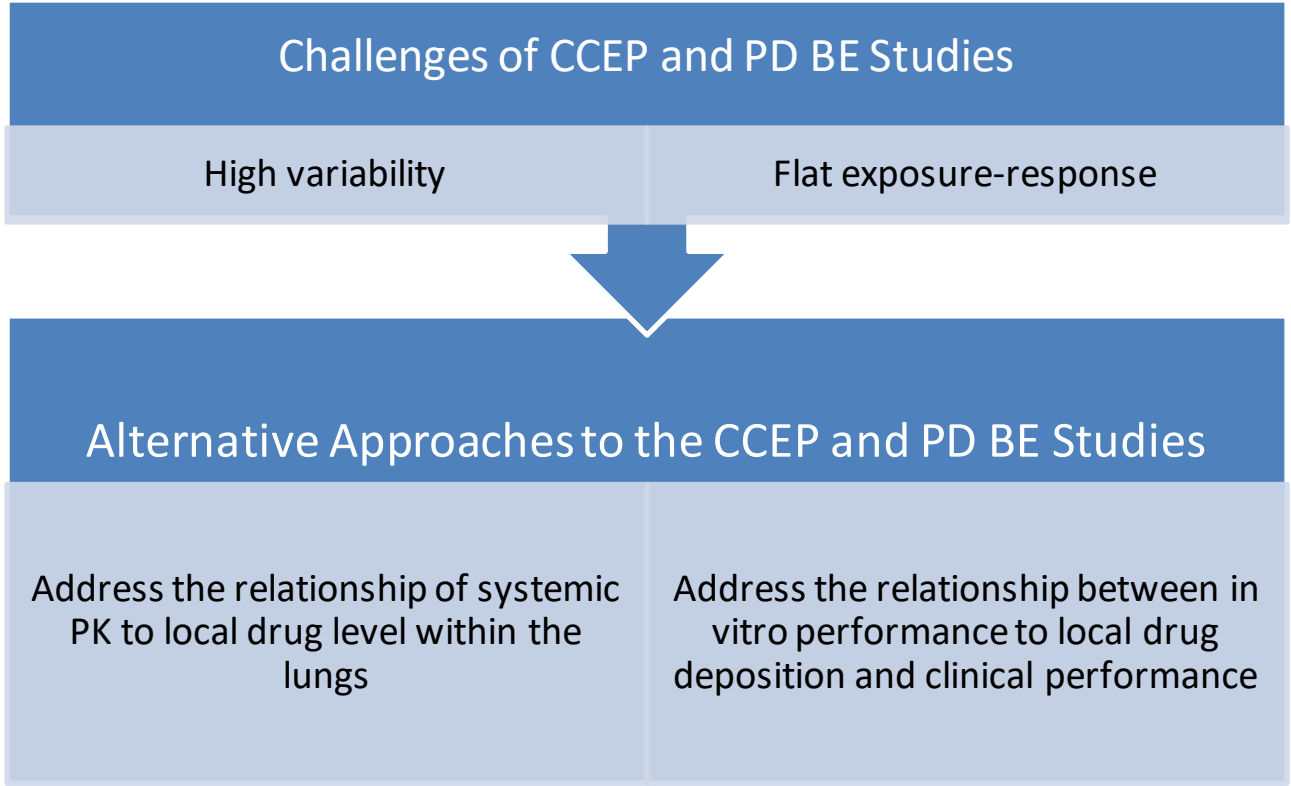
Parameter	DPIs	MDIs
Study Type	A single dose, two-way crossover fasting in healthy subjects	
Strength	All strengths should be tested (Relation between PK dose proportionality across multiple strengths, in vitro performance parameters, and product characteristics are not well understood, **therefore all strengths need to be studied**)	
Dose	A minimum number of inhalations sufficient to describe pharmacokinetic profile using a sensitive analytical method	
Statistical Analysis	90% confidence interval (CI) of AUCs and C_{max} should meet the BE limits of 80 - 125%	

Equivalent Local Delivery at the Site of Action

Parameter	DPIs	MDIs
Study Type	Comparative clinical endpoint (CCEP) or pharmacodynamic (PD) BE Study in patients	
Strength	Lowest strength	

- A dose-response PD BE study is generally preferred over a BE study with a comparative clinical endpoint (CCEP)
- PD study is used if there is adequate dose-response (e.g., bronchodilators)

Alternative Thinking Regarding CCEP or PD BE Studies for OIDPs



Alternative Approach for Solution-based MDIs

For solution-based MDI, if the T formulation is Q1 and Q2 the same as the R formulation, and if the T device is sufficiently similar to the R device with respect to critical design attributes and user interface, additional supportive data may provide a foundation to help ensure the equivalence of T and R products at the local sites of action in the lungs, and thus, could be considered as a potential alternative to the currently recommended comparative clinical endpoint BE study, in the context of the weight-of-evidence approach.

- Additional supportive in vitro studies may include, but are not limited to,

(i) more predictive APSD testing using representative mouth-throat models and breathing profiles
(ii) characterization of emitted aerosol sprays with respect to velocity profiles and evaporation rates
(iii) dissolution
(iv) morphology imaging comparisons, including characterization of the full range of residual drug particle sizes
(v) quantitative methods and modeling (e.g., physiologically-based PK and computational fluid dynamic studies)
(vi) alternative in vivo PK BE studies

PSGs for *Beclomethasone Dipropionate Inhalation Aerosol, Metered* [RLD: QVAR Redihaler® (Posted May 2019); RLD: QVAR® (Posted Jan 2016; Revised Mar 2020)]

EMA Approach to Establish TE for OIDPs

Step 1: In vitro equivalence tests

Step 2: Pharmacokinetics to demonstrate equivalent pulmonary deposition and systemic exposure

- With and without charcoal (if necessary) to evaluate pulmonary deposition and total systemic exposure
- Preferred in healthy volunteers

Step 3: Pharmacodynamics/Clinical Studies to demonstrate the local bioequivalence

- Confirmation of therapeutic equivalence using pharmacodynamics (PD) /clinical studies using well-validated study designs
- Before conducting a less sensitive PD study it may be advisable to reformulate the test product if large differences between test and reference product are observed in the PK studies

https://www.ema.europa.eu/en/requirements-clinical-documentation-orally-inhaled-products-oip-including-requirements-demonstration

PMDA Approach to Establish BE for DPIs

Recommends a synthetically comprehensive approach, judging bioequivalence on the basis of all data from in vitro, pharmacokinetic, and clinical studies.

	In vitro studies	PK studies	PD or clinical studies
Study design	1. Delivered dose 2. Fine particle mass 3. At least 4 groups of stages, etc. 4. APSD	Systemic exposure Single-dose, two-way crossover Fasting Strength: Not specified Subject: Normal healthy adult	Single-dose or multiple-dose Crossover or parallel-group design Asthma or COPD patients Strength: Appropriate strength for assessing the therapeutic equivalence
Criteria	Not specified	AUC and C_{max} Equivalent with or less than exposure or below the permissible level	Clinically acceptable range on the basis of the differences between the innovator product and an appropriate comparator in patients

Ministry of Health, Labour and Welfare. Basic principles on the bioequivalence evaluation for the generic DPI drug products. 11 March 2016.

NMPA Approach to Establish BE for Orally Inhaled Drug Products

- Inhaled solution:
  - Demonstrate qualitative and quantitative sameness
  - Demonstrate equivalent critical quality attributes
  - In vivo study can be waived
- Inhaled suspension, MDI, and DPI
  - Qualitatively the same and quantitatively similar
  - Demonstrate equivalent critical quality attributes
  - Pharmacokinetics bioequivalence study
  - Pharmacodynamic study (e.g., short-acting β2 adrenoceptor agonist (SABA), long-acting β2 adrenoceptor agonist (LABA)) or clinical endpoint study (e.g., Inhaled corticosteroid)

Health Canada Approach to Establish BE for OIDPs

Health Canada recognizes that it may be possible to establish the safety and efficacy of some products based on in vivo comparative pharmacokinetic studies, combined with in vitro studies, without studies using clinical endpoints.

- Subsequent-entry inhalation products should be shown to be equivalent to the reference product
  - Formulation
  - Physicochemical properties of the drug substance and drug product
  - Delivery device

  All differences between the subsequent-entry device and the reference device should be reported. Significant differences should be supported by data (e.g., in-use studies in both device-naïve and-trained subjects) to demonstrate that they do not pose an unacceptable risk of error by the end user.
  - In vitro performance
  - Comparative pharmacokinetics

Comparative Pharmacokinetic Studies for Orally Inhaled Products: Guidance Document - Canada.ca. 2020

Health Canada Approach to Establish BE for OIDPs

For those products where in vivo comparative pharmacokinetic studies are not appropriate, comparative in vivo pharmacodynamic studies may be necessary to establish the safety and efficacy of the proposed product.

- Forced expiratory volume in the first second (FEV1) as the primary endpoint
- Sputum Eosinophils as the Primary Endpoint

Guidance Document: Data Requirements for Safety and Effectiveness of Subsequent Entry Inhaled Corticosteroid Products Used for the Treatment of Asthma. 2018

https://www.canada.ca/en/health-canada/services/drugs-health-products/drugproducts/applications-submissions/guidance-documents/inhaled-corticosteroidprofile/inhaled-corticosteroid-guidance.html

ANVISA Approach to Establish BE for Inhalation Medicine

Device similarity + Qualitatively the same

- Solutions: in vitro comparison
- Suspension and solids: in vitro + in vivo comparison

Silva et al. Overview of Brazilian Requirements for Therapeutic Equivalence of Orally Inhaled and Nasal Drug Products. The AAPS Journal. 2019 20:235

ANVISA Approach to Establish BE for Inhalation Medicine

For suspension and solids

Step 1: In vitro equivalence tests + In vivo pharmacokinetic equivalence

- In vitro
- PK studies with and without charcoal (if necessary) to evaluate lung deposition and total systemic exposure

Step 2: In vivo pharmacodynamic equivalence

- Protocol submitted at ANVISA prior to conducting the study
- Pharmacodynamic study should be sensible
- Dose/response relation demonstrated.

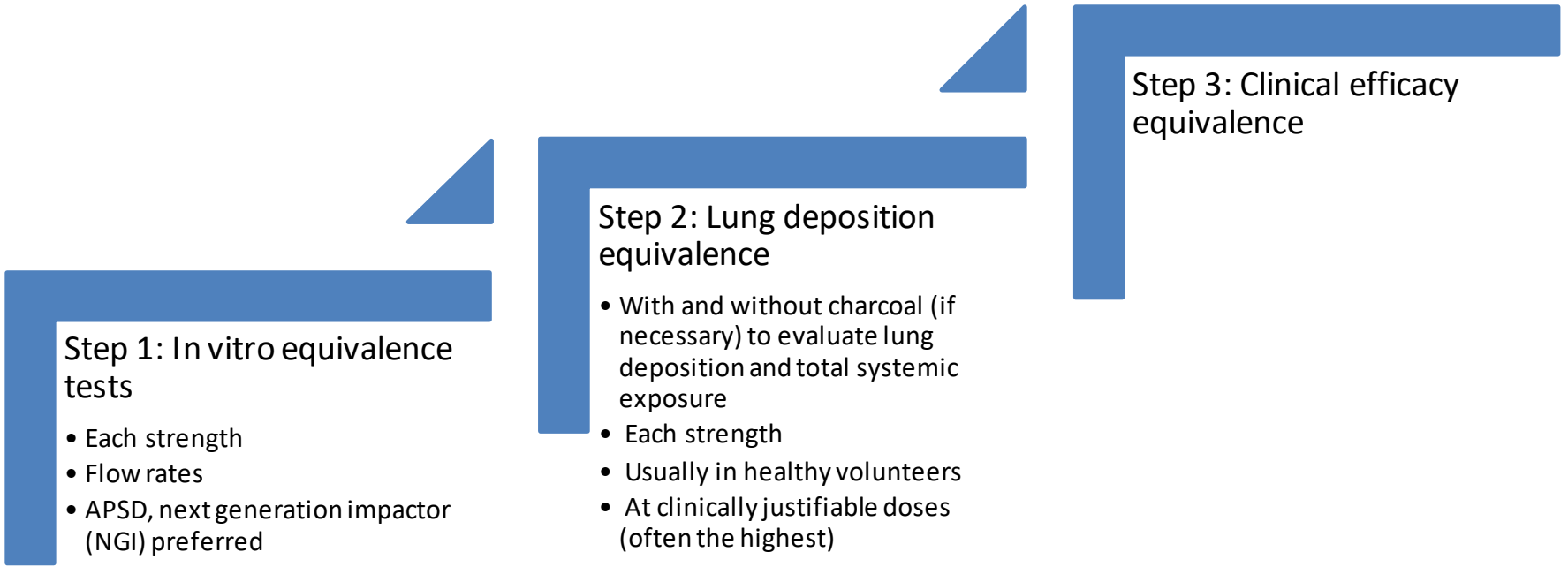
Silva et al. Overview of Brazilian Requirements for Therapeutic Equivalence of Orally Inhaled and Nasal Drug Products. The AAPS Journal. 2019 20:235

TGA Approach to Establish BE of Nebulised Medicines

- Solution:
  - Demonstrate qualitative and quantitative sameness
  - Demonstrate physicochemical property the same, e.g., pH, buffer capacity, density, surface tension, viscosity, osmolality
- Suspension:
  - Demonstrate qualitative and quantitative sameness
  - Demonstrate the same particle morphology and size distribution of the drug substance, and the same droplet size distribution

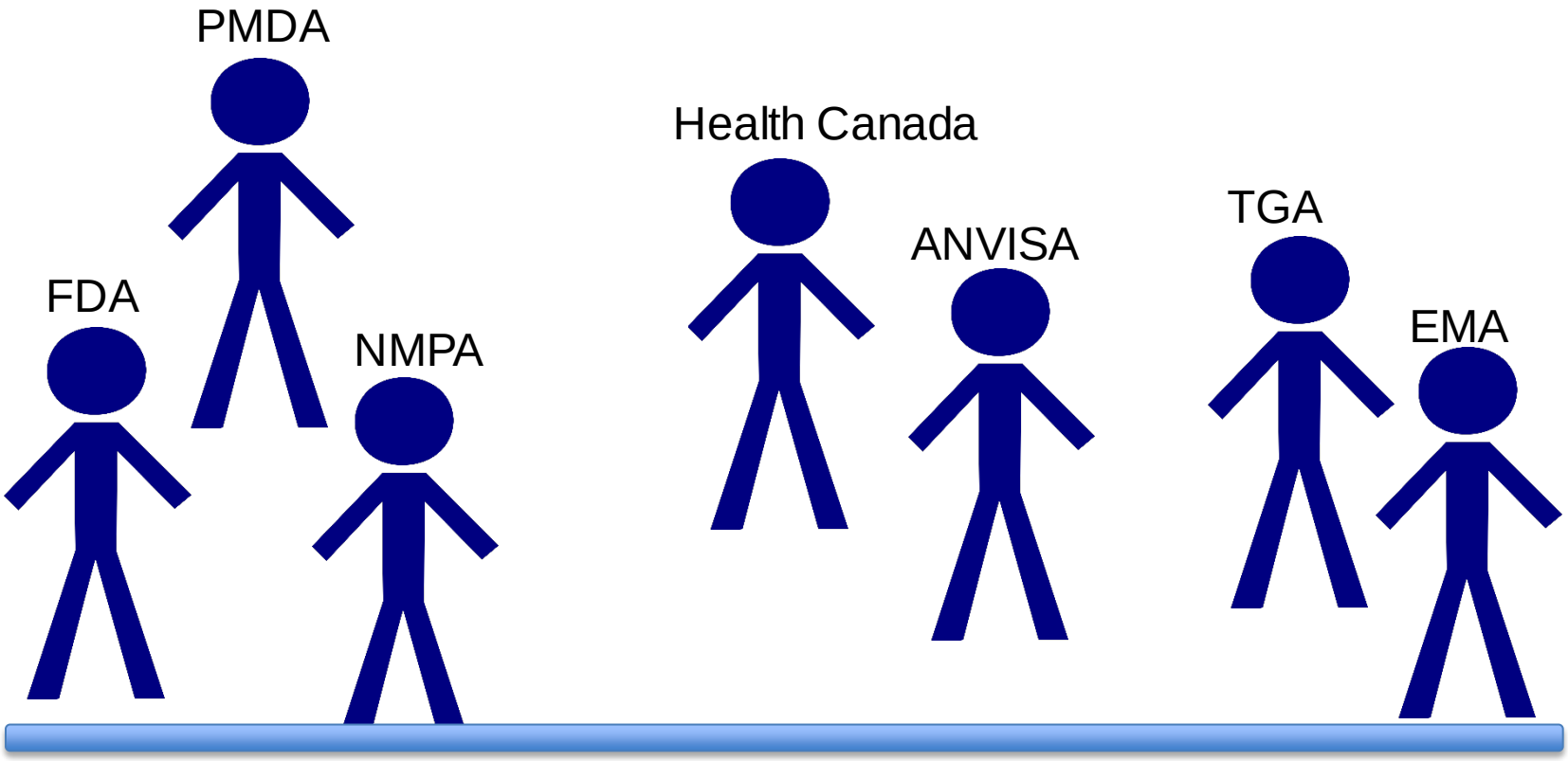
Inhalation and nasal spray registered medicines (tga.gov.au)

TGA Approach to Establish BE of Metered-dose Inhalation Medicine

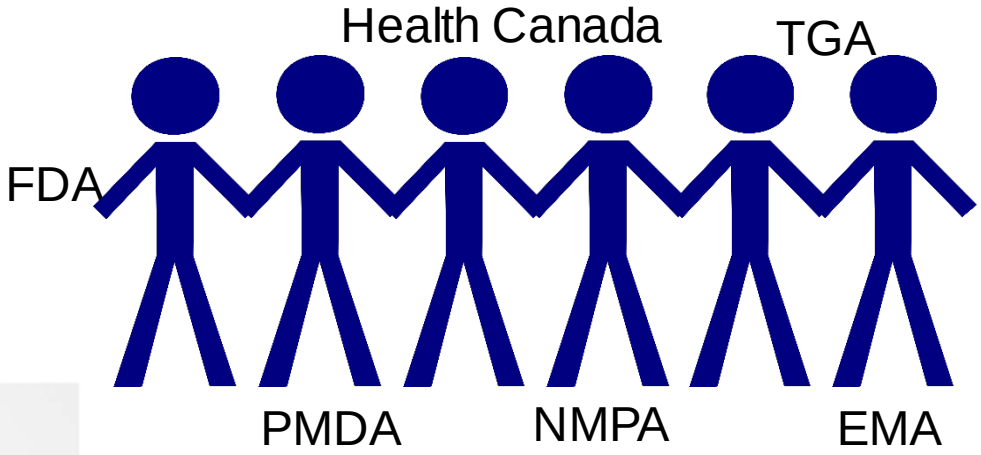


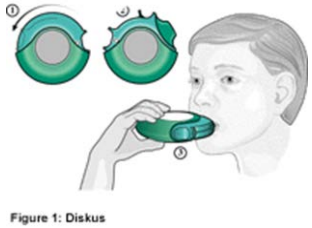
Inhalation and nasal spray registered medicines (tga.gov.au)

Summary of BE Requirements for OIDPS



Need for Global Harmonization of BE Requirements for OIDPs





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U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Questions?


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