HOW CAN SCIENTIFIC ADVANCEMENTS HELP ALIGN GLOBAL DEVELOPMENT OF COMPLEX GENERIC PRODUCTS

SESSION 5: THE GLOBAL NATURE OF THE GENERIC DRUG INDUSTRY

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Complex Products

Complex active pharmaceutical ingredient (API)	• Any drug product containing a complex API, regardless of administration routes and dosage forms e.g., Conjugated Estrogen Tablet, Glatiramer Acetate Injection
Complex routes of delivery	• Any non-solution drug product with a non-systemic site of action (e.g., topical, ophthalmic, local gastrointestinal (GI) action) e.g., Cyclosporine Emulsion, Acyclovir Cream
Complex dosage forms/ formulations	• Any non-oral complex formulation/dosage form product where there are often two or more discrete states of matter within the formulation e.g., Doxorubicin HCl Liposomes, Leuprolide Acetate for Depot Suspension
Complex drug-device combinations	• Where the drug constituent part is pre-loaded in a product-specific device constituent part or is specifically cross-labeled for use with a specific device, in which the device design affects drug delivery to the site of action and/or absorption e.g., Epinephrine Injection (autoinjector)
Other products	• Any solid oral opioid drug products with FDA approved labeling for that show properties (and thus gaining their labeling) to meaningfully deter drug abuse e.g., Hydrocodone Bitartrate ER Tablet

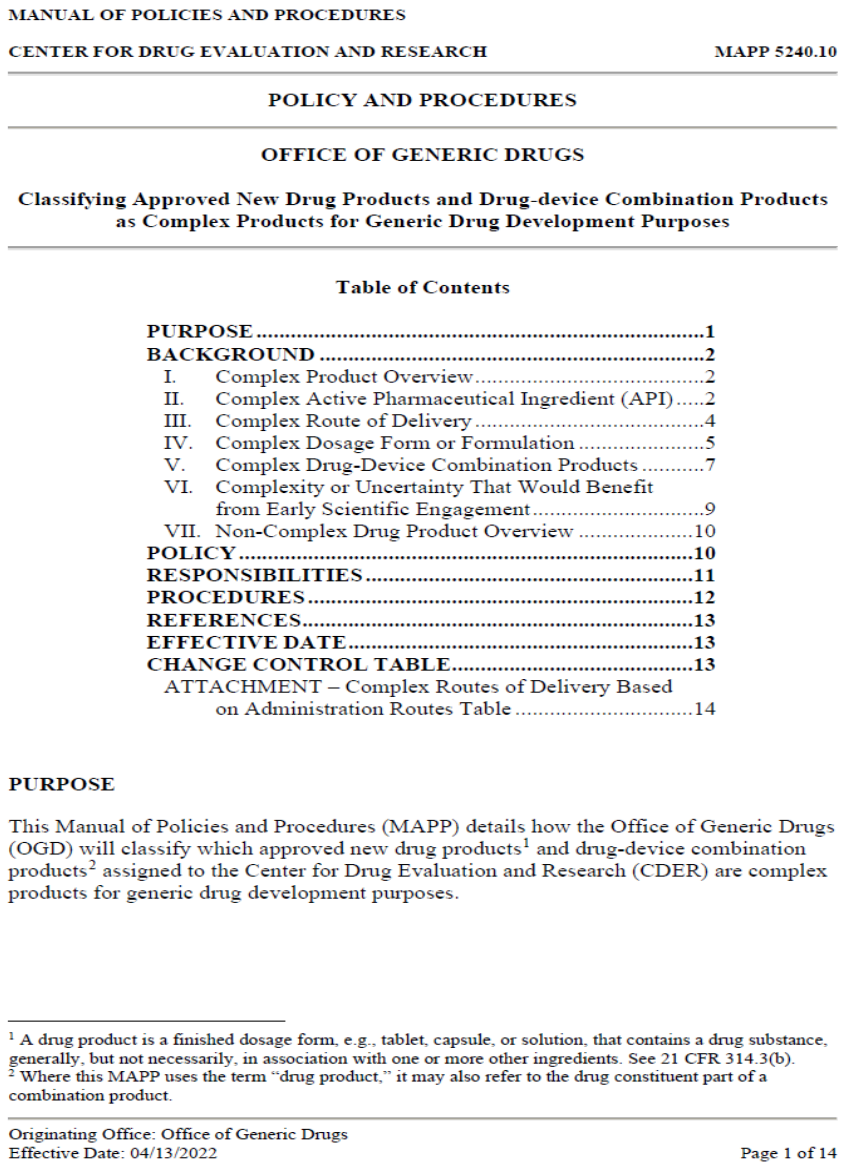
Lionberger R. Innovation for Generic Drugs: Science and Research Under the Generic Drug User Fee Amendments of 2012, *Clinical pharmacology & therapeutics*, 2019, Vol.105(4), p.878-885

Scientific and Regulatory Complexity of Global Development of Complex Generic Products

- Diverse complexity in drug substance, dosage form, devices, and others
- Different classification about complex drug products among different regulatory agencies
- Evolving thinking about drug product complexity
- Different regulatory standards are used for the approval of some important complex generics or follow-on products among different jurisdictions

https://admin.ich.org/sites/default/files/2019-04/ICH_ReflectionPaper_GenericDrugs_Final_2019_0130.pdf

U.S. FDA's Efforts to Clarify Understanding and Classification about Complex Products



MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5240.10

POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS

Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes

Table of Contents

PURPOSE

This Manual of Policies and Procedures (MAPP) details how the Office of Generic Drugs (OGD) will classify which approved new drug products[1] and drug-device combination products[2] assigned to the Center for Drug Evaluation and Research (CDER) are complex products for generic drug development purposes.

[1] A drug product is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. See 21 CFR 314.3(b).
[2] Where this MAPP uses the term "drug product," it may also refer to the drug constituent part of a combination product.

Originating Office: Office of Generic Drugs
Effective Date: 04/13/2022 Page 1 of 14

Manual of Policies and Procedures (MaPP) Published on 04/13/2022

Provide definitions and examples of complex drugs and drug-device combination products, as well as the responsibilities and procedures for complex drug classification and database maintenance.

https://www.fda.gov/media/157675/download

U.S. FDA Regulatory Science Efforts to Support Generic Drug Development and Approval

Generic Drug User Fee Amendments (GDUFA) science and research support

1. Development of generic drug products

2. Generation of evidence needed to support efficient review and timely approval of Abbreviated New Drug Applications (ANDAs)

3. Evaluation of generic drug equivalence

GDUFA Science and Research Outcomes for Fiscal Year 2020 | FDA

GDUFA research supporting the development of generic drug products

Outcome type	FY2018	FY2019	FY2020
Number of pre-ANDA meetings impacted by research	62	93	92
Number of Controlled Correspondences impacted by research	113	178	291
Number of PSGs impacted by research	86	82	86
Number of publications, presentations, and posters that are relevant to this category	244	162	156
Number of workshops that communicate scientific advances and regulatory advice to the generic drug industry	8	5	5
Number of other items that fall in this category (e.g., general guidances for industry)	2	2	3

GDUFA research supporting the generation of evidence needed to support efficient review and timely approval of ANDAs

Outcome type	FY2018	FY2019	FY2020
Number of ANDA submissions impacted by research	138	167	166
Number of ANDA reviews impacted by research	44	36	62
Number of ANDA approvals impacted by research	63	102	152

Bioequivalence (BE) Requirements for Orally Inhaled and Nasal Drug Products (OINDPS)

Limited Generics Available

EMA: European Medicines Agency

NMPA: National Medical Products Administration, China

PMDA: Pharmaceuticals and Medical Devices Agency, Japan

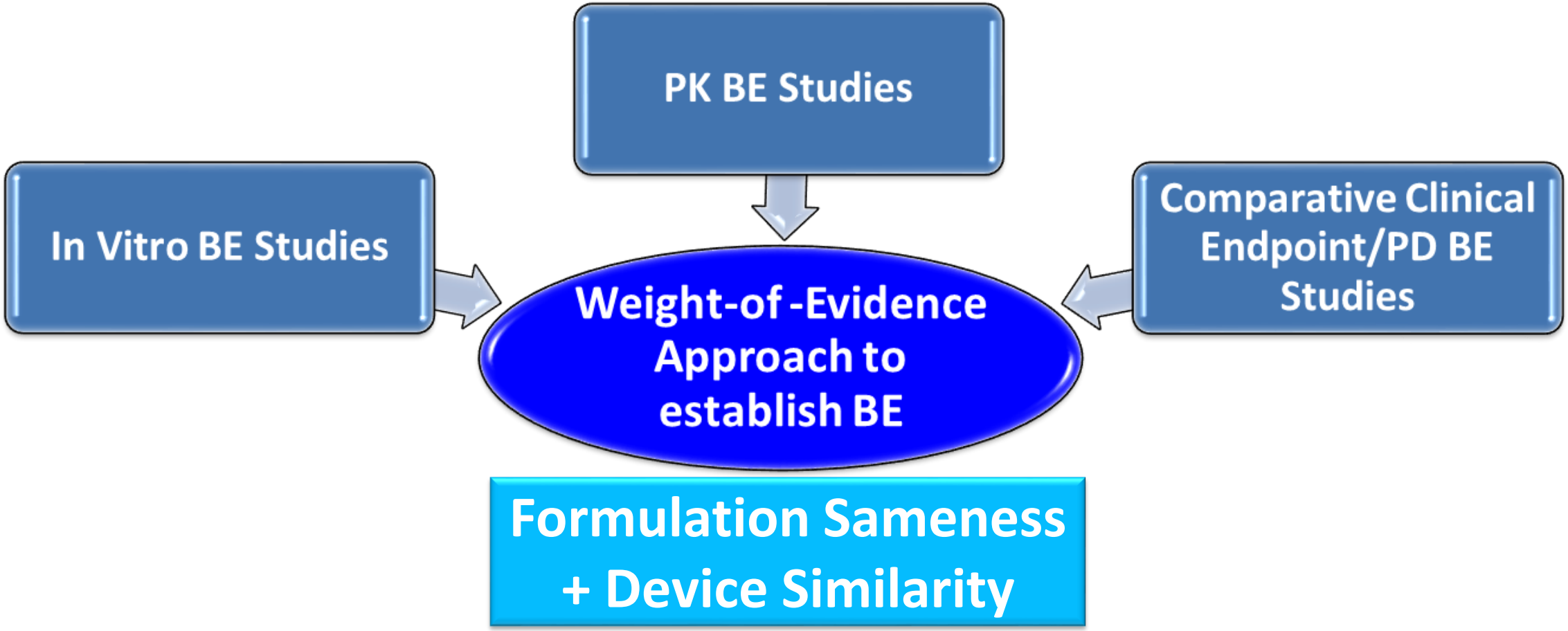
TGA: Therapeutic Goods Administration, Australia

ANVISA: Agência Nacional de Vigilância Sanitária, Brazil

Wenlei Jiang, Global Bioequivalenc Requirements of Orally Inhaled Drug Products. Presented at AAPS Bay Lung Therapeutics Oral Inhalation Symposium 2021

U.S. FDA Approach to Establish BE for OINDPs

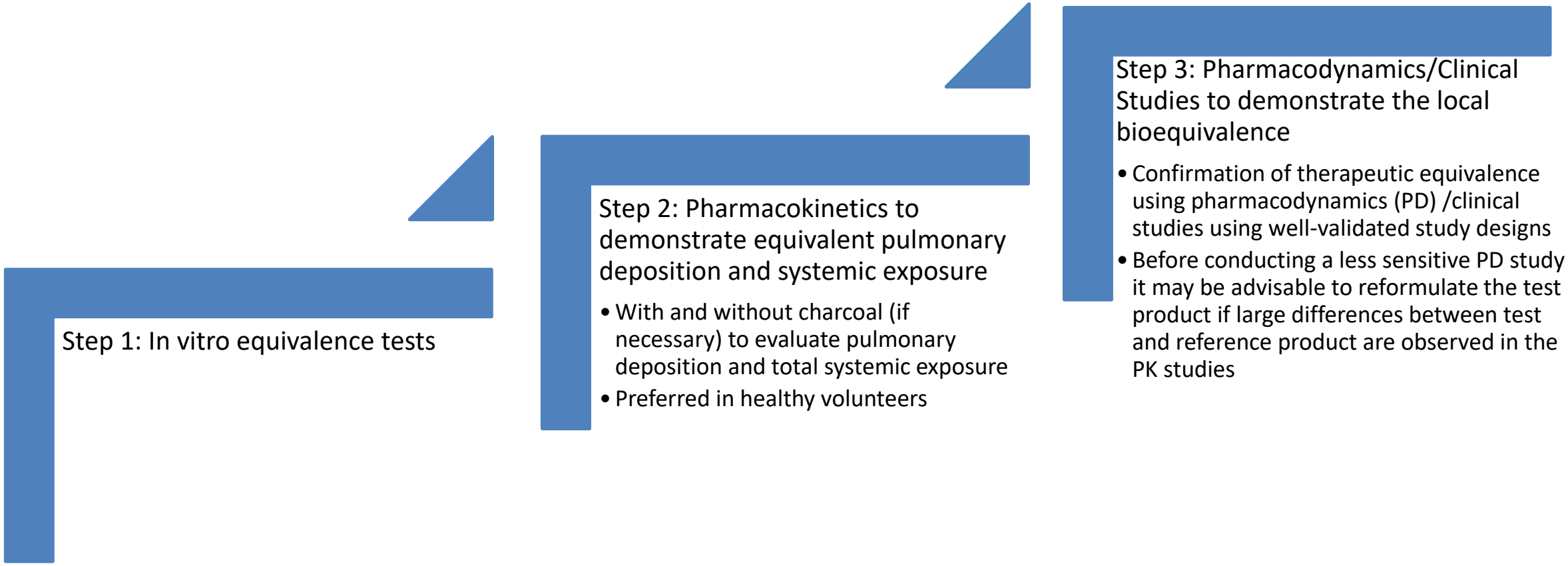
For locally-acting OINDPs



Wenlei Jiang, Global Bioequivalenc Requirements of Orally Inhaled Drug Products. Presented at AAPS Bay Lung Therapeutics Oral Inhalation Symposium 2021

PK: pharmacokinetic; PD: pharmacodynamic

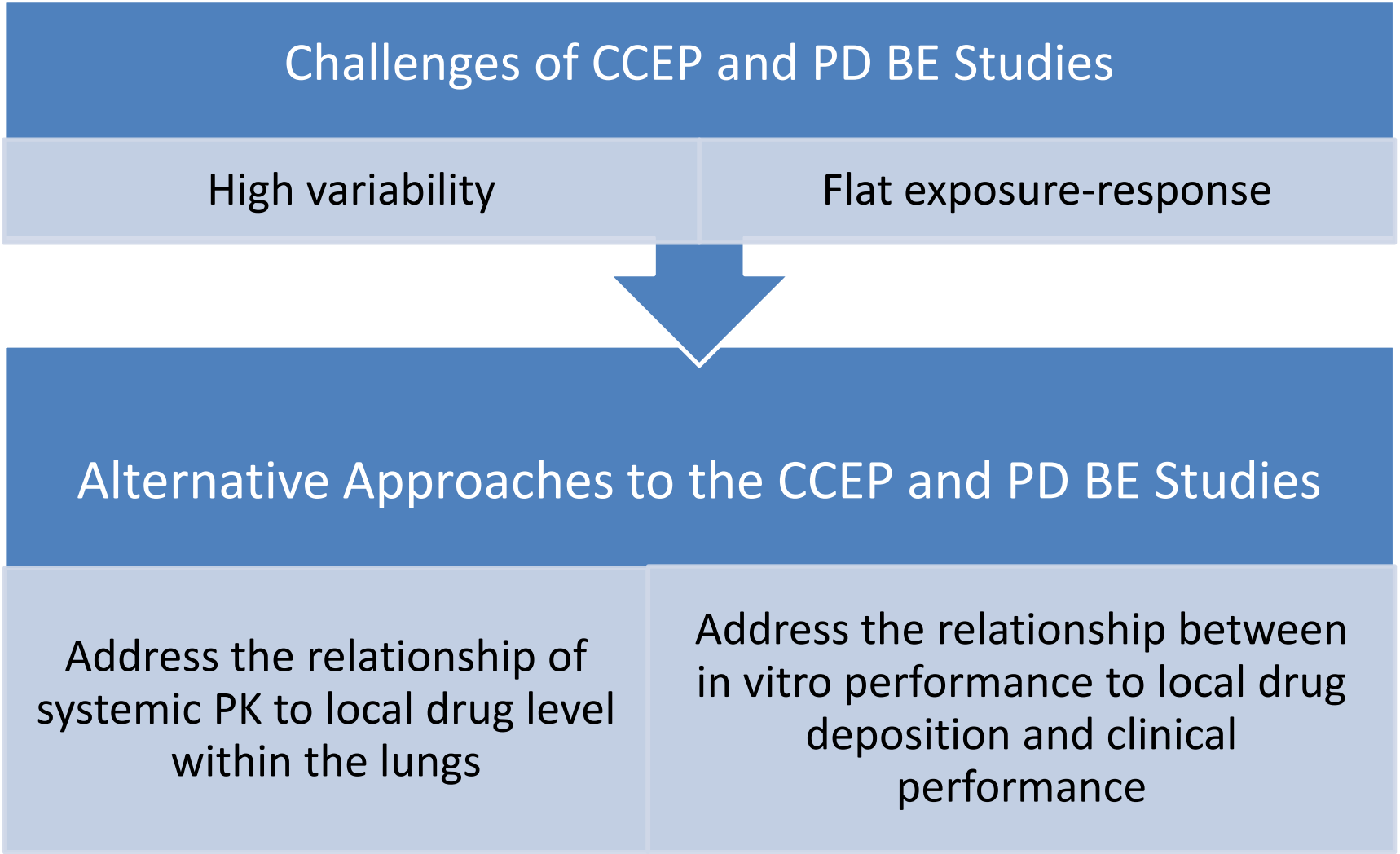
EMA Approach to Establish Therapeutic Equivalence (TE) for OIDPs



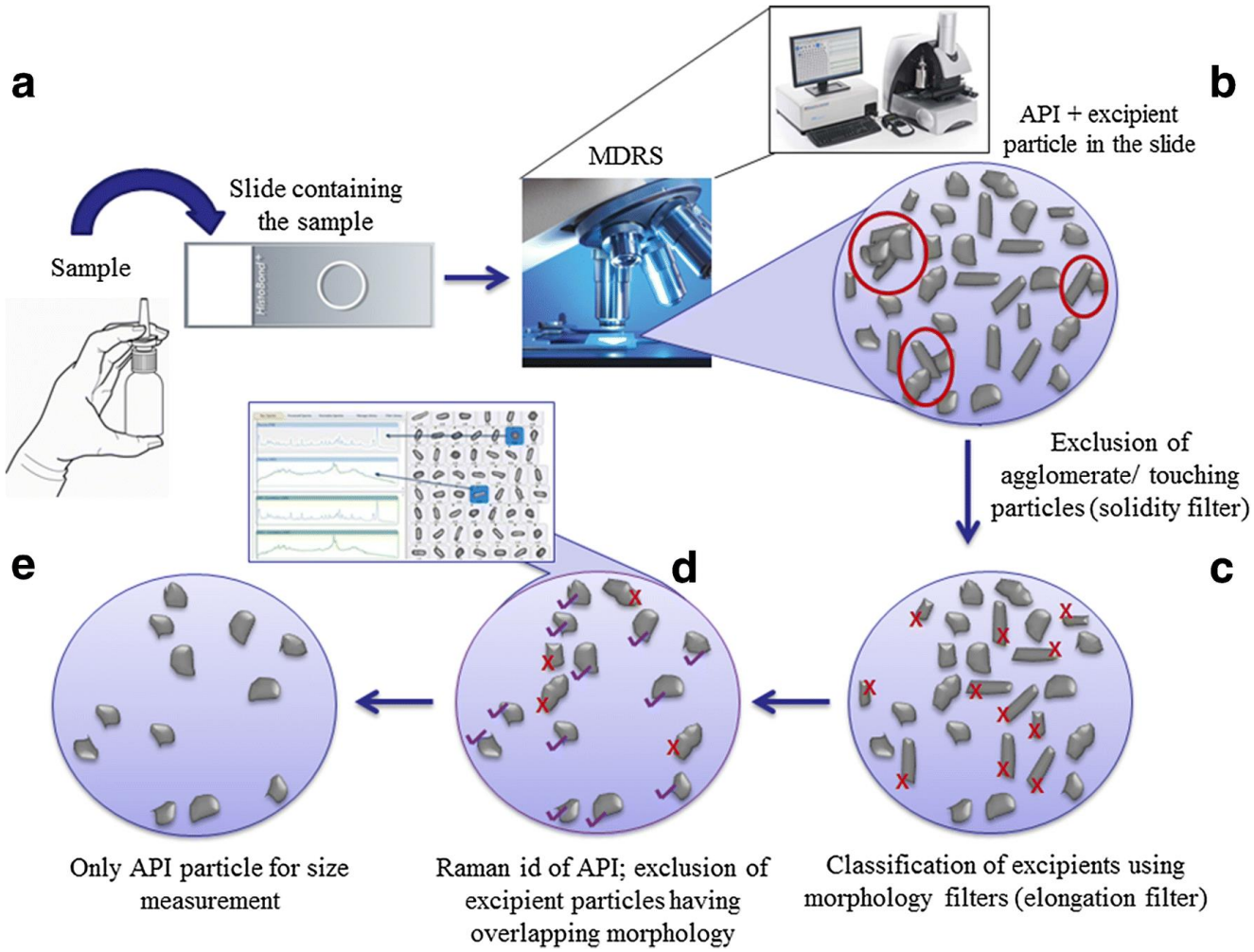
https://www.ema.europa.eu/en/requirements-clinical-documentation-orally-inhaled-products-oip-including-requirements-demonstration

Wenlei Jiang, Global Bioequivalenc Requirements of Orally Inhaled Drug Products. Presented at AAPS Bay Lung Therapeutics Oral Inhalation Symposium 2021

Alternative Thinking Regarding Comparative Clinical Endpoint (CCEP) or PD BE Studies for OIDPs



Advancements in Analytical Technologies Supported the U.S. FDA Approval of Complex Generic Nasal Suspension



Basic operating steps of MDRS. **a** Sample preparation; **b** morphological measurement of particles in the sample, exclusion of aggregates, and touching particles; **c** selection of particle of interest using morphology filters; **d** identification of particles using Raman spectra; **e** size measurement of the particle of interest

- Nasonex® (mometasone furoate) Nasal Spray contains a suspension of an anti-inflammatory corticosteroid and is indicated for the treatment of seasonal and perennial allergic rhinitis symptoms in patients 2 years of age and older.

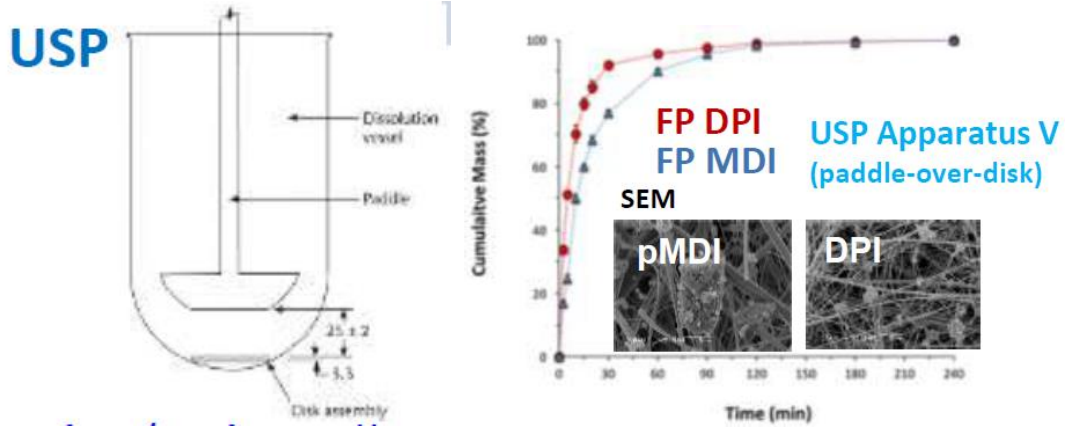
- U.S. FDA considered supportive data generated by a novel in vitro method, **Morphologically-Directed Raman Spectroscopy (MDRS),** to characterize the particle size distribution (PSD) of active pharmaceutical ingredient (API) to support the approval of first generic Mometasone Furoate Nasal Suspension Spray

  - MDRS measures particle morphological characteristics (size and shape) using its microscopic component and performs chemical identification by analyzing Raman spectra.

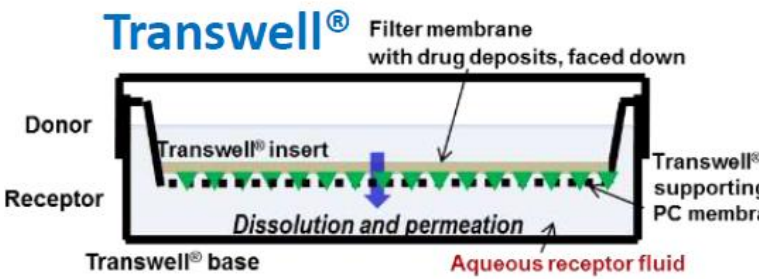
  - MDRS data eliminated the need for a comparative clinical endpoint bioequivalence study.

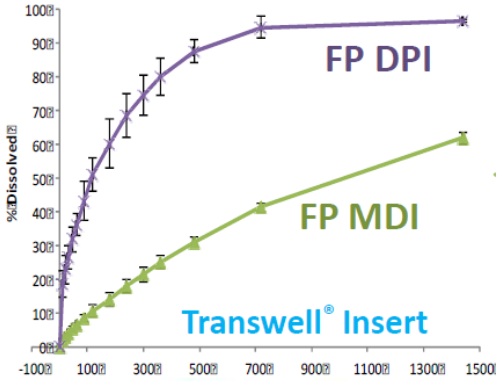
Scientific Considerations for the Review and Approval of First Generic Mometasone Furoate Nasal Suspension Spray in the United States from the Bioequivalence Perspective | SpringerLink

Advancements in In Vitro Studies for Alternative BE Approaches to CCEP



FP: Fluticasone Propionate

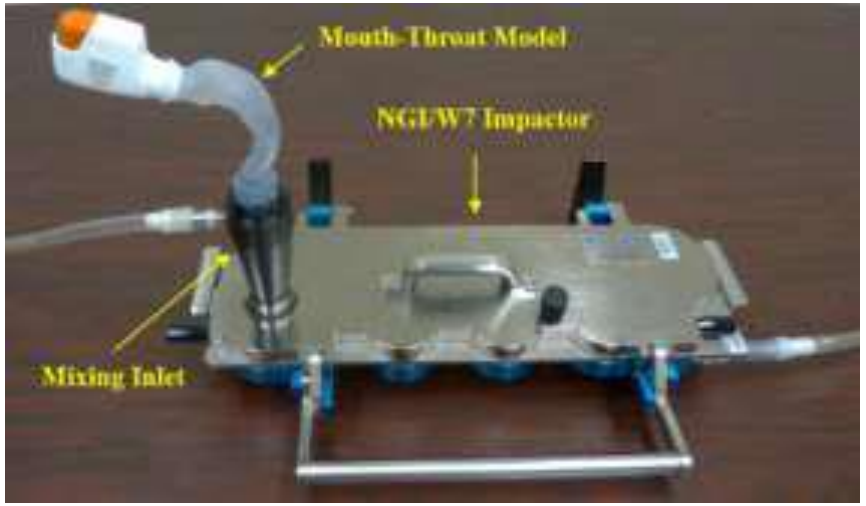




- In vitro dissolution can capture differences in formulations

[Optimization of the Transwell ® System for Assessing the Dissolution Behavior of Orally Inhaled Drug Products through In Vitro and In Silico Approaches - PubMed (nih.gov)]
[Can Pharmacokinetic Studies Assess the Pulmonary Fate of Dry Powder Inhaler Formulations of Fluticasone Propionate? - PubMed (nih.gov)]

- Realistic in vitro APSD methods (e.g., *MT models* and a *realistic range of inhalation profiles)* can provide a *better prediction of deposition of inhaled particles in the lungs and capture patient variability*



[In Vitro Tests for Aerosol Deposition. VI: Realistic Testing with Different Mouth-Throat Models and In Vitro-In Vivo Correlations for a Dry Powder Inhaler, Metered Dose Inhaler, and Soft Mist Inhaler - PubMed (nih.gov)]

Translating GDUFA Research to Guidance Development and U.S. FDA Approval of Generic Topical Dermatological Products

Research Focus

- Support the expansion of characterization-based BE approaches to a majority of topical dermatological products
- Understand the mechanisms that allow T and R topical products to be clinically bioequivalent when they are not the same, but are similar in components, composition, and/or Q3 attributes
- Explore the development of efficient PK-based methods to directly monitor the rate and extent of a drug's bioavailability at or near its site(s) of action in the skin.
- Enhance mechanistic physiologically based pharmacokinetic (PBPK) models for dermatological drug products to predict the absorption of active ingredients through the skin

FY 2021 GDUFA Science and Research Report
https://www.fda.gov/media/156481

Example Draft Guidance

- Estradiol Transdermal Gel, Metered (August 2021)
- Ethinyl Estradiol; Levonorgestrel Transdermal System (August 2021)
- Trifarotene Topical Cream (May 2021)

Generic Topical Dermatological Product Approval

Over 80 generics approved between Jan 1st 2020 and present

"The Government Accountability Office report identified competition (e.g., multisource generic drugs) as a key factor affecting drug pricing, noting that there can be a 20% price decline with each new market entrant."

A new paradigm for topical generic drug products: Impact on therapeutic access - ScienceDirect

Translating GDUFA Research to Guidance Development and U.S. FDA Approval of Generic Long-acting Injectable (LAI) Products

Research Focus

- Develop new tools for characterizing complex polymeric excipients
- Better understand the impact of variation in raw materials on formulation physicochemical characteristics and drug release
- Explore new in vitro drug release testing (IVRT) methods that have better clinical relevance
- Investigate advanced imaging tools to explore correlations between formulation characteristics and in vitro/in vivo drug release
- Develop new modeling tools to support the development of alternative bioequivalence (BE) approaches

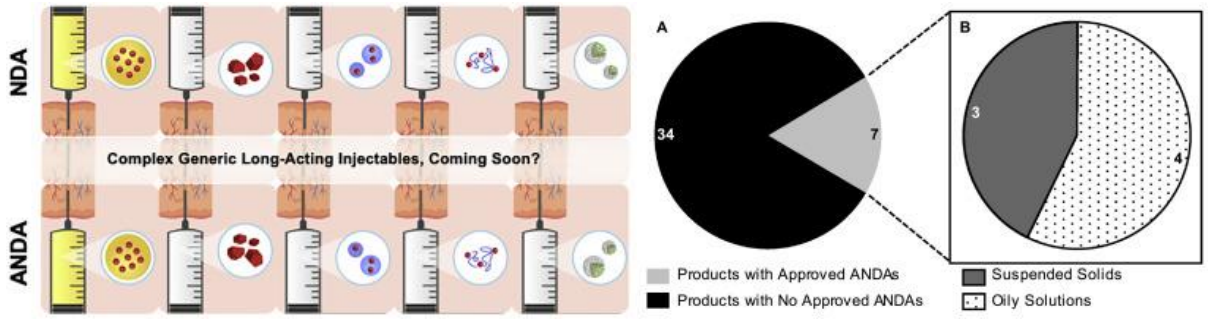
FY 2021 GDUFA Science and Research Report
https://www.fda.gov/media/156481

Example Draft Guidance

- Leuprolide Acetate Subcutaneous Powder (February 2022)
- Paliperidone Palmitate Extended Release Suspension for Intramuscular Injection (August 2021)
- Degarelix Acetate Subcutaneous Powder (March 2021)

Generic LAI Product Approval

ANDA 211149, Paliperidone Palmitate Suspension, Teva Pharms USA. July 2021



Challenges and opportunities in the development of complex generic long-acting injectable drug products - PubMed (nih.gov)

Global Dialogues Help Communicate Scientific Advancements and Bridge Gaps for Complex Generic Approval

- Generic Drug Cluster (Launched in June 2021)
- FDA-EMA Parallel Scientific Advice Pilot Program for Complex Generic/Hybrid Products (Launched in September 2021)
  Global Generic Drug Affairs | FDA
- Global Bioequivalence Harmonization Initiative Workshop
  https://gbhi.eufeps.org/
- ICH Generic Drug Discussion Group
  - https://database.ich.org/sites/default/files/ICH_GDG_Remit_Final_2019_0130.pdf
  - https://database.ich.org/sites/default/files/DG_GDG_WorkPlan_2021_0210.pdf
- International Pharmaceutical Regulators Programme (IPRP) Nanomedicine Working Group
  http://www.iprp.global/working-group/nanomedicines

FDA Generic Drug Cluster Complex Product Discussion

Discussion Focus:

- Pinpoint key differences among different agencies regarding regulatory standards for the approval of complex generics
- Aid in the identification of aspects hindering approval of complex generics
- Exchange regulatory scientific advancements
- Reach convergence regarding approval standards if possible

Discussed Topics:

- Parenteral nanomedicine products
- Long-acting injectable products
- Physico-chemical characterizations
- pAUC consideration
- Modeling and simulation research

Summary

- There are unique scientific and regulatory challenges for global development of complex generic drug products.
- FDA is committed to support complex generic product development through GDUFA research and GDUFA II enhancements.
- Significant regulatory science advancements have facilitated guidance development and approval of complex generic products.
- Global collaborations help accelerate scientific advancements and align global development of complex generic drug products.

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  - Office of Research and Standards
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