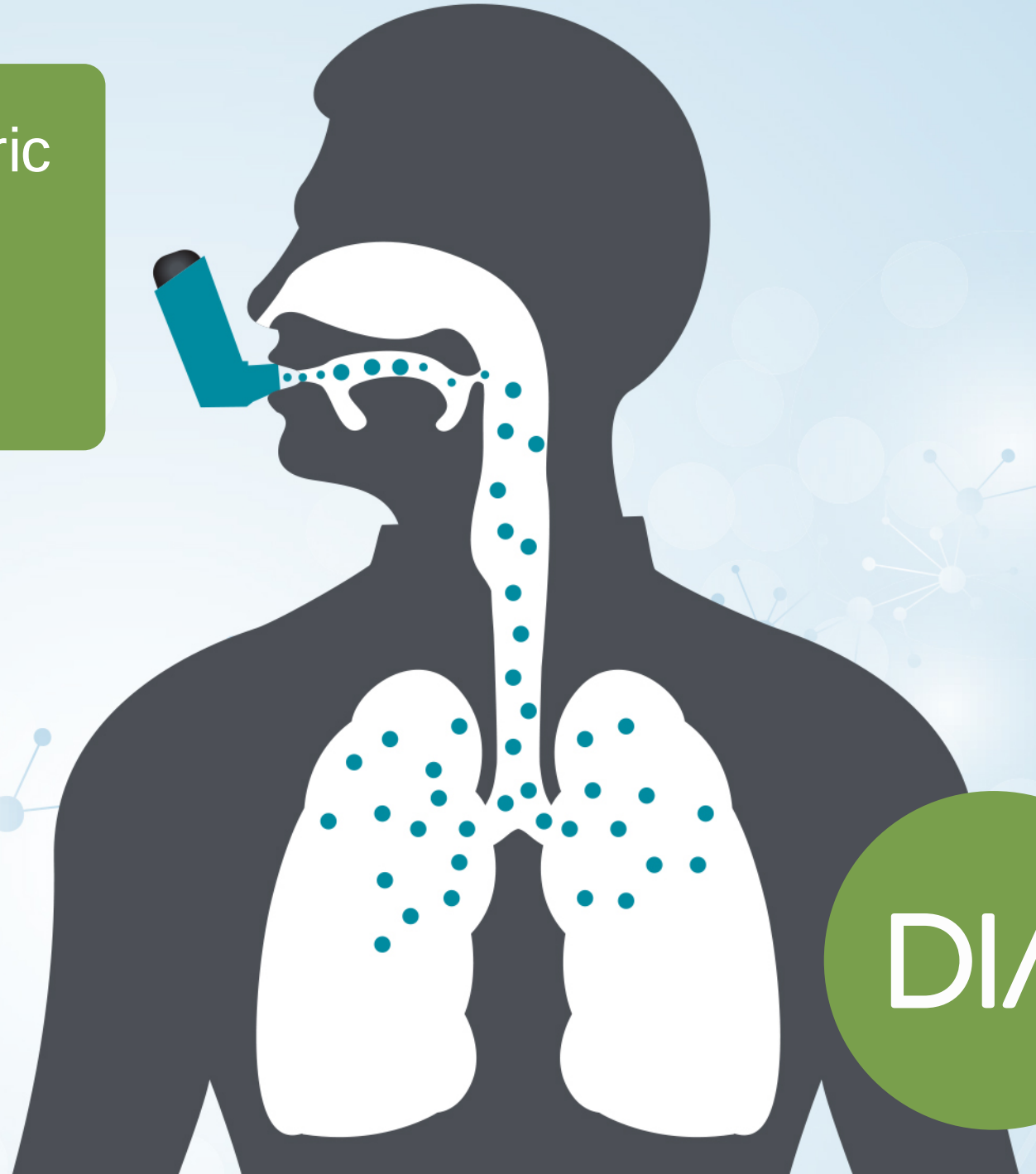
Complex Drug-Device Generic Combination Products

October 9-10
Sheraton Silver Spring, MD



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Overview of Complex Generic Inhalation, Nasal and Auto-Injector Drug-Device Combination Products

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Reviewer, Office of Generic Drugs
CDER | FDA

Outline

- Orally Inhaled and Nasal Drug Products (OINDPs)
- Auto-Injector Drug Products
  - Overview
  - Challenges in establishing bioequivalence (BE)
  - BE recommendations
  - Role of product-specific guidances (PSGs)

Orally Inhaled and Nasal Drug Products (OINDPs)

- Drug-device combination products
- Treatment of diseases of respiratory tract
  - Asthma, chronic obstructive pulmonary disease (COPD), rhinitis
- Complex products*
  - Formulations, routes of delivery, dosage forms

* As per GDUFA II Commitment Letter: https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf

Complexity of OINDPs

Drug State	Site of Action	Dosage Form	Route
Solution	Systemic	Aqueous Spray	Nasal
	Local	Aerosol Metered	Nasal
			Inhalation
		Aqueous Spray	Nasal
			Inhalation
Suspension	Local	Aqueous Spray	Nasal
		Aerosol Metered	Inhalation
Solid blend	Systemic	Powder	Nasal
			Inhalation
	Local	Powder	Inhalation

Generic Drug Products Are Therapeutic Equivalents

- In relation to the Reference Listed Drug (RLD), generic drug products are expected to be:

  - **Pharmaceutically Equivalent (PE)**
    The same active ingredient, dosage form, strength, route of administration, and meet the same compendial standards (strength, quality, purity, and identity)

  - **Bioequivalent (BE)**
    No significant difference in the rate and extent of absorption of the active ingredient at the site of action

  - **Therapeutically Equivalent (TE)**
    Drug Products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to produce the same clinical effect and safety profile as the RLD, when administered to patients under the conditions specified in labeling

(See 21 CFR 314.3)

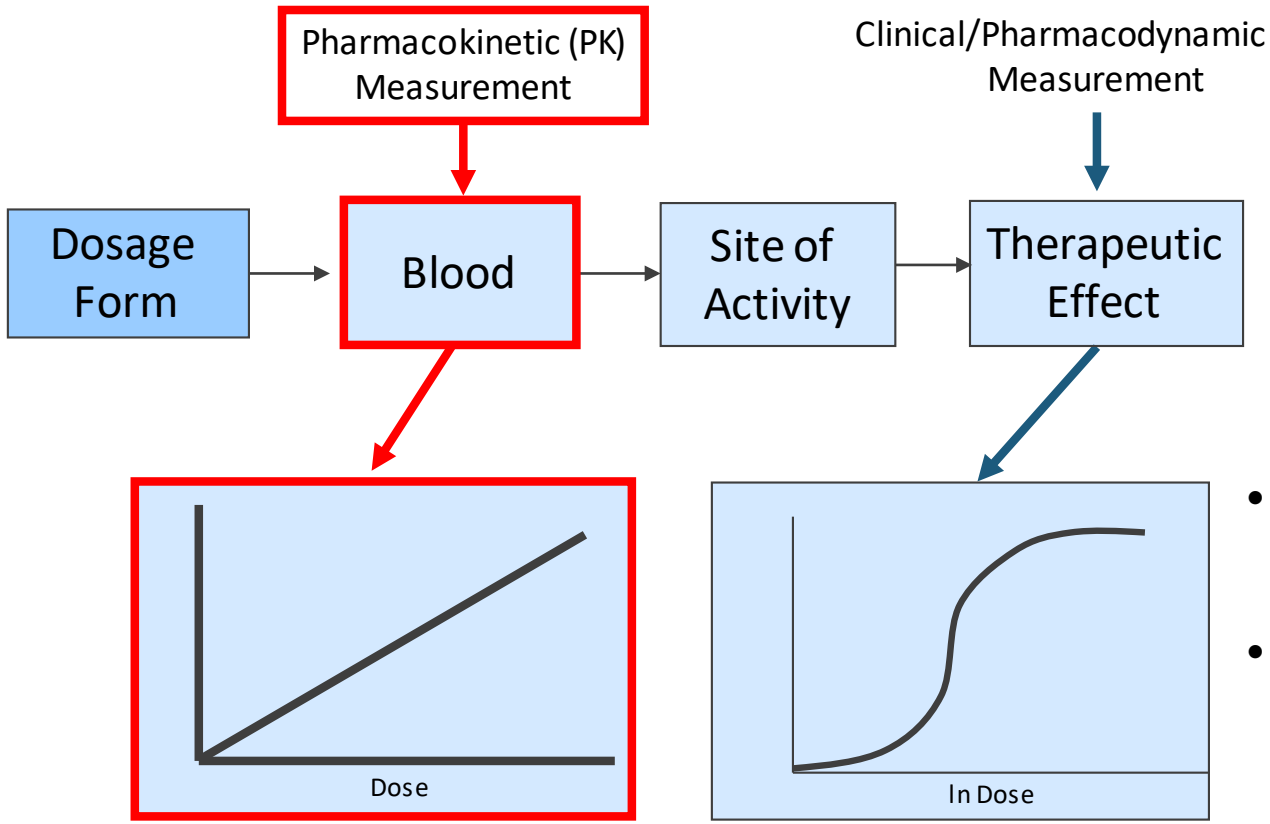
Challenges in Establishing BE for Locally Acting Generic OINDPs

- Device plays an essential role in delivering the dose

- Several factors influencing drug bioavailability:
  - Patient-device interactions (e.g., patient effort for inhalation)
  - Device-formulation interactions
  - Regional drug distribution
  - Local dissolution/permeability/clearance

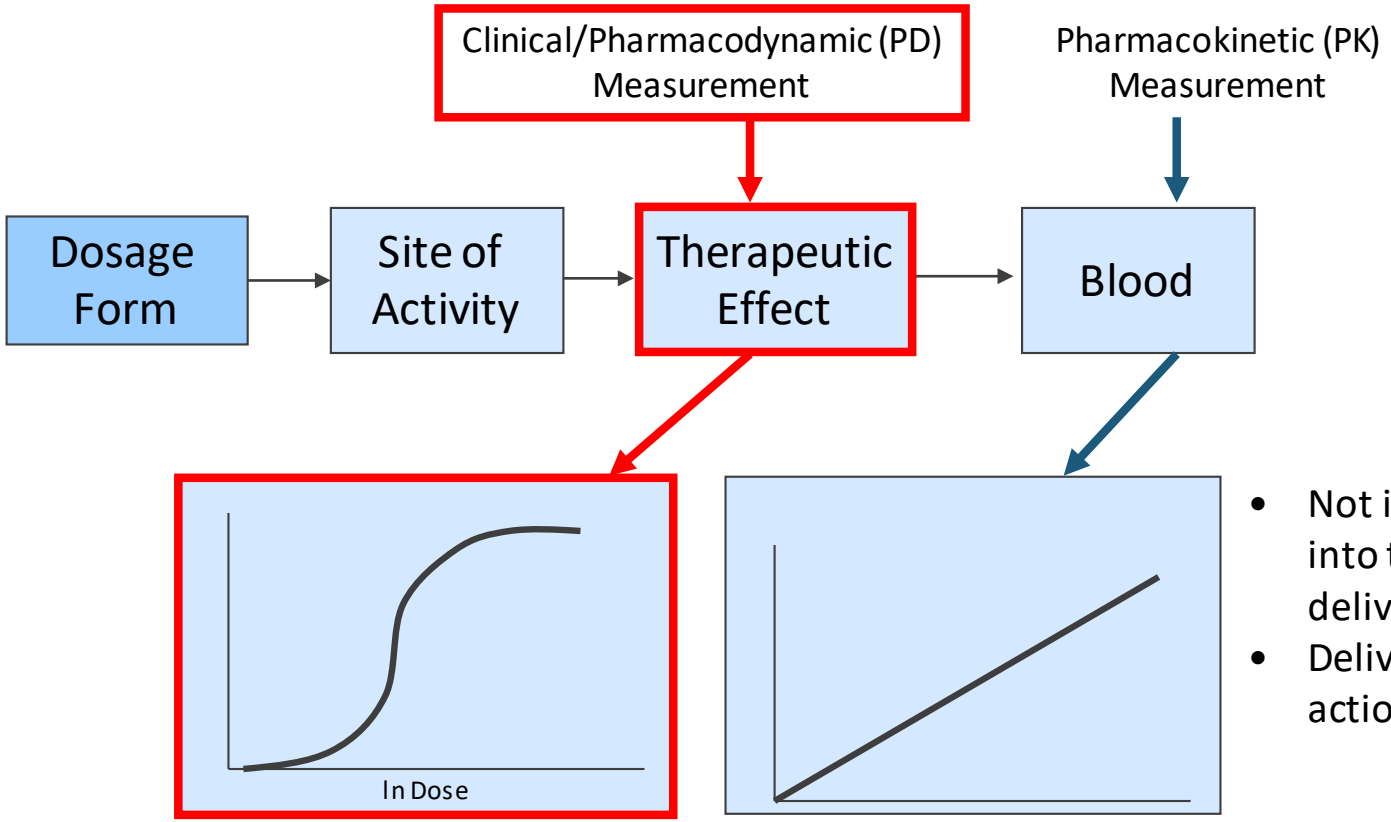
- Drug delivery is local to the site of action (e.g., lung tissue or nasal cavity), not systemic:
  - Intended target effect does not rely primarily on systemic absorption
  - Challenges to measuring local effect

BE for Systemically Acting Drugs



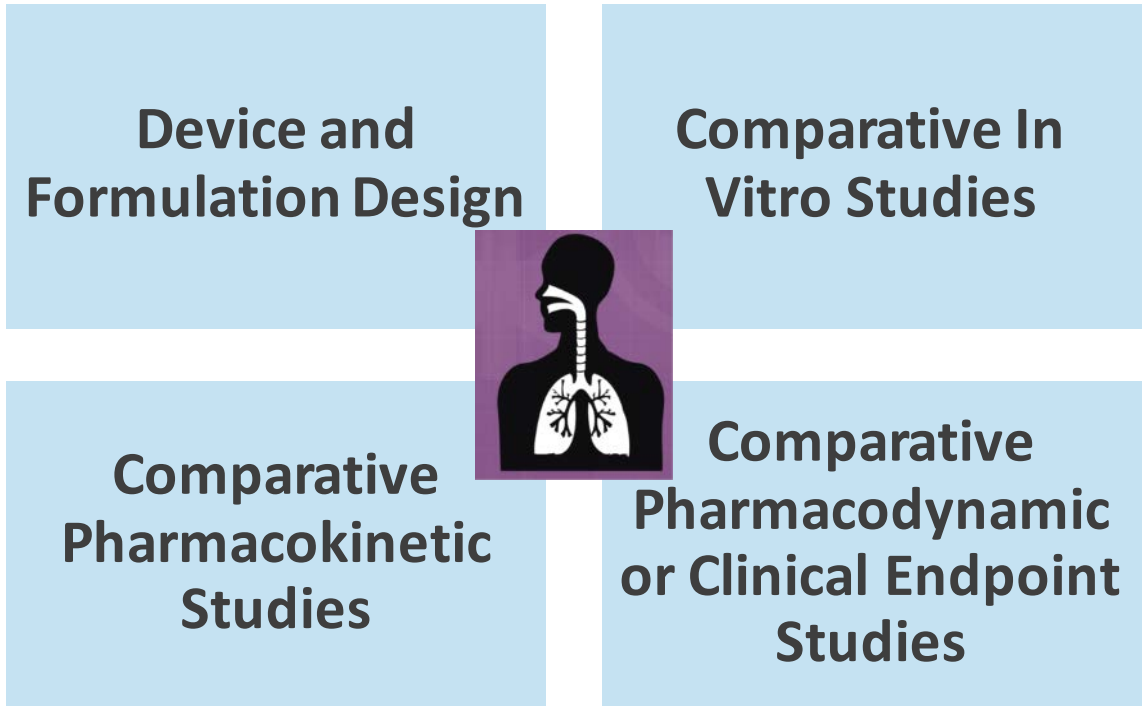
- Delivered to the bloodstream for distribution to site(s) of action in the body
- BE determined with PK studies
  - Relatively short studies
  - Relatively small number of subjects

BE for Locally Acting Drugs



- Not intended to be absorbed into the bloodstream to deliver its effect
- Delivered directly to sites of action (lung or nose)

Weight of Evidence Approach for Establishing BE for OINDPs



- Currently recommended for locally acting dry powder inhaler (DPI), metered dose inhaler (MDI) and nasal suspension products
- Incomplete understanding of the relevance of results from BE studies to drug concentrations at local site of action
- Uncertainties regarding sufficiency of correlation of in vitro to in vivo PK data to establish BE

Formulation Considerations for OINDPs

- Qualitative (Q1) sameness
  - Recommend same inactive ingredient(s)
    - May be critical to establishing bioequivalence between the test and reference MDI, DPI and nasal products
- Quantitative (Q2) sameness*
  - Recommend same inactive ingredient(s) but may differ in concentration
    - Cannot exceed the levels used in other FDA approved products administered by the same route of administration
    - Effect of Q2 difference on BE assessed by in vitro and in vivo studies
    - Submit pharmaceutical development data to support the selected test formulation

* As per the FDA Guidance for Industry, "ANDA Submissions – Refuse-to-Receive Standards" (December 2016), quantitative sameness generally is interpreted by OGD to mean a concentration that is within 95-105% of the RLD concentration. That is, sameness as discussed herein does not suggest an exact value, but rather a range of values.

User Interface Considerations for OINDPs

- External critical design attributes
  - Refers to those features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product

- User interface
  - Refers to all components of a product with which a user interacts, such as the delivery device constituent part, any associated controls and displays, as well as labeling and packaging

In Vitro Considerations for OINDPs

- Attributes that are believed to affect the total and regional deposition of drug(s) in the site of action

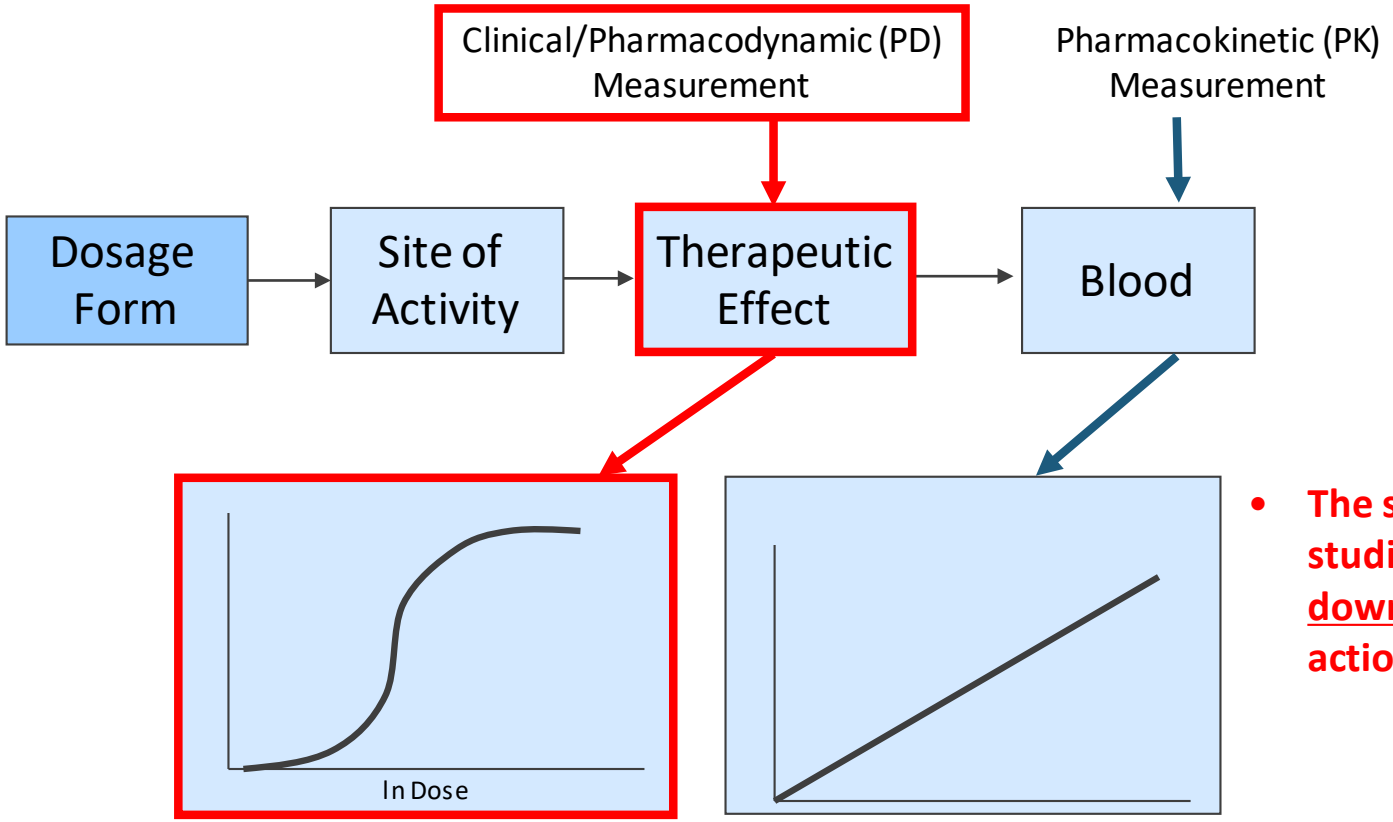
- Dependent on, and sensitive to, product- and process-related factors
  - Physicochemical properties of drug(s) and excipient(s)
  - Device properties
  - Process conditions

- Conducted with all strengths, at least 3 batches of test (T) and reference (R) products, with no fewer than 10 units from each batch

In Vitro BE Studies for OINDPs

DPIs	MDIs	Nasal Suspensions
- Single Actuation Content (SAC) at beginning (B), middle (M) and end (E) lifestages and using 3 flow rates - Aerodynamic Particle Size Distribution (APSD) at B and E lifestages and using 3 flow rates	- SAC at B, M and E lifestages - APSD at B and E lifestages - Spray Pattern at B lifestage and 2 distances from actuator mouthpiece - Plume Geometry at B lifestage - Priming and Repriming (if required by the R product)	- SAC at B and E lifestages - Droplet Size Distribution by Laser Diffraction at B and E lifestages and 2 distances from actuator orifice - Drug in Small Particles/Droplets at B lifestage - Spray Pattern at B lifestage and 2 distances from actuator orifice - Plume Geometry at B lifestage - Priming and Repriming (if required by the R product)

In Vivo Pharmacokinetic (PK) Considerations for OINDPs



- **The sampling site for PK studies (plasma) is <u>downstream</u> of the site of action (lung or nose)**

In Vivo Pharmacokinetic (PK) BE Studies for OINDPs

- Reliable and sensitive method to determine differences in drug product characteristics
- Fasting, single-dose studies in healthy subjects for all strengths, endpoints: AUC and Cmax
- Dose based on minimizing the number of actuations, but justified by assay sensitivity
- Relation between PK dose proportionality across multiple strengths, in vitro performance parameters, and product characteristics are not well understood, **therefore all strengths are needed**

In Vivo Pharmacodynamic (PD) BE Study for OINDPs

- Dose-response PD BE study preferred over a comparative BE study with clinical endpoint
- PD study used if there is adequate dose-response (e.g., short-acting β-agonists)
- Dose-response ensures the sensitivity of a PD study to distinguish potential differences between T and R products
- Establishing dose-response for inhaled corticosteroids has been challenging
- Comparative BE studies with clinical endpoints for products which do not demonstrate adequate dose-response

In Vivo Comparative BE Study With Clinical Endpoints for OINDPs

- Three arms: Test, Reference, Placebo control
- Comparison to placebo demonstrates sensitivity of the study to detect a difference
- Lowest labeled dose used
- Study supports demonstration of bioequivalence of Test to the RLD
- Study in one indicated population
- Endpoint based on FEV1
- BE met if 90%CI for T/R ratio for endpoint(s) falls within 80.00-125.00%

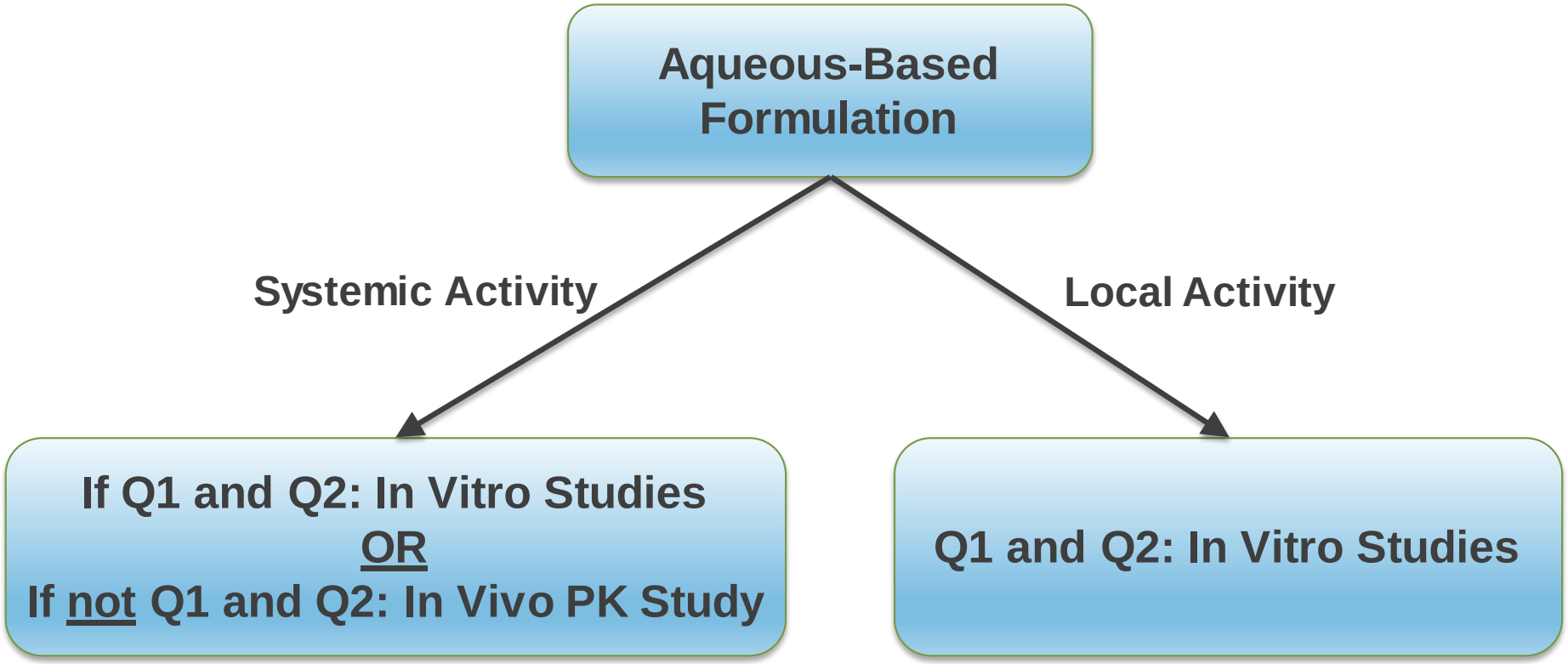
In Vivo Comparative BE Study with Clinical Endpoints for OINDPs

- Less sensitive than other methods for BE
- Patient behaviors may introduce variation
- Must meet the established BE limits
- May require several hundred patients
- Study duration may be several weeks depending upon the approved labeling
- Expensive to conduct
- Information about the clinical effect at the local sites of action (lung and nose)

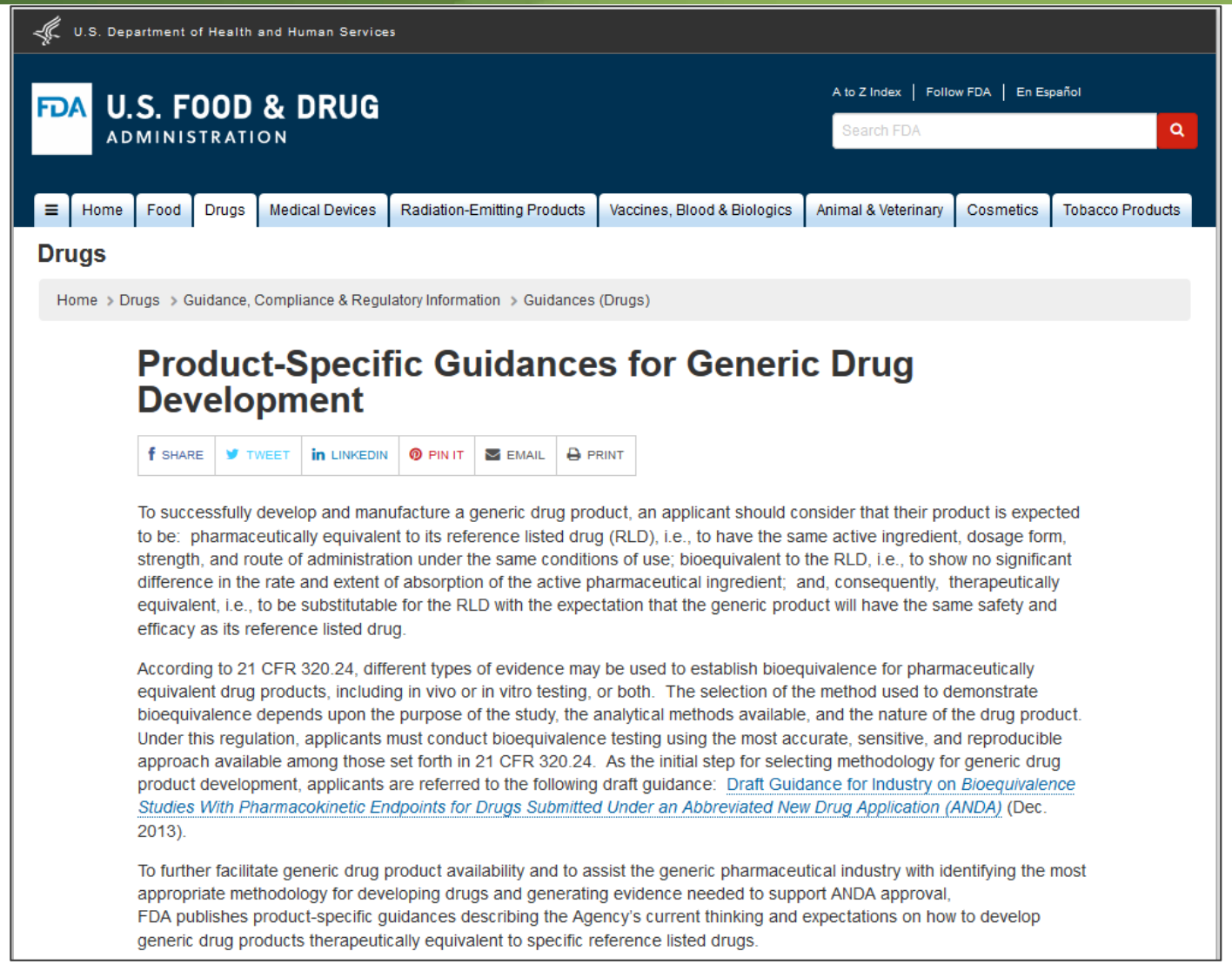
In Vivo PD or Comparative Clinical Endpoint BE Studies for OINDPs

DPIs	MDIs	Nasal Suspensions
- Multiple-dose or single-dose (based on the drug mechanism of action), randomized, placebo-controlled, parallel group or crossover, placebo run-in period followed by the treatment period of placebo, T and R, patients with asthma or chronic obstructive pulmonary disease (COPD), lowest strength, endpoint: FEV1 - Bronchoprovocation or bronchodilatation dose-response PD study (e.g., short-acting β-agonists), endpoints: PC20 (or PD20), or FEV1		- Multiple-dose, randomized, double-blind, placebo-controlled, parallel group, placebo run-in period, three-arm, patients with seasonal allergic rhinitis, endpoint: TNSS

BE Considerations for Nasal Solution Products



Product-Specific Guidance's (PSGs)



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Product-Specific Guidances for Generic Drug Development

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To successfully develop and manufacture a generic drug product, an applicant should consider that their product is expected to be: pharmaceutically equivalent to its reference listed drug (RLD), i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use; bioequivalent to the RLD, i.e., to show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient; and, consequently, therapeutically equivalent, i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its reference listed drug.

According to 21 CFR 320.24, different types of evidence may be used to establish bioequivalence for pharmaceutically equivalent drug products, including in vivo or in vitro testing, or both. The selection of the method used to demonstrate bioequivalence depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Under this regulation, applicants must conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24. As the initial step for selecting methodology for generic drug product development, applicants are referred to the following draft guidance: Draft Guidance for Industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)* (Dec. 2013).

To further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval, FDA publishes product-specific guidances describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs.

- > **60%** of all MDI and DPI products have PSGs
- > **55%** of all nasal products have PSGs

PSGs for Generic Products

- Roles
  - To facilitate generic drug product availability
  - To assist generic pharmaceutical industry
  - To identify the most appropriate methodology for generating evidence that could support ANDA approval
- Guiding Principles
  - 21 CFR 320.24
  - Different types of evidence may be used to establish BE for pharmaceutically equivalent drug products
  - Recommend use of the most accurate, sensitive, and reproducible approach available
  - Selection for BE method depends upon
    - Purpose of study
    - Analytical methods available
    - Nature of the drug product
  - Based on the attributes of RLD

Current PSGs for OINDPs

MDIs	DPIs	Nasal Solutions	Nasal Suspensions
1. Fluticasone Propionate	1. Mometasone Furoate	1. Ketorolac Tromethamine	1. Azelastine Hydrochloride and Fluticasone Propionate
2. Mometasone Furoate	2. Fluticasone Propionate	2. Oloppatadine Hydrochloride	2. Triamcinolone Acetonide
3. Formoterol Fumarate and Mometasone Furoate	3. Salmeterol Xinafoate	3. Azelastine Hydrochloride	3. Mometasone Furoate Monohydrate
4. Ciclesonide	4. Tiotropium Bromide	4. Cyanocobalamin	4. Fluticasone Propionate
5. Beclomethasone Dipropionate	5. Glycopyrrolate	5. Tetracaine Hydrochloride and Oxymetazoline Hydrochloride	
6. Albuterol Sulfate	6. Budesonide	6. Naloxone Hydrochloride	
7. Levalbuterol Tartrate	7. Umeclidinium Bromide	7. Nicotine	
8. Budesonide and Formoterol Fumarate Dihydrate	8. Indacaterol Maleate	8. Zolmitriptan	
9. Ipratropium Bromide	9. Fluticasone Furoate	9. Sumatriptan	
	10. Fluticasone Furoate and Vilanterol Trifenatate	10. Fentanyl	
	11. Formoterol Fumarate	11. Calcitonin-Salmon	
	12. Aclidinium Bromide	12. Ciclesonide	
	13. Fluticasone Propionate and Salmeterol Xinafoate	13. Beclomethasone Dipropionate	

(Current through September 3, 2018)

Auto-Injector Drug Products

- Drug-device combination products
  - Drug constituent part is a systemically acting parenteral solution formulation
  - Device constituent part is auto-injector
- Emergency treatment
  - Allergic reactions (Type I) including anaphylaxis
  - Poisoning by susceptible organophosphorous nerve agents
- Chronic treatment
  - Migrane
  - Other indications
- Complexity comes mainly from the specialized devices

Considerations for Generic Epinephrine Auto-Injector Combination Product

- An in vivo bioequivalence study will likely not be necessary if the following criteria are met
  - Same active ingredient, dosage form, strength, route of administration, and meet the same compendial standards (strength, quality, purity, and identity)
  - Assessment also includes the following:
    - Formulation evaluation
    - Comparative in vitro studies
    - User interface considerations

Formulation and User Interface Considerations- Generic Epinephrine Auto-Injector Combination Product

- **Formulation Considerations**
  - Qualitative (Q1) and quantitative (Q2) sameness
- **Device Considerations**
  - External critical design attributes
    - Refers to those features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product
  - User interface
    - Refers to all components of a product with which a user interacts, including the delivery device constituent part, any associated controls and displays, as well as labeling and packaging.

In Vitro Considerations – Generic Epinephrine Auto-Injector Combination Product

- Attributes that are believed to affect the drug delivered to the site of action
- Conducted with all strengths, at least 3 batches of T and R products, with no fewer than 10 units from each batch
- The 3 batches of T product prepared from 3 different batches of the same critical device components
- T and R products studied under the same instrumental conditions
- Method validation performed using the R product

In Vitro Studies – Generic Epinephrine Auto-Injector Combination Product

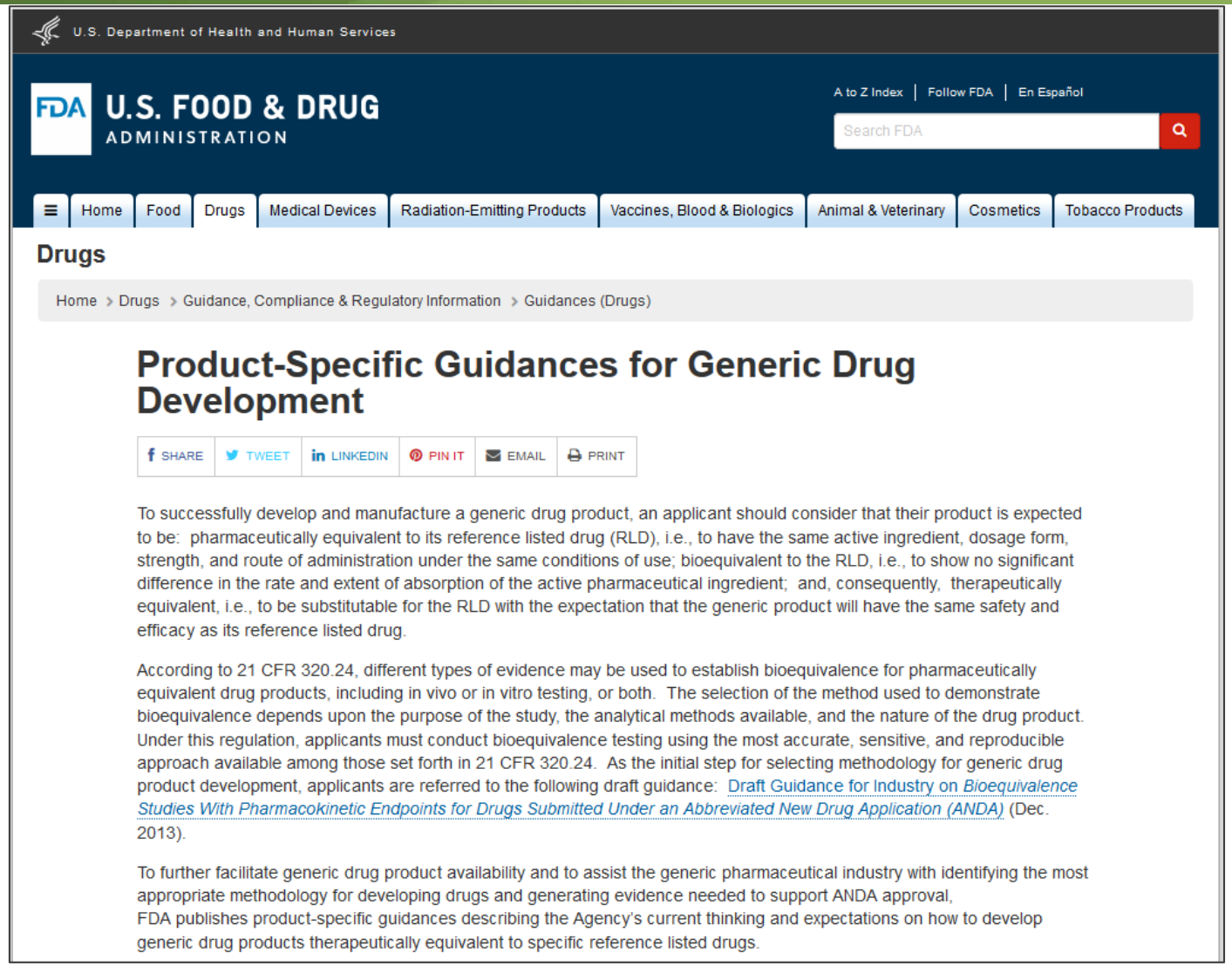
- Delivered volume
- Ejection time
- Trigger force
- Extended needle length

} Assessment based on population bioequivalence (PBE) analysis

- Needle integrity post-injection
  - Assessment based on qualitative comparisons with respect to ability to trigger the injection at the angle of incidence, ability to the needle to penetrate the material, and integrity of the needle post-injection

- Applicability of these tests depends on the attributes of the R product

Product-Specific Guidances (PSGs)



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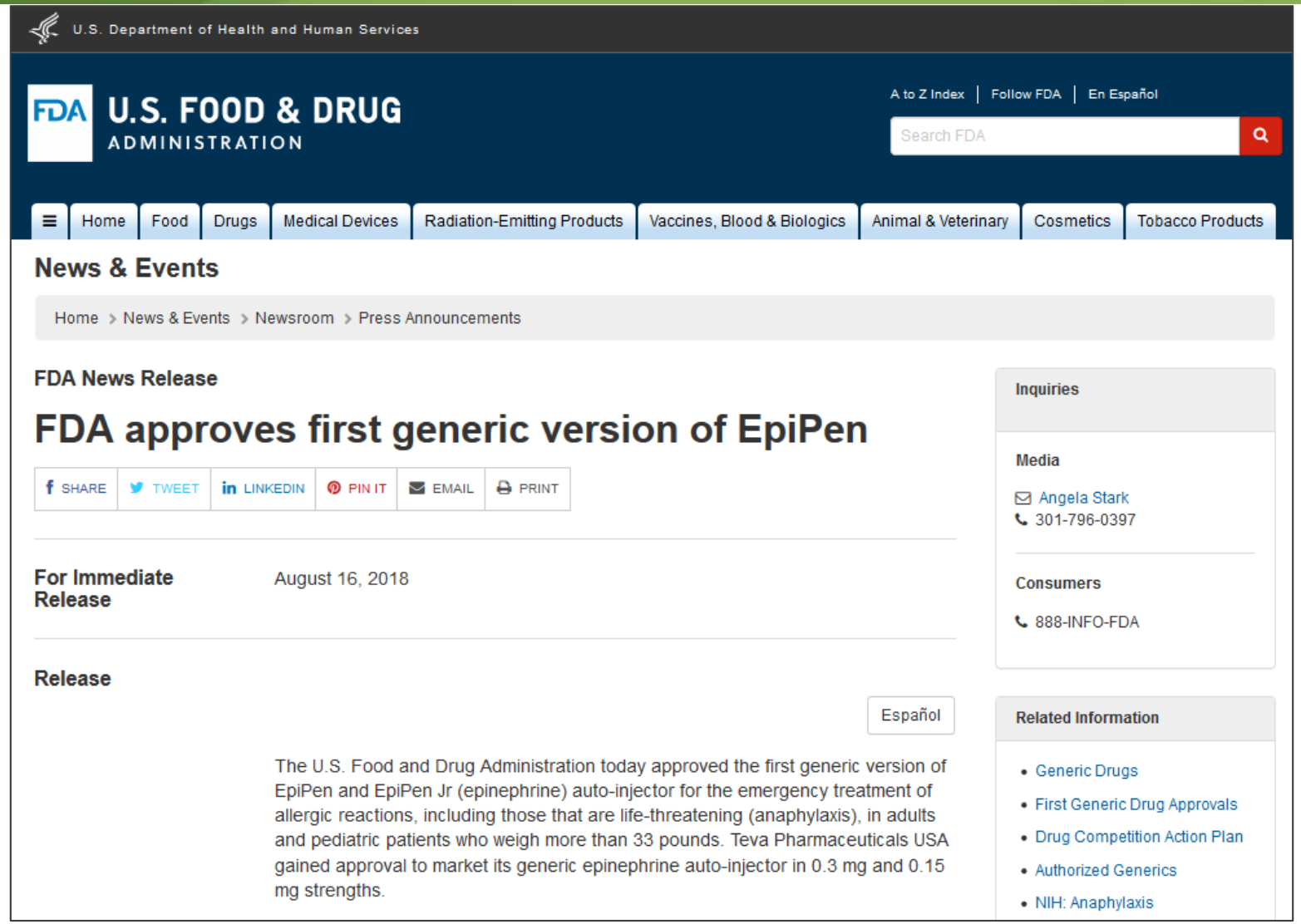
- Currently, 3 PSGs for epinephrine injectable products

First Generic Emergency-Use Epinephrine Auto-Injector Drug Product



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FDA News Release

FDA approves first generic version of EpiPen

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For Immediate Release August 16, 2018

Release

Español

The U.S. Food and Drug Administration today approved the first generic version of EpiPen and EpiPen Jr (epinephrine) auto-injector for the emergency treatment of allergic reactions, including those that are life-threatening (anaphylaxis), in adults and pediatric patients who weigh more than 33 pounds. Teva Pharmaceuticals USA gained approval to market its generic epinephrine auto-injector in 0.3 mg and 0.15 mg strengths.

Inquiries

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Consumers

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Related Information

- Generic Drugs
- First Generic Drug Approvals
- Drug Competition Action Plan
- Authorized Generics
- NIH: Anaphylaxis

Takeaways

- OINDPs and auto-injector drug products are complex generic drug-device combination products
- Described the determining factors to establish BE for
  - Locally-acting OINDPs: current weight of evidence approach
  - Systemically-acting auto-injector drug products
- Product-specific guidances (PSGs)
  - Facilitate generic drug product availability
  - Assist generic pharmaceutical industry
  - Recommend use of the most accurate, sensitive, and reproducible approach available
  - Identify the current thinking methodology to support ANDA

Thank you for your attention!