U.S. FOOD & DRUG ADMINISTRATION

Path to Bioequivalence for Complex Products: Past, Present and Future

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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**

Past

- Pharmacokinetic based bioequivalence evolved out of arguments in the 1960's about whether tablets and capsules with the same active ingredient could be "different"
- Formulation and manufacturing of tablets and capsules can change their bioavailability
- An in vivo comparative evaluation of bioavailability (Bioequivalence) became recognized as the standard and was incorporated into statute and regulations governing generic drugs

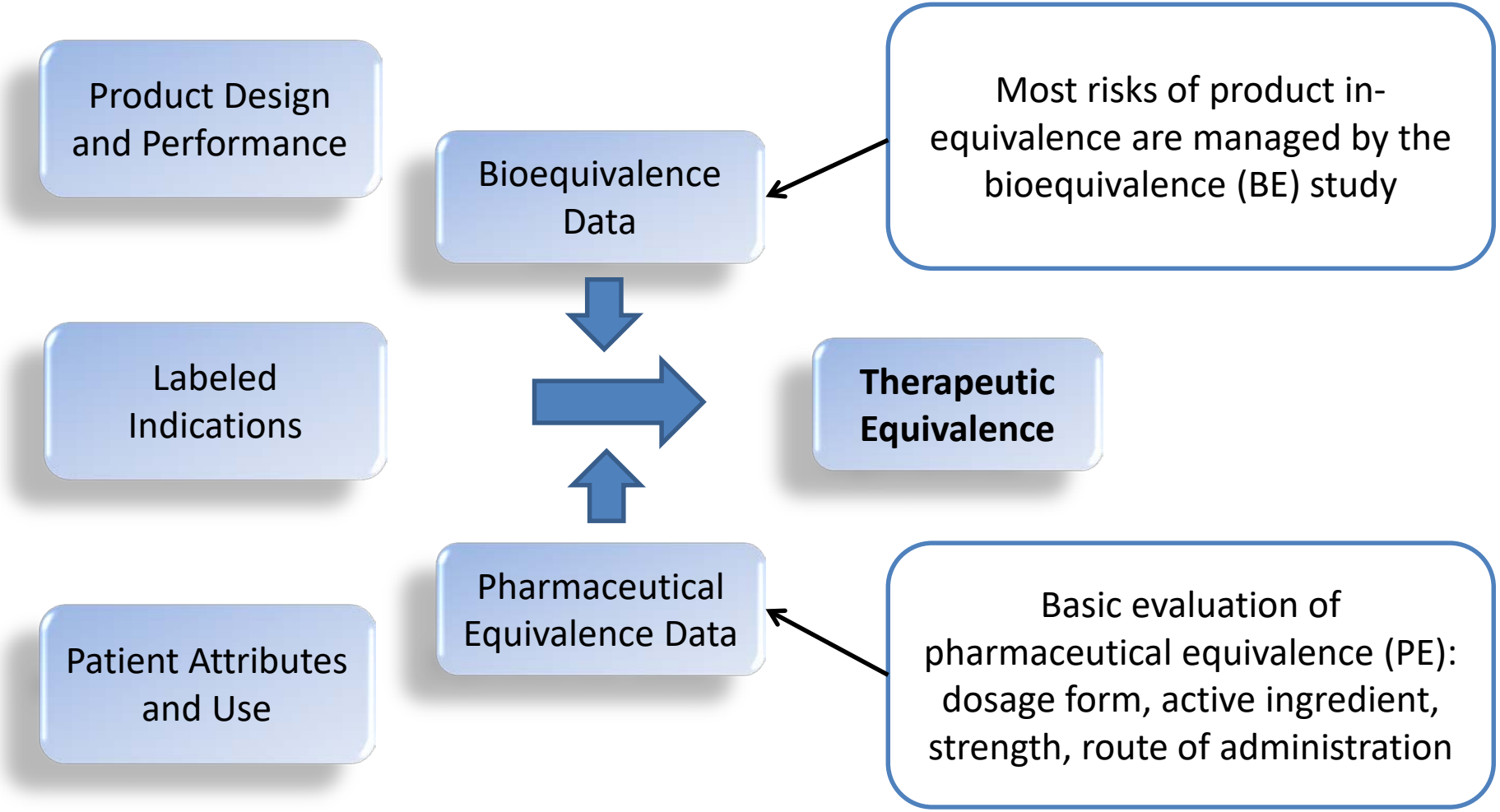
Equivalence Concepts

- **Pharmaceutical Equivalence (PE)**
  - Same active ingredient(s) and
  - Same dosage form and
  - Same route of administration and
  - Same strength

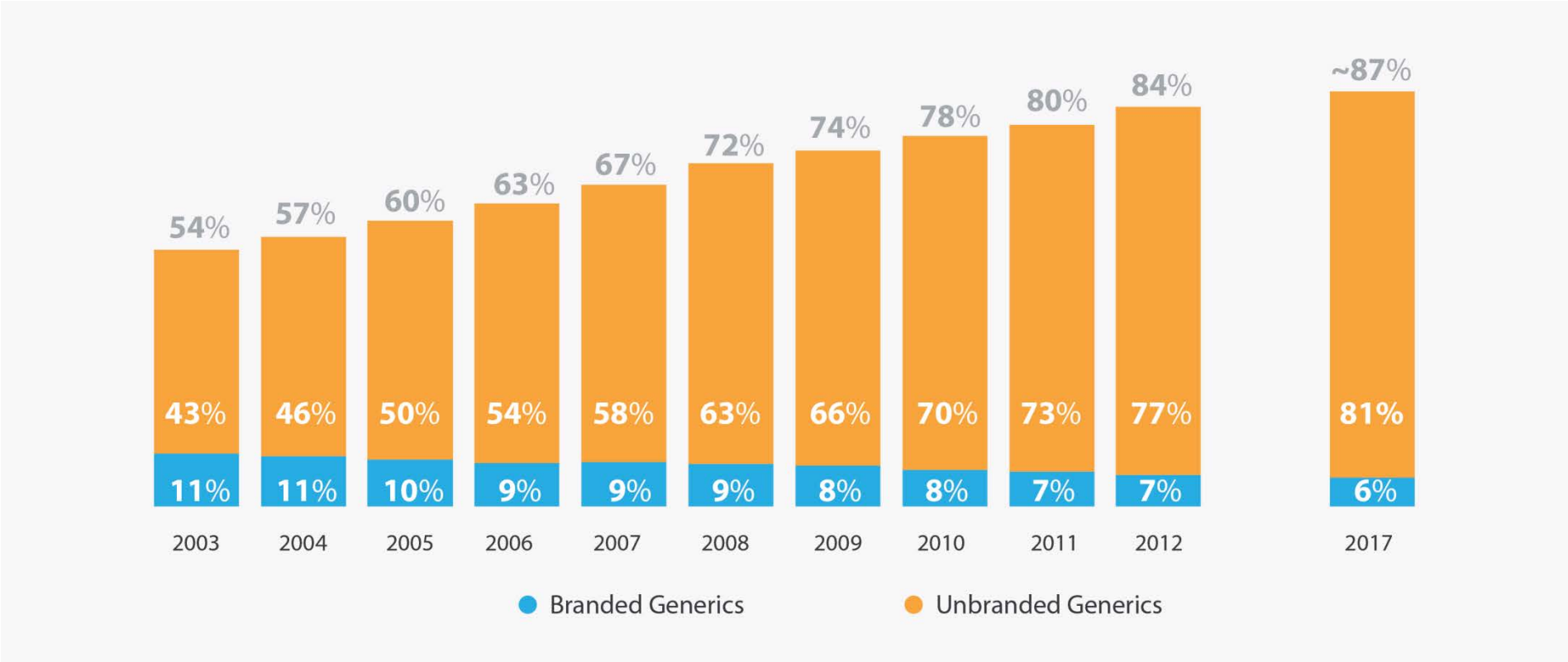
- **Bioequivalence (BE)**
  - No significant difference in rate and extent of drug at site of action

- **Therapeutic Equivalence (TE) of Generic Products**
  - Generics must demonstrate PE and BE to the reference product
  - Generics rely on the safety and efficacy of the reference product
  - Generics must have adequate labeling and cGMP manufacturing
  - TE products can be substituted freely

Old Paradigm of Equivalence



Historical Percent Share of Prescriptions for Generic Drugs



A incredible success for non-complex products!

IMS Report: Declining Medicine Use and Costs: For Better or Worse? May 2013

Present

- Under GDUFA I, FDA focused on the science related to non-systemically acting drugs
  - Scientific Areas
    - PBPK and physics-based models for non-local routes
    - Advanced characterization of complex pharmaceutical materials
    - Better understanding of complex drug delivery systems
  - Regulatory Approaches
    - Weight of evidence approaches (for nasal and inhalation products)
    - Q3 similarity (for topical and ophthalmic) which are more complex and levels of complexity solution, suspension, gel

Regulatory Basis for Alternatives

- A 2003 addition to the Federal Food Drug and Cosmetic Act at Section 505(j)(8)(A)(ii) indicates that
  - "For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action".

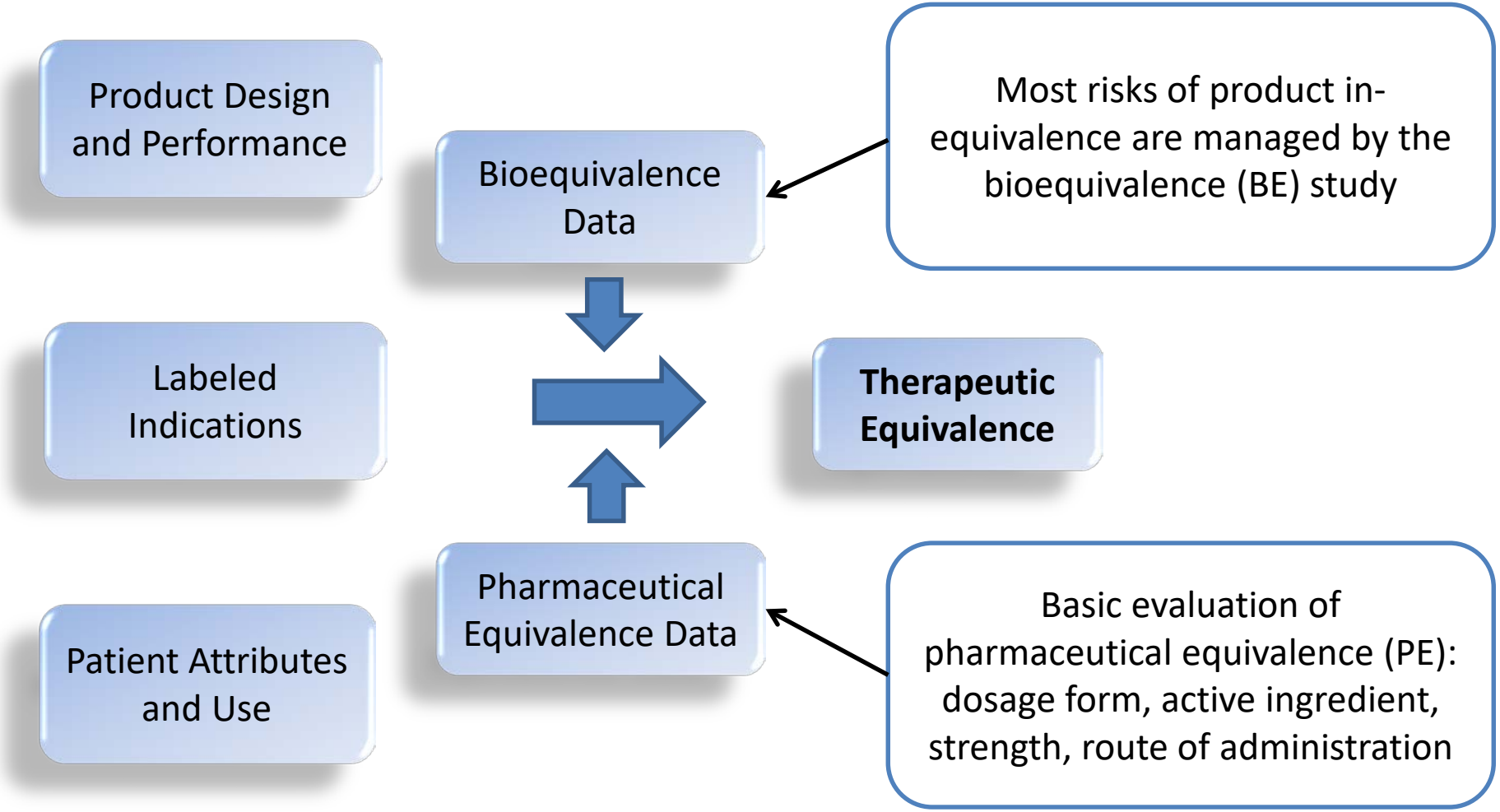
BE Approaches for Locally Acting Products

- Q3: FDA has begun to make Q3 characterization based recommendation for Q1 and Q2 formulations for locally acting drugs
  - Vancomycin, Acarbose, Acyclovir
- For other locally acting products FDA has recommended “weight of evidence” or combined approaches
  - PK,PD, in vitro for inhalation
  - Dissolution and PK for mesalamine

Q1 and Q2 and Q3 Definitions

- Classify product similarity
  - Q1: Same components
  - Q2: Same components in same concentration
  - Q3: Same components in same concentration with the same arrangement of matter (microstructure)
    - Characterization and performance data can support Q3 equivalence

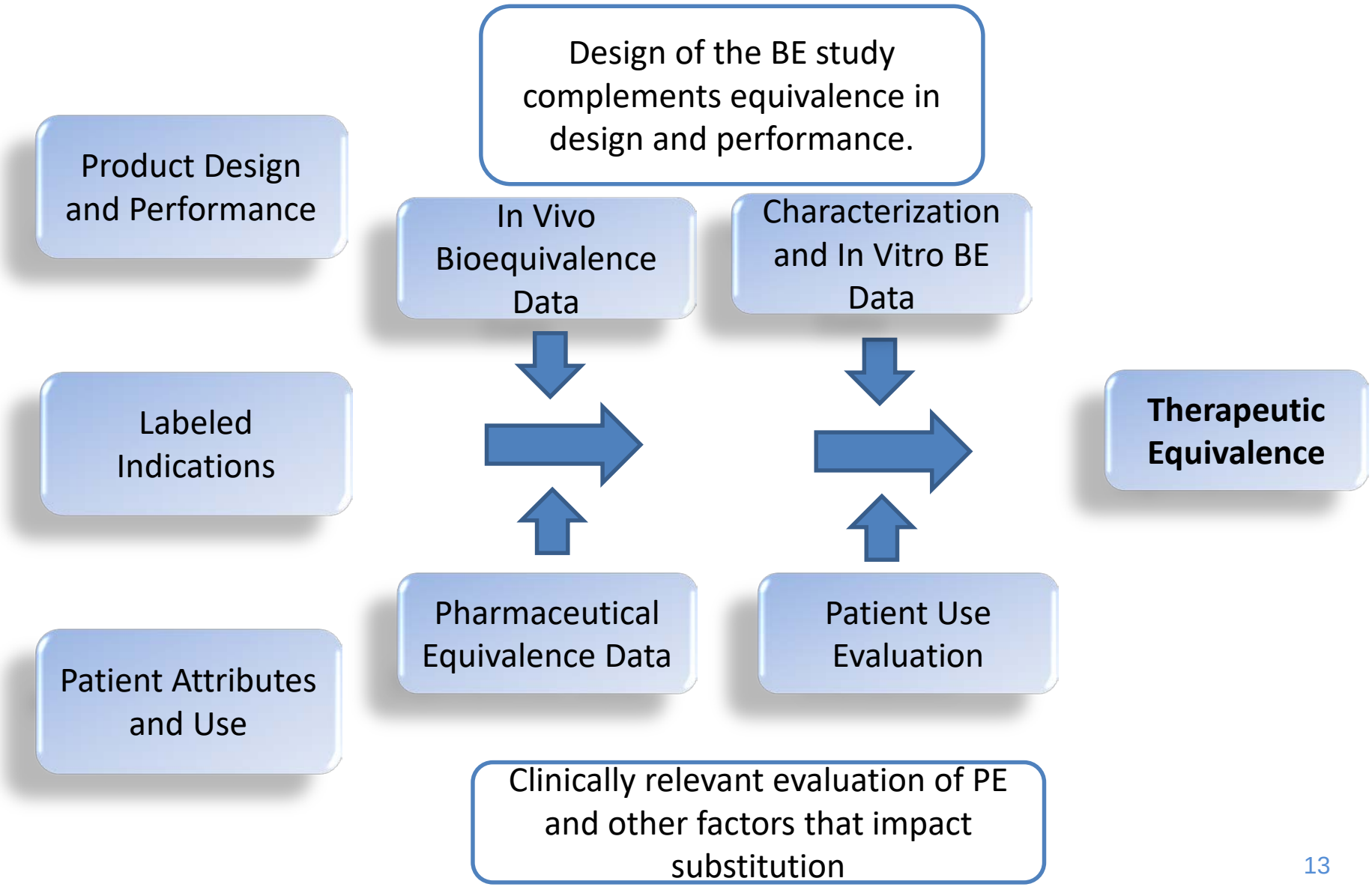
Old Paradigm of Equivalence



Equivalence of Complex Products

- Regulatory Science Challenges:
  - To align BE study recommendations and essential product characterizations as part of therapeutic equivalence evaluation
  - To evolve product development and regulatory assessment to broader physicochemical and functional product characteristics that matter to patients for equivalence and successful generic substitution

New Paradigm of Equivalence

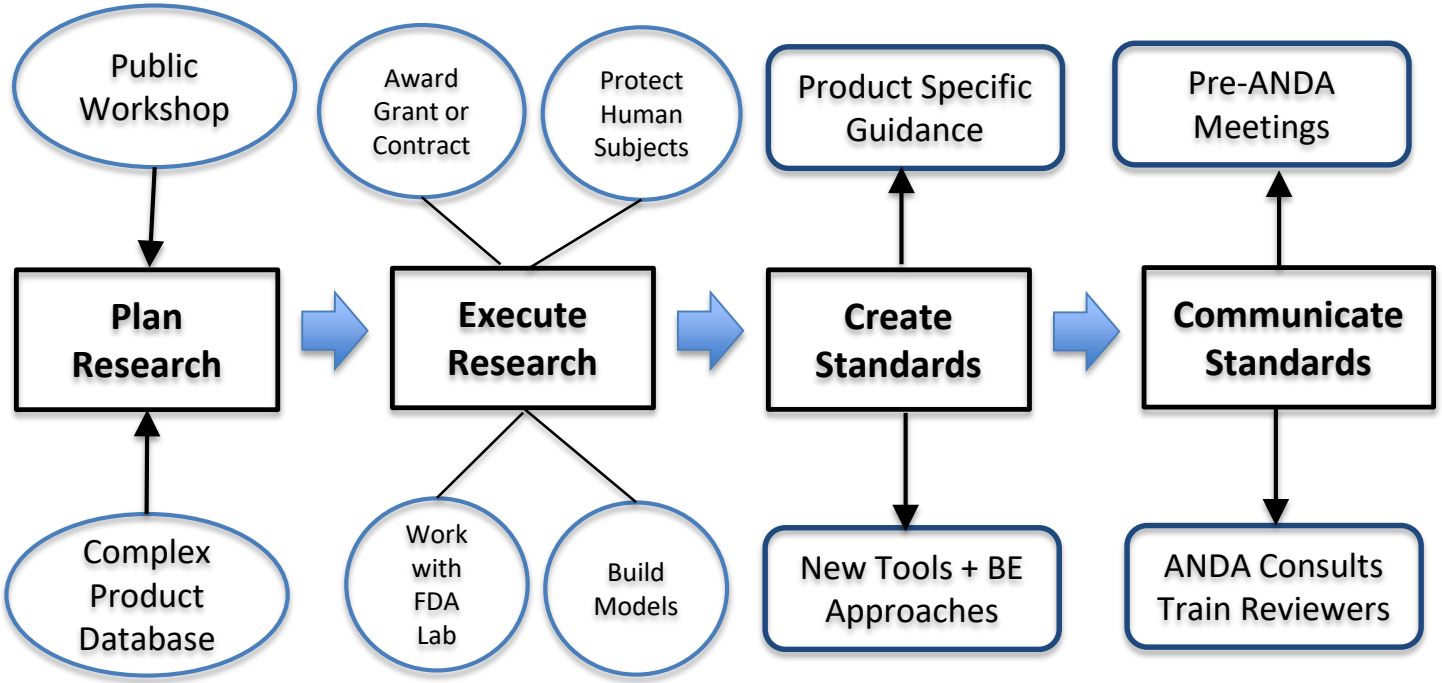


Research Supports New Approaches to Equivalence

- Establishes the scientific foundations for product development for complex products that lack generic competition.
- Provides ANDA assessment methods for evaluation of complex generics
- Ensures confidence in the approval pathway and the equivalence of any approved products.

Office of Research and Standards Operational Model

- ORS is a multidisciplinary **Office** that plans and conducts **Research** and translates the results into generic drug **Standards**



FY2018 GDUFA Priority Areas

- **Complex active ingredients, formulations, or dosage forms (1)**
  - (1) Improve advanced analytics for characterization of chemical compositions, molecular structures and distributions in complex active ingredients
  - (2) Improve particle size, shape and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products
  - (3) Establish predictive in silico, in vitro and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products
  - (4) Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables
  - (5) Develop better methods for evaluating abuse deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal studies
- **Complex routes of delivery (2)**
  - (6) Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)
  - (7) Expand characterization-based bioequivalence (BE) methods across all topical dermatological products
  - (8) Expand characterization-based BE methods across all ophthalmic products
  - (9) Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) clinical endpoint BE studies for inhaled corticosteroids
  - (10) Develop alternatives to clinical endpoint BE studies for locally-acting nasal products

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

FY2018 GDUFA Priority Areas

- **Complex drug-device combinations (3)**
  - (11) Evaluate the impact of identified differences in the user-interface on the substitutability of generic drug-device combination products
- **Tools and methodologies for BE and substitutability evaluation (4)**
  - (12) Improve quantitative pharmacology and bioequivalence trial simulation to optimize design of BE studies for complex generic drug products
  - (13) Integrate predictive dissolution, PBPK and PK/Pharmacodynamic (PD) models for decision making about generic drug bioequivalence standards
  - (14) Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System of Class 3 bio-waivers to non-Q2 (quantitatively inequivalent) formulations
  - (15) Develop methods that will allow FDA to leverage large data sets (such as bioequivalence study submissions, electronic health records, substitution and utilization patterns and drug safety and quality data) for decisions related to generic drug approval and post-market surveillance of generic drug substitution

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Research Outcomes: Examples

- **ANDA Approvals**
  - Glatiramer acetate, Mometasone nasal spray
- **ANDA Receipts**
  - Inhalation products including Albuterol MDIs and DPIs containing FP and SX (Advair)
- **General Guidance**
  - Abuse deterrence of generic solid oral opioids
  - Transdermal adhesion and irritation
  - Synthetic peptides referencing recombinant RLDs
- **Product-specific guidance (PSG)**
  - Conjugated estrogen
  - Cyclosporine ophthalmic emulsion
  - Acyclovir topical cream

Future

- Integrate new approaches into generic drug development programs in industry and expand FDA-industry pre-ANDA interactions and guidance
- Build the capacity to do these in the generic industry and in the scientific and regulatory community (consultants, suppliers, academics)
- Globalization of the development of complex generics

Complex Generic Products in GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables and implantables, transdermals, MDIs
- Complex drug-device combinations
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

GDUFA: Generic Drug User Fee Amendment
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Enhanced Pre-ANDA Process in GDUFA II

NEW

- **Improve access and approvals**
- **Decrease cycles to approval**

Complex Products

- **Early Stage**
  - GUDFA research
  - Pre-ANDA meetings with goals
- **Mid-stage**
  - Product-specific guidance (PSG) when available
  - Pre-ANDA product development meetings with goals for alternatives to PSG (different class)
  - 120 day controls for alternatives to PSG (same class)
- **Submission and Review**
  - Pre-ANDA pre-submission meetings with goals
  - Mid-cycle meetings

Non-complex Products

- **Early Stage**
  - GDUFA research
  - Goals on product-specific guidance (PSGs) for NME (2 years after NDA approval)
- **Mid-stage**
  - 60 day controls
  - 120 day controls for alternatives to product-specific guidance
  - IID enhancements
- **Submission and Review**
  - Shorter review goals for eligible priority applications with complete and accurate PFC.

NME: new molecular entity; IID: inactive ingredient database; PFC: pre-submission facility correspondence

Key Future Capabilities for Generic Drug Development

- Go Beyond Q3
  - Q1/Q2/Q3 sameness approaches limit formulation flexibility
  - Could limit generic competition
- Patient Interactions
  - RLD with more complicated patient interactions are appearing
  - Ensure substitutability
- Advanced Modeling
  - Mechanistic PBPK models to identify when Q1/Q2/Q3 differences are not clinically significant
- Data Analytics
  - Machine learning
  - Interpreting real world data on product substitution

Globalization

- Generic Drugs used in the US have global supply chains for raw materials, manufacture and bioequivalence studies
- ICH is considering an FDA authored reflection paper on harmonization of scientific and technical standards for generic drugs

Closing

- Exciting and impactful scientific activity related to complex generic drugs
  - Four talks this morning illustrate the details
    - Three speakers are research collaborators with FDA