

**SCIENTIFIC DESIGN OF PHARMACEUTICAL PRODUCTS:
21st Century Methodologies, Technologies & Perspectives**

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**THE IMPORTANCE OF PRODUCT CHARACTERIZATION
TO DEMONSTRATING EQUIVALENCE
FOR COMPLEX DRUG PRODUCTS**

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The Promise of Generic Drugs

- FDA approved generic drug products are **Therapeutically Equivalent**
- Generic drug products can be interchanged or substituted for the RLD (brand) or for other generics for that RLD
- Generic and RLD drug products will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

GDUFA: Science of Equivalence



- Research to make generic versions available in all product categories and for all available RLDs, including products that have unique characteristics.
- FDA Office of Generic Drugs spends an increasing amount of time reviewing and developing policy for complex drug products
- Characterizing bioavailability for locally-acting complex drug products is particularly challenging.
- Future generic products will need to demonstrate equivalence to increasingly complex RLDs.

Complexity in Drug Products

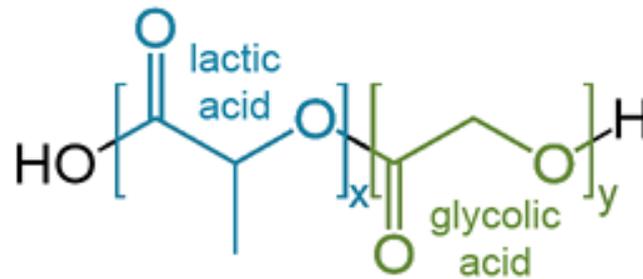
- Complex compositions of matter in the product
 - Immiscible mixtures of several “inactive” ingredients
- Complex states of matter in the product
 - Partially dissolved, partially dispersed drug(s)
- Complex arrangements of matter in the product
 - Multiple phases/components in the drug product
- Complex drug diffusion within the dosage form
 - Potentially complex and dynamic distribution of drug(s)
- Complex drug/device-patient interactions
 - Potentially altered bioavailability at target site of action
- Complex active ingredients, formulations, modified release profiles, and/or drug-device combinations

Complex Drug Products

- As the complexity of a dosage form increases so do the potential failure modes for therapeutic performance and equivalence.
- A few examples of complex drug products include:
 - Long Acting Injectables
 - Ophthalmic Suspensions
 - Nasal & Inhalation Dosage Forms
 - Transdermal Patches (TDS)
 - Topical Semisolids (Creams, Gels, etc.)

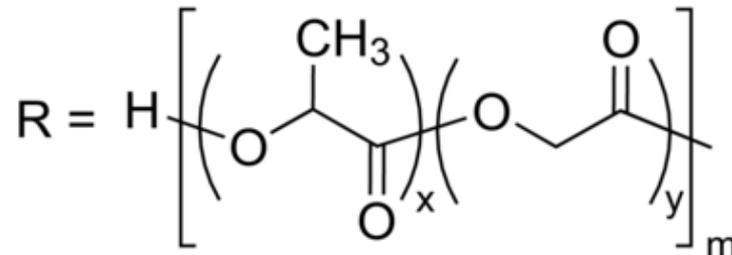
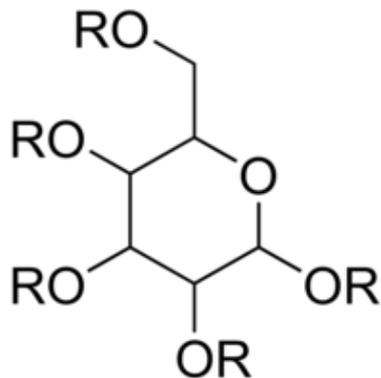
Case Study: Long Acting Injectables

- Complex Poly(lactic-co-glycolic acid) (PLGA) copolymer



x and y indicate the number of times each unit repeats.

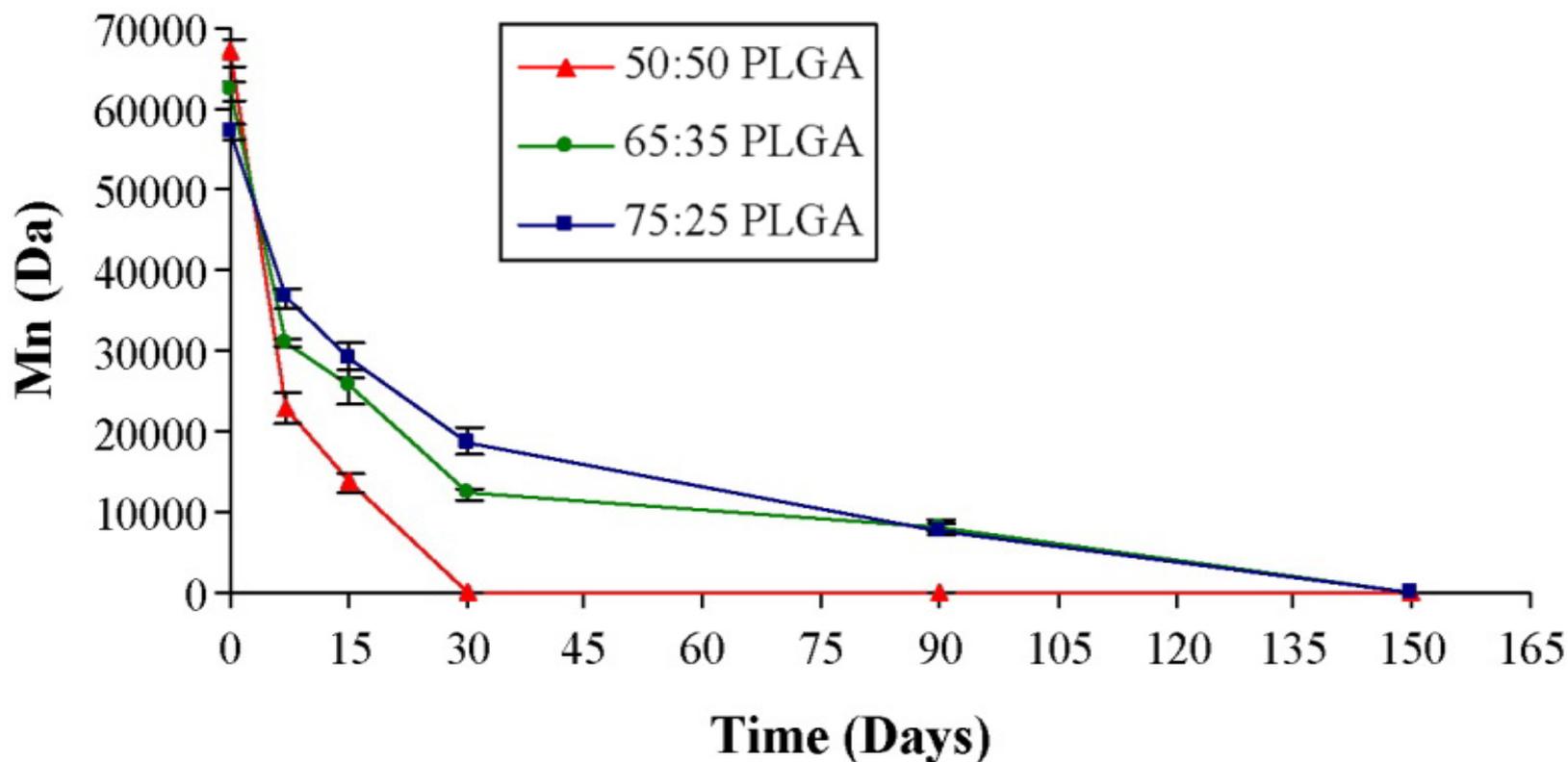
- Glucose star, lactic and glycolic acids copolymer



Case Study: Long Acting Injectables



- Effect of PLGA L:G monomer ratio on hydrolysis

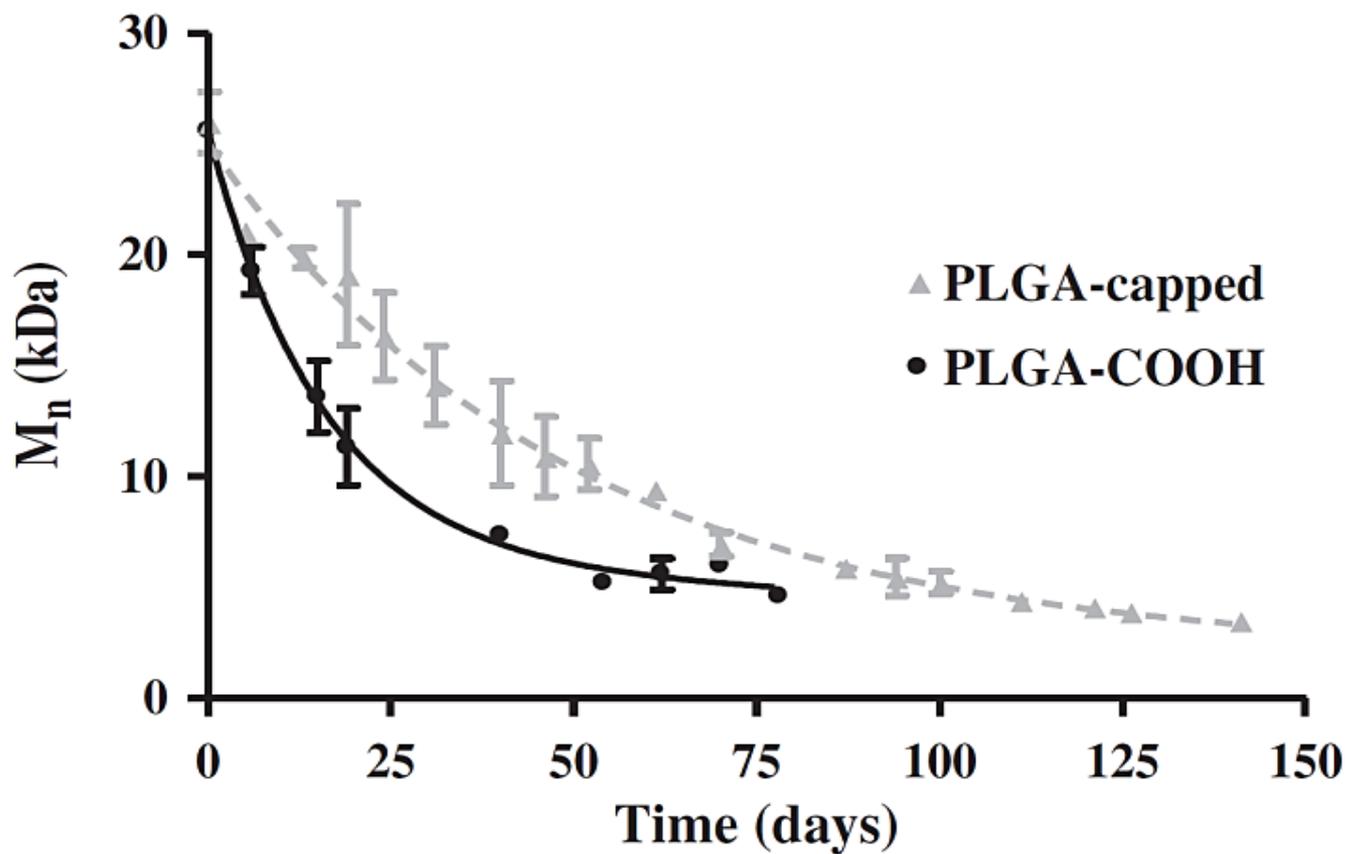


Results published in Engineer, et al. (2011) Effect of copolymer ratio on hydrolytic degradation of poly(lactide-co-glycolide) from drug eluting coronary stents. *Chemical Engineering Research & Design*. 89(3):328-334 DOI: 10.1016/j.cherd.2010.06.013

Case Study: Long Acting Injectables



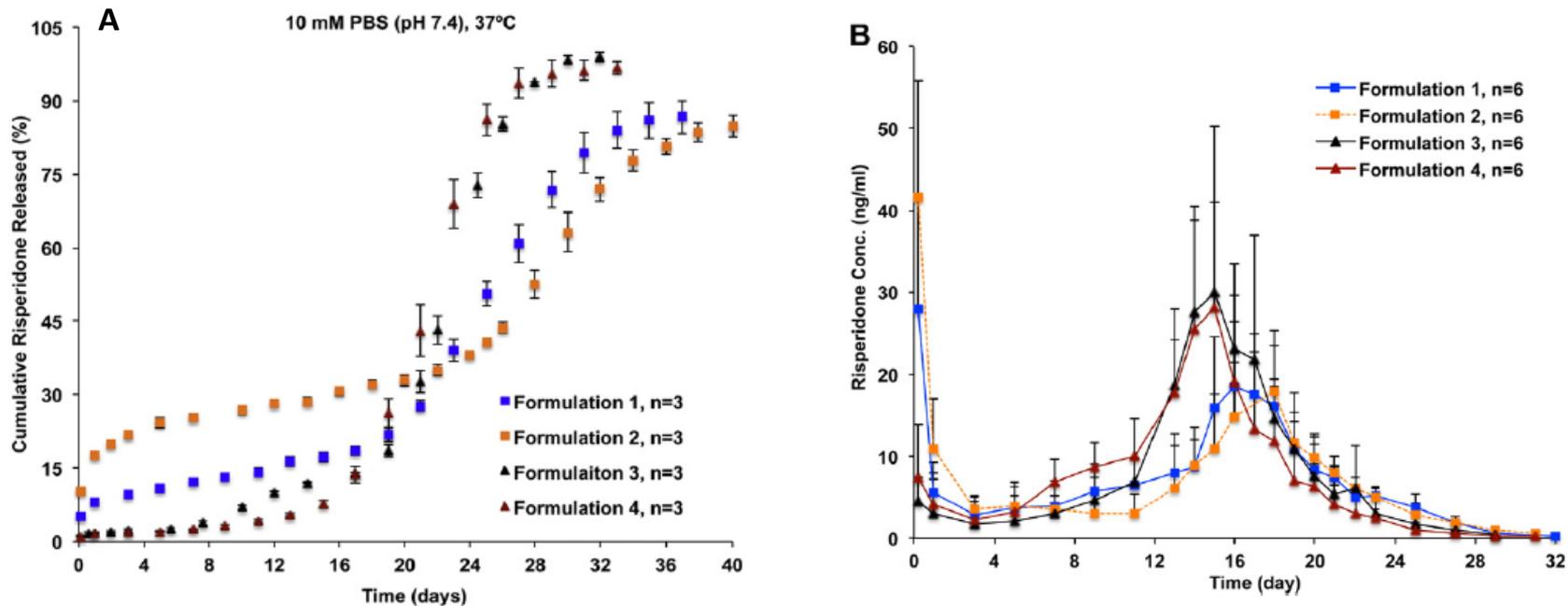
- Effect of PLGA lauryl end-capping on hydrolysis



Case Study: Long Acting Injectables



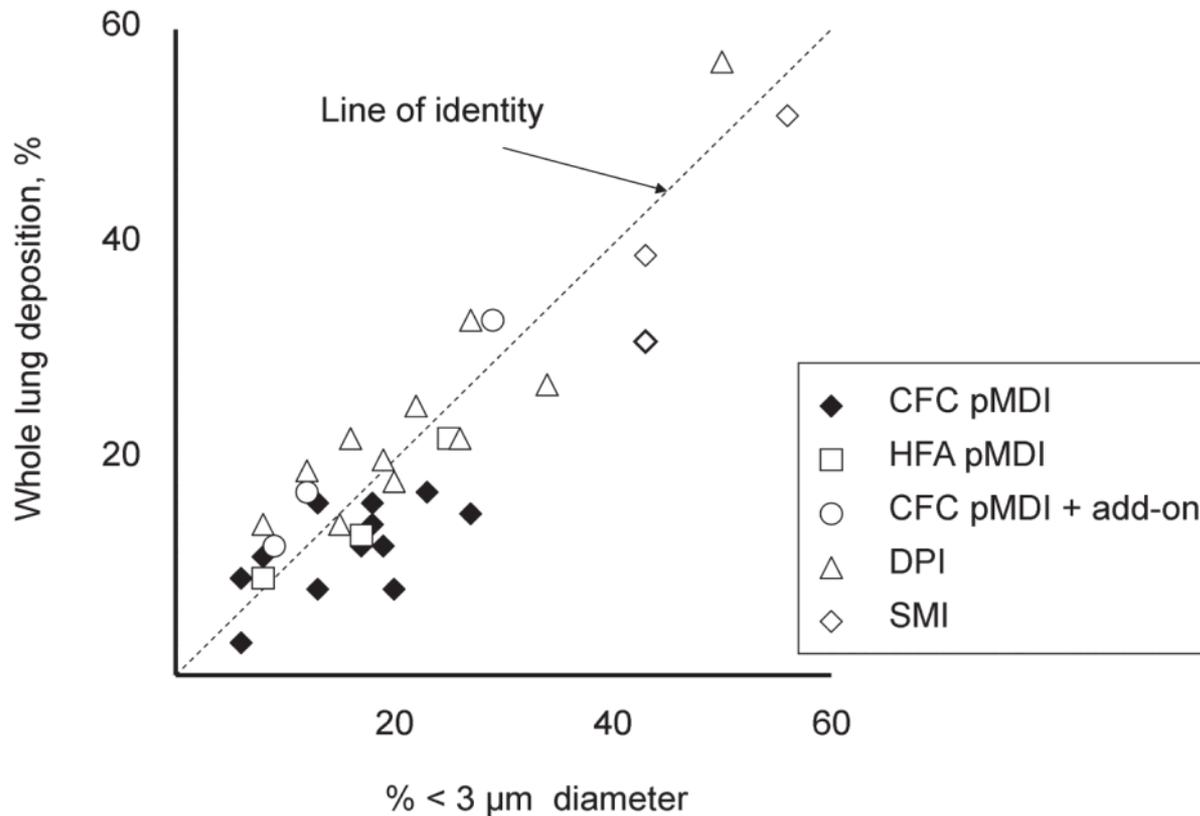
- Effect of PLGA formulation on bioavailability



(A) In vitro release profiles in USP 4 method at 37°C in 10 mM PBS (pH 7.4), and (B) mean rabbit plasma concentration-time profiles following IM administration. Formulations 1-4 are risperidone PLGA microspheres with manufacturing differences.

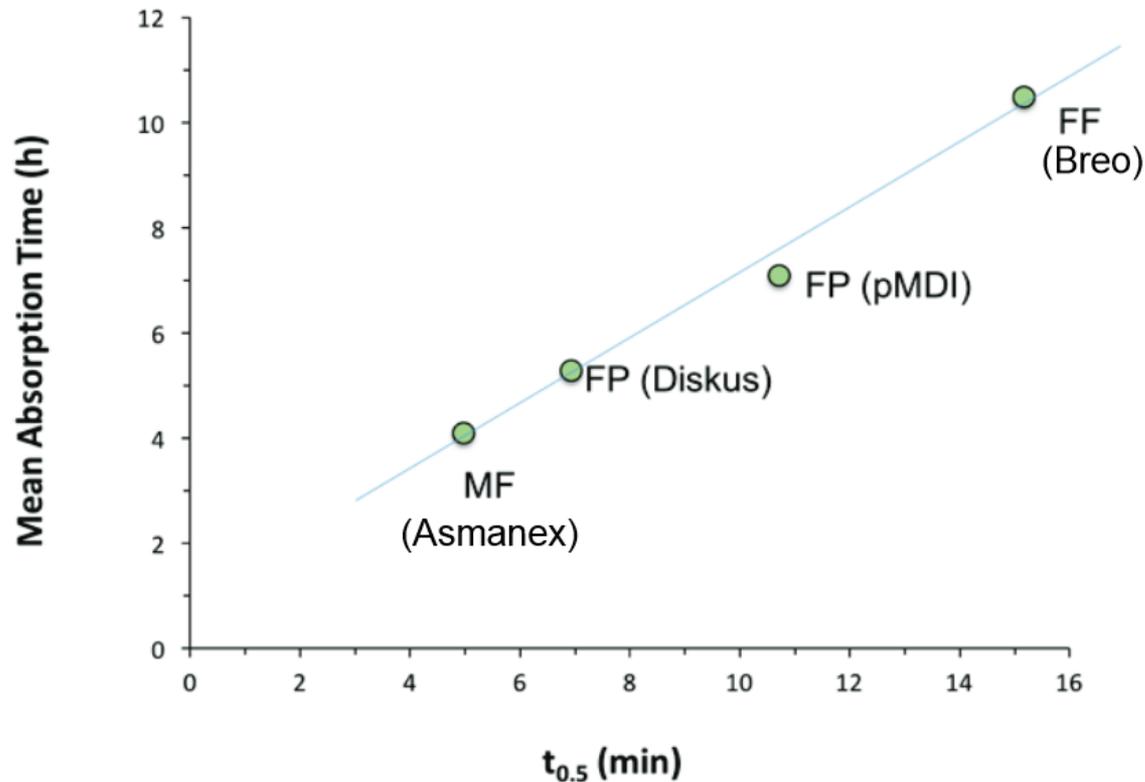
Case Study: Inhalers

- Effect of fine particle mass on lung deposition



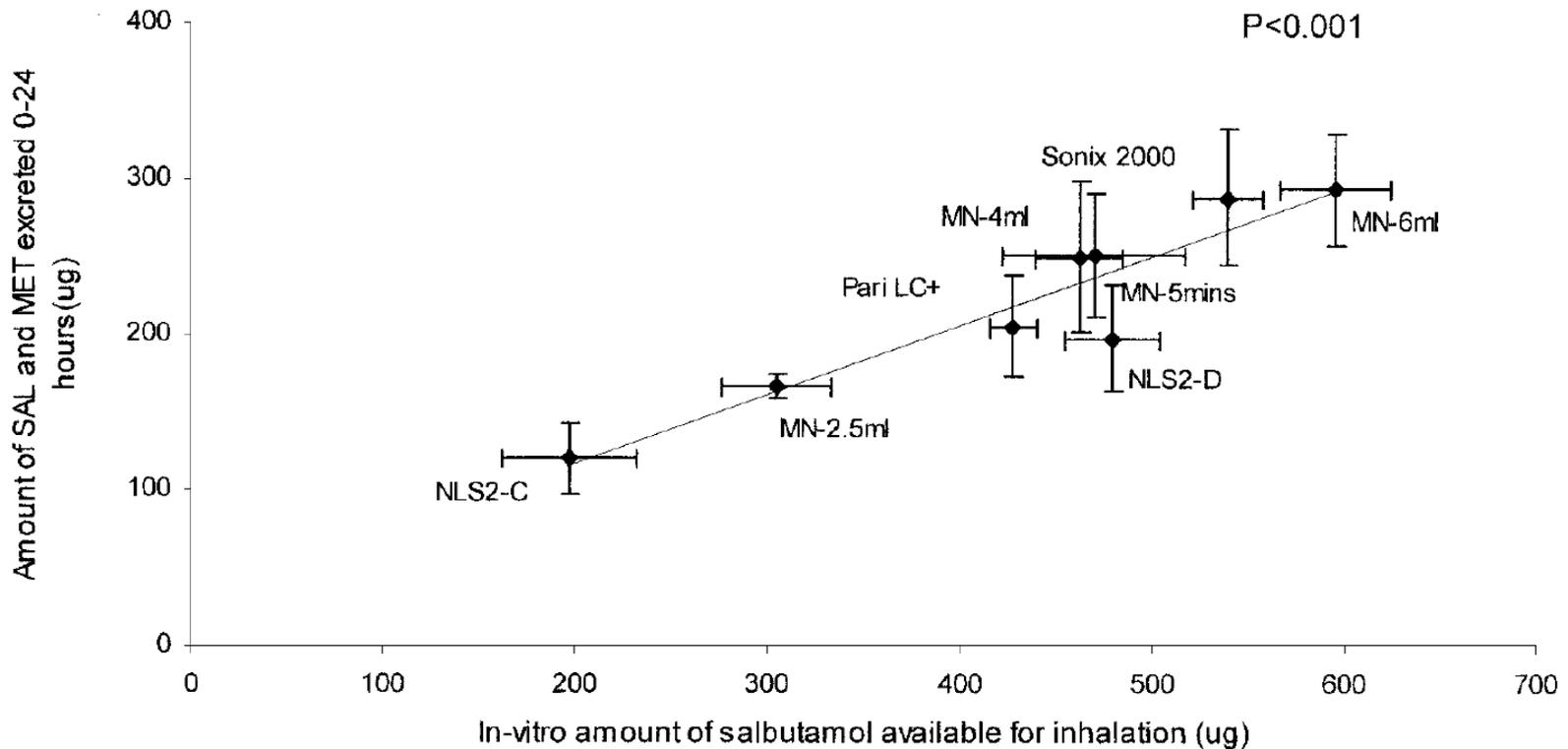
Case Study: Inhalers

- Effect of fine particle dissolution half-life on bioavailability of poorly soluble drugs



Case Study: Vaporizers

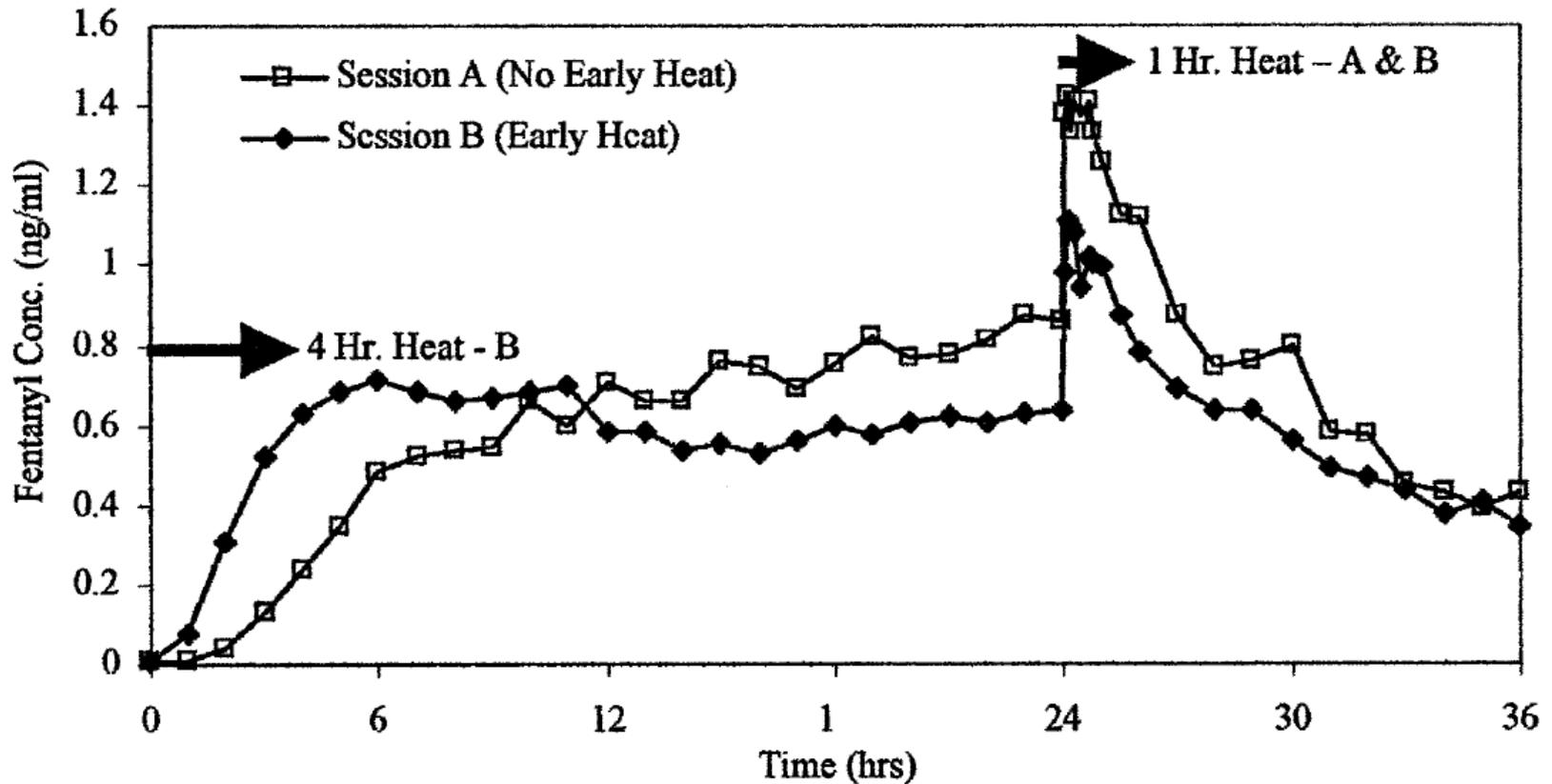
- Effect of dose available for inhalation on bioavailability to the lung



Results published in Silkstone et al. (2002) An Investigation of In Vitro/In Vivo Correlations for Salbutamol Nebulized by Eight Systems. *Journal of Aerosol Medicine*. 15(3):251-259

Case Study: Transdermal Patches

- Effect of heat on bioavailability

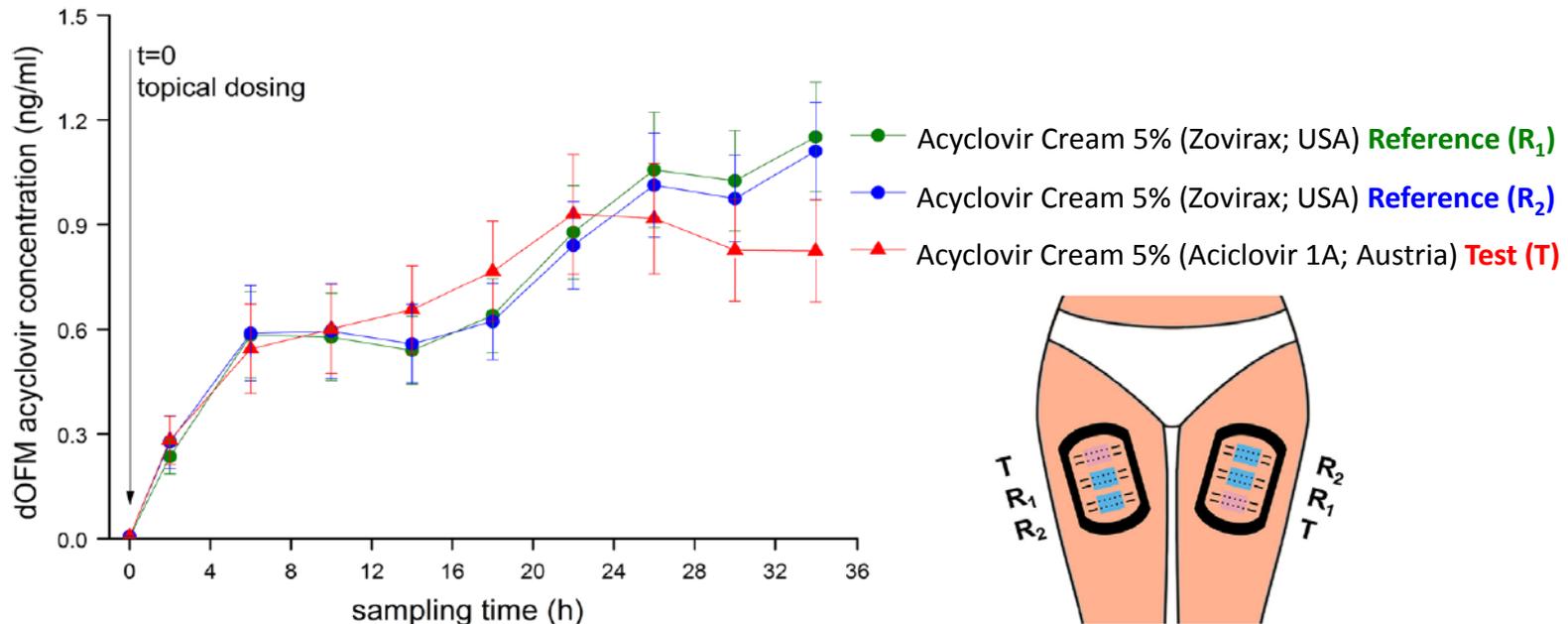


Results published in Ashburn et al. (2003) The Pharmacokinetics of Transdermal Fentanyl Delivered With and Without Controlled Heat. *The Journal of Pain*. DOI: 10.1016/S1526-5900(03)00618-7.

Case Study: Topical Semisolids

- Effect of Q3 properties bioavailability

Acyclovir Cream 5% Products:	Zovirax (USA) Reference (R)	Aciclovir-1A (Austria) Test (T)
Water Activity	0.75	0.95
Drying Rate (Time to 30% Loss)	>12h	<1h
Drug in Aq (mg/g)	0.49	0.26



Results courtesy of Professor Narasimha Murthy (in vitro) and Dr. Frank Sinner (in vivo). Results presented at The American Association of Pharmaceutical Scientists 2015 Annual Meeting Symposium: Bio-Equivalence Standards for Topicals (BEST). Funding for this project was made possible, in part, by the FDA through research awards FD005223 (in vitro) and FD004946 (in vivo). In vivo results published in Bodenlenz et al. (2016) Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence. *Clinical Pharmacokinetics*. DOI: 10.1007/s40262-016-0442-z

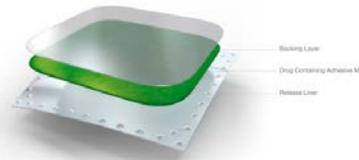
Equivalence Concepts

- **Pharmaceutical Equivalence (PE)**
 - Same active ingredient(s) and
 - Same dosage form and
 - Same route of administration and
 - Same strength
- **Bioequivalence (BE)**
 - Pharmaceutical equivalence and
 - Comparable bioavailability (rate and extent at site of action)
- **Therapeutic Equivalence (TE) of Generic Products**
 - Generics rely on the safety and efficacy of the reference product
 - Generics must have adequate labeling and cGMP manufacturing
 - Generics must demonstrate PE and BE to the reference product

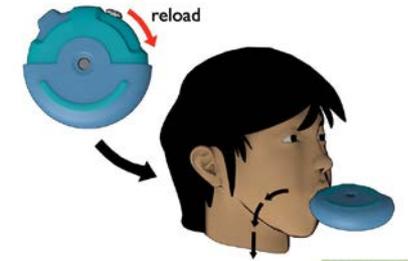
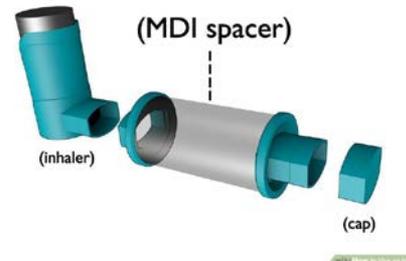
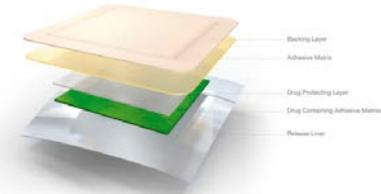
Pharmaceutical Equivalence

- Generics must be the same: **Dosage Form**
- But, complex products might have different:
 - Product design?
 - TDS/Patches (Reservoir/Matrix)
 - Inhalers (DPI/MDI/SMI)
 - Nebulizers
 - Injectors
 - Operational steps?
 - Size or shape?
 - Compliance and medication error issues?

Monolithic Matrix-TTS



Matrix-TTS with Overlapping Backing layer



Pharmaceutical Equivalence

- Generics must have the same: **Active Ingredient**
- But, complex products might have different:
 - Adhesives, excipients, impurities, penetration enhancers?
 - Patient exposure to impurities in the formulation?
 - Irritation/sensitization/adhesion performance?
 - Heat effects due to product design & composition?
 - Taste, smell, feel, etc. affecting patient compliance?
 - (Aerodynamic) particle size distribution?
 - PLGA copolymer monomer ratios or branching?
 - Stability, dissolution, bioavailability, or other issues?

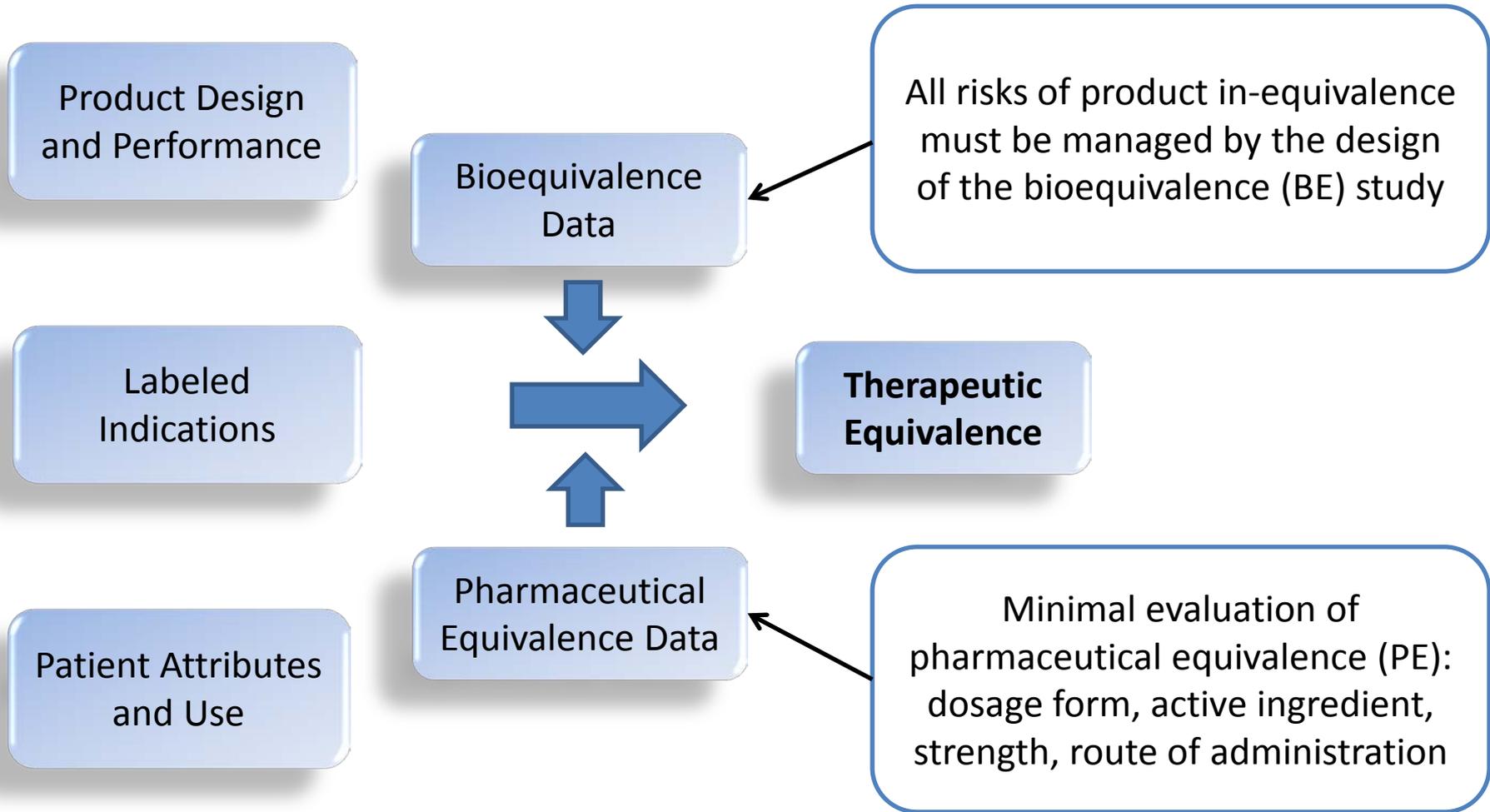
Pharmaceutical Equivalence

- Generics must use same: **Route of Administration**
- But, complex products might have different:
 - Bioavailability from different anatomical sites?
 - Adhesion on different anatomical sites?
 - Heat effects in response to heated car seats or blankets?
 - Airflow resistance or inhalation synchronization issues?
 - Biodistribution profile in the lung or at the injection site?
 - Bioavailability profile due to solubility or dissolution?
 - Patient pain or discomfort following administration?
 - Patient compliance or medication errors?

Pharmaceutical Equivalence

- Generics must have the same: **Strength**
- But, complex products might have different:
 - Drug load in the product?
 - Residual drug excess following product use?
 - Measures of strength as evaluated by different methods?
 - Overdose risks due to drug load, formulation and design?
 - Delivered dose uniformity (single actuation content)?
 - Drug stability and product shelf life?
 - Abuse deterrent properties?

Old Paradigm of Equivalence



Equivalence of Complex Products



- Regulatory Science Challenges:
 - To align BE study recommendations and essential product quality characterizations as part of therapeutic equivalence evaluation
 - To evolve pharmaceutical equivalence from evaluating simply “*is this dosage form an emulsion*” to broader physicochemical and functional product characteristics that matter to patients for equivalence and successful generic substitution

New Concept for Equivalence: Q3



Classifying Aspects of Product Quality (“Q” Terminology)

- Q1 = characterizes the components
- Q2 = characterizes the specific concentrations of those components
- Q3 = characterizes the physicochemical properties and the arrangement of matter in the drug product, which could be associated with potential therapeutic equivalence failure modes

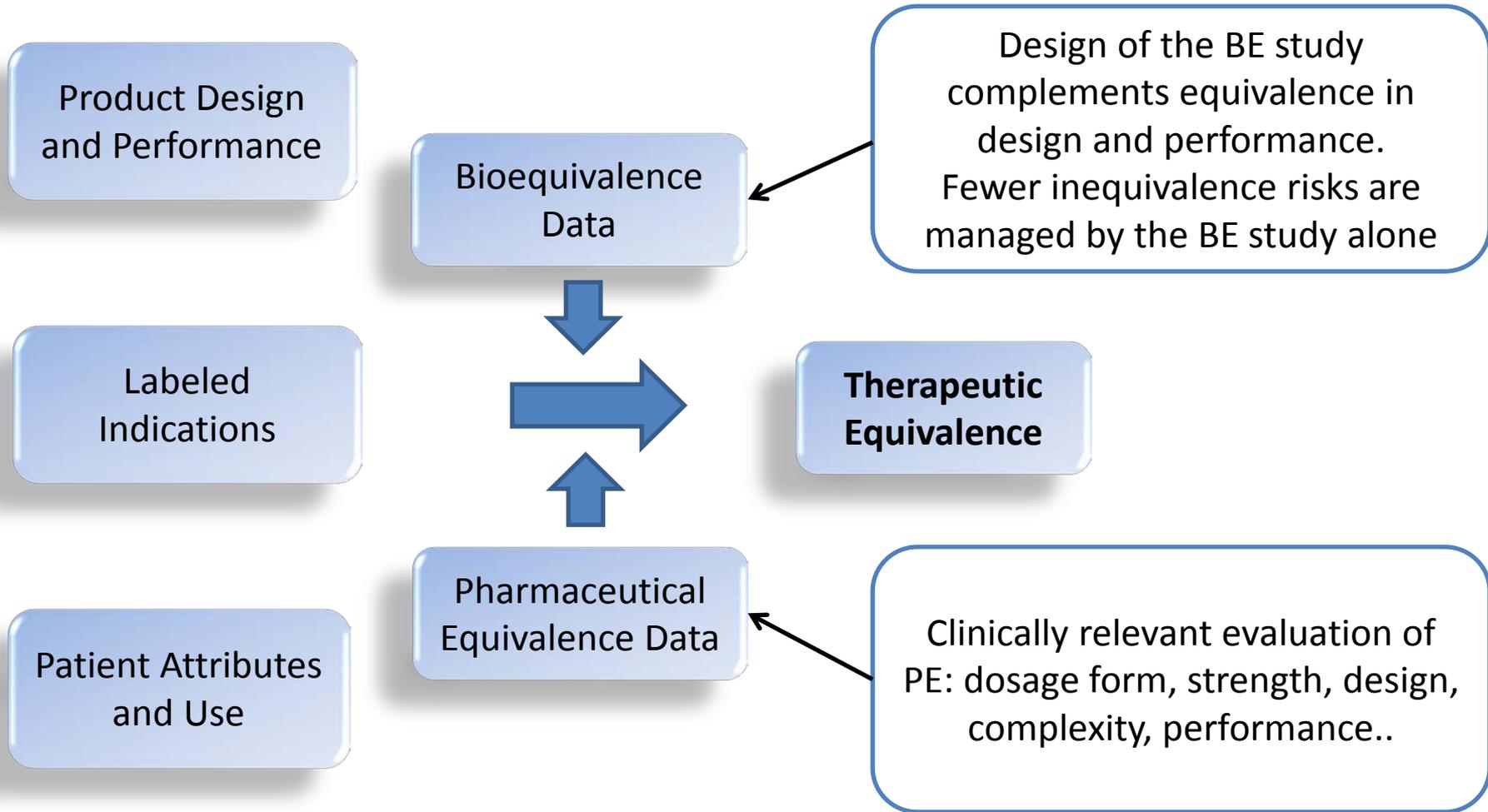
Examples of Characterizations to Evaluate Q3

- metamorphosis of the drug product following dose administration
- molecular heterogeneity of the active or inactive ingredients
- rheological behavior of the drug product or its components
- design features of the drug product’s dispenser or device
- (aerodynamic) particle size distribution of the drug
- release rate of the drug from the drug product
- polymorphic form(s) of the active ingredient

Linking Q3 to Failure Modes

- Differences in any of numerous physicochemical properties may alter product performance
- For example, pH alone can influence
 - Ionization state(s) of the drug(s)
 - Polymorphic form(s) of the drug(s)
 - Particle size distribution of the drug(s)
 - Stability of the drug (s) in the drug product
 - Solubility of the drug(s) in phases of the formulation
 - Distribution of drug(s) in the product microstructures
 - Ratio of dissolved to undissolved drug(s)
 - Dosage form properties and metamorphosis in vivo
 - Drug deposition/release/delivery and bioavailability
 - Patient use considerations and perceptions of quality

New Paradigm of Equivalence



Scientific Challenges

- To define concepts for physicochemical functions in a dosage form and then profile these properties to characterize the complexity of a dosage form
- To determine which physicochemical attributes are associated with specific failure modes and are therefore critical to product performance
- To establish functional ranges for each quality attribute within a larger product design space
- To control product design, formulation and manufacture to ensure therapeutic equivalence
 - **From batch to batch & throughout the product lifecycle**

Summary

- Consider the patient's needs and expectations
- Consider how to characterize the physicochemical properties and the complexity of the product
- Consider the relationship between quality attributes and potential failure modes, individually and collectively
- Consider dynamic ranges of conditions during formulation, manufacture, packaging, storage, dispensing, dosing, and metamorphosis in vivo
- Consider appropriate test methods for specific product qualities in relevant contexts, throughout QbD and as part of a program to fully characterize and control the product performance and therapeutic equivalence



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