



Pharmaceutical Science for Generic Drugs: The Science of Equivalence

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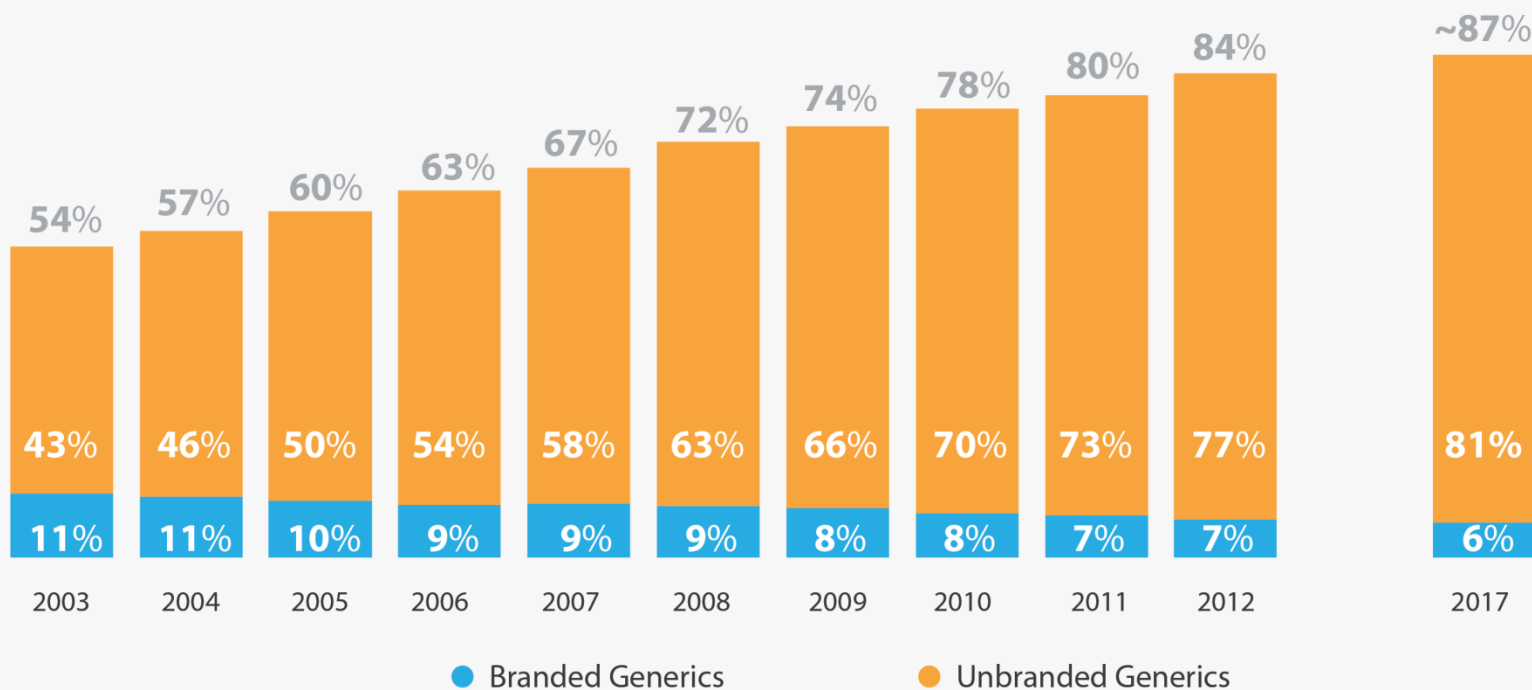
Office of Generic Drugs

Center for Drug Evaluation and Research, FDA

Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration (FDA).

Impact of Generic Drugs



Modernize Generic Drug Manufacturing

- Generic industry should be the manufacturing experts
- Meet the same quality standards as brand products
- Alleviate drug shortages or price spikes due to limited supply

CDER Offices in One Word

- OND: Efficacy
- OSE: Safety
- OPQ: Quality
- OGD: Equivalence

Promises about Generic Drugs

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

What is the Science of Equivalence?

- Science of bridging
 - product A works as well as product B
- Generic drugs are affordable because we usually do not repeat clinical studies in patients
- Generic drugs are intended to be used by patients
- The science of therapeutic equivalence is to combine
 - In vivo and in vitro performance data
 - Product design
 - Patient characteristics and product use
- To ensure successful generic substitution

Determinants of Therapeutic Equivalence

Product Design and Performance

Labeled Indications

Patient Attributes and Use

What is Evaluated in an ANDA

Bioequivalence Studies



Pharmaceutical Equivalence

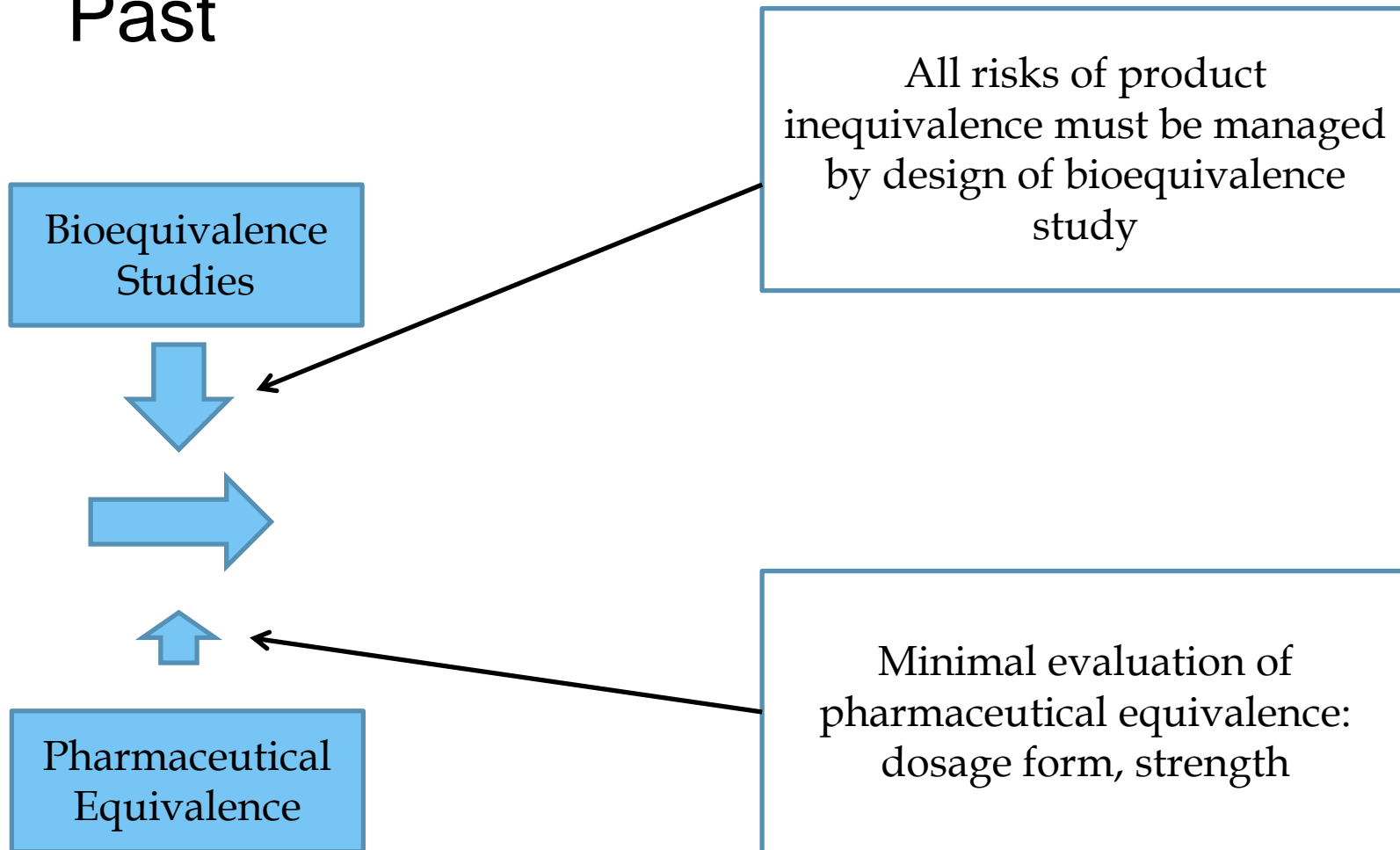
The Goal

Therapeutic Equivalence

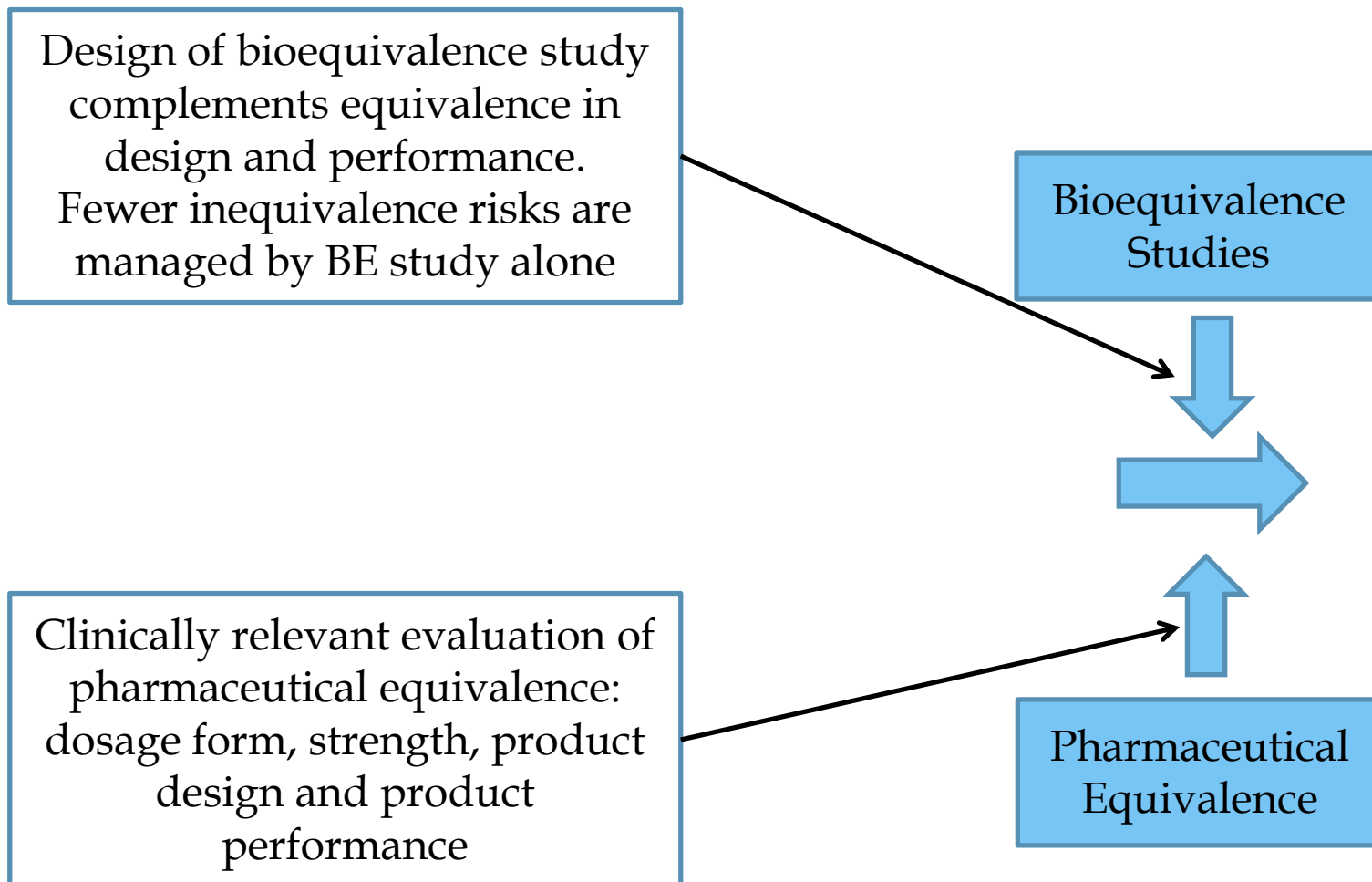
Therapeutic Equivalence of Complex Products

- **Challenge:** to align recommended bioequivalence studies and essential quality attributes as part of therapeutic equivalence evaluation
- **Challenge:** evolve pharmaceutical equivalence evaluation from *is this a emulsion* to quality attributes that matter to patients and successful generic substitution

Past



Future



Design of bioequivalence study complements equivalence in design and performance. Fewer inequivalence risks are managed by BE study alone

Bioequivalence Studies

Clinically relevant evaluation of pharmaceutical equivalence: dosage form, strength, product design and product performance

Pharmaceutical Equivalence

GDUFA and the Science of Equivalence

- How is GDUFA advancing pharmaceutical science for generic drugs?
- Research to make generic versions available in all product categories and for all available RLDs, including products that have unique characteristics.
- Office of Generic Drugs spends an increasing amount of time reviewing and developing policy for complex drug products, and future generic products will need to demonstrate equivalence to increasingly complex RLDs.
- Engagement: 75 external collaborations: over 200 pharm scientists who now have work on generic drug issues in their experience

GDUFA

FY 2014 Regulatory Science Accomplishments

- Continuing External Collaborations
 - 20 of 30 ongoing projects received additional resources
- New External Collaborations
 - 33 New Grants, 2 New Contracts for \$20 million in Regulatory Science
- New Internal Collaborations
 - FDA lab (7 internal projects \$1 million)
 - 20 new ORISE fellows for Generic Drug Research (10 to FDA lab)
- New Plan for FY 2015 Regulatory Science
 - Public Meeting and comments there and to the docket

GDUFA

FY 2015 Regulatory Science Priorities

<http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM417234.pdf>

- Post-market Evaluation of Generic Drugs
- Equivalence of Complex Products
- Equivalence of Locally Acting Products
- Therapeutic Equivalence Evaluation and Standards
- Computational and Analytical Tools

What are Complex Generic Drugs?

- **Complex Active Ingredients**
 - LMWH, peptides, complex mixtures, natural source products
- **Complex Formulations**
 - Liposomes, iron colloids, nanomaterials, emulsions
- **Complex Route of Delivery**
 - Locally acting drug products
- **Complex Drug-Device Combinations**
 - DPI, MDI, nasal spray, transdermal system
- **Complex Drug Release Profile**
 - Modified release drug products

Complex Drugs ...

- Can have Generics (ANDA Approvals)
 - Budesonide inhalation suspension (2009) [in vitro only]
 - Enoxaparin (2011)
 - Sodium Ferric Gluconate (2011)
 - Doxorubicin HCl liposome injection (2013)
 - Acyclovir topical ointment (2013) [in vitro only]
 - Glatiramer Acetate (2015) [in vitro only]
- Can be Controversial
 - Citizen petitions on all of these
- Are More Work than Other ANDA
 - More complex development
 - Longer reviews that impact GDUFA goals
 - One of the reasons for GDUFA support of regulatory science
- Demand New Thinking about Equivalence
 - Pharmaceutical equivalence and Bioequivalence
 - Q3 characterization instead of clinical endpoint bioequivalence

Highlights of Work in Progress

- **Complex Active Ingredients**
 - LMWH, peptides, complex mixtures, natural source products
 - Multivariate data analysis for complex mixtures in collaboration with FDA labs and external grantees
- **Advancing In Vitro Equivalence Methods for Complex Formulations**
 - 7 grants on semi-solids for topical or ocular delivery
 - 6 grants on liposomes/sustained release implants
- **Complex Drug-Device Combinations**
 - DPI, MDI, nasal spray, transdermal system
 - Adhesion for transdermal systems

Highlights of Work in Progress

- Topical Dermatological Products
 - Six coordinated grants (international: US, Europe, Australia) that include
 - New in vivo data
 - Manufacturing of semi-solid formulations
 - Characterization of semi-solid formulations
 - New PBPK modeling approaches
- Inhalation Products
 - Role of dissolution, particle size and PK studies
 - CFD modeling of deposition
- Ophthalmic Products
 - Seven coordinated grants on in vitro characterization, drug release, and drug delivery modeling
- Nasal Products
 - Use of PK studies alone for BE: in vitro, in vivo and modeling projects

Highlights of Work in Progress

- Pathway for generic versions of abuse-deterrent formulations
 - October 2014 Public Meeting
- Risk-based equivalence standards for narrow therapeutic index (NTI) drugs
 - Methods for identifying NTI drugs and ensuring risk-based BE and product quality standards
- Equivalence of modified release solid oral dosage forms
 - Value of replicate design BE studies, pAUC and IVIVC

Highlights of Work in Progress

- FDA lab
 - Formulation development and characterization
 - CY 2014: 24 completed lab projects to support generic drug program
- Modeling and simulation tools for the evaluation of generic drug equivalence
 - 7 grants on PBPK for non-oral delivery routes
 - 4 grants on pharmacometrics for generic drugs

Results

- **Complex Product Guidance**
 - Conjugated Estrogens Tablets (Dec 2014)
 - Liposomal Injections: Verteporfin and Daunorubicin Citrate
 - Sublingual Film: Buprenorphine hydrochloride; Naloxone hydrochloride
 - Transdermal ER films: Buprenorphine and Estradiol
 - IUD: Levonorgestrel
 - Subq injection: Lanreotide acetate (nanomaterial injection)
 - Sevelamer Carbonate: Recommended characterization
 - NTI: tacrolimus ER, phenytoin, levothyroxine, carbamazepine
- **Locally Acting Drug Guidance**
 - Menthol Methyl Salicylate Topical Patch (PK bioequivalence)
 - Prednisolone Acetate Ophthalmic suspension
 - Brinzolamide Ophthalmic suspension
 - Mesalamine DR capsules
 - Sucralfate Oral Suspension
 - Budesonide Tablet Draft Guidance (PK bioequivalence)

New Concept for Equivalence: Q3

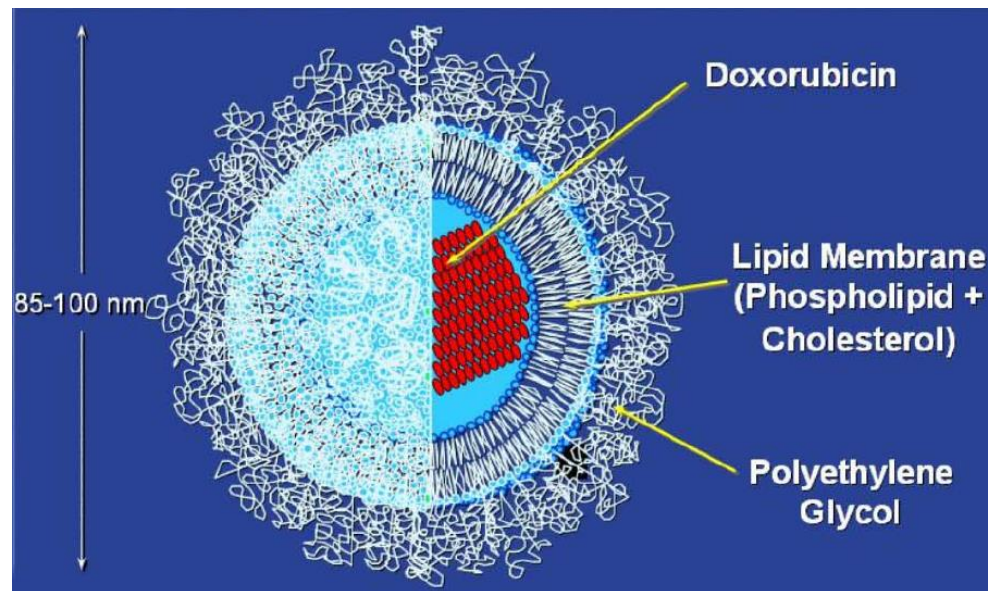
- Classify product similarity
 - Q1: Same components
 - Q2: Same components in same concentration
 - Q3: Same components in same concentration with the same arrangement of matter (microstructure)
- Q3 Physiochemical Properties
 - Appearance
 - pH
 - Globule Size Distribution
 - Rheological behavior
 - Drug Release (IVRT)
 - Drug Polymorphic Form
 - Drug particle size distribution
 - Specific Gravity

Equivalence for Q1 and Q2 Identical

- Uncertainty Due to Differences in Manufacturing
 - Is the rheology the same?
 - Is the solubility of the drug in the formulation the same?
 - Are excipients released at same rate?
 - Is particle size the same? (suspensions)
- Path Forward
 - In vitro tests are the best evaluation method for manufacturing process
 - Rheology
 - In vitro release (diffusion cell)
 - Particle size (suspension) or droplet size
- Precedent:
 - Budesonide inhalation suspension (BE on particle size, no in vivo studies),
 - Acyclovir topical ointment,
 - Cyclosporine Ophthalmic Emulsion (draft guidance)

Liposomes

- Draft BE recommendation for Doxil posted in 2010: First ANDA approved in 2012



- Other Liposome Guidance posted
 - Amphotericin B, Daunorubicin citrate, Verteporfin

Liposome Product Guidance

- In vivo BE study
 - Measure both free and encapsulated drug
- In vitro BE study
 - Demonstrate equivalence of particle size distribution
- Recommended characterization
 - Lipid excipients
 - Liposome composition and size
 - Internal environment
 - Liposome morphology and number of lamellae
 - Lipid bilayer phase transitions
 - Electrical surface potential or charge
 - In vitro leakage under multiple conditions

Three for the Future of NIPTE

- Ensure modern manufacturing for the 5 out of 6 products that are generics
- Advance the science of equivalence:
 - Prioritize tools and science that make equivalence evaluation clear and development easier
 - Product design for human use
- Engage with GDUFA regulatory science