Novel Methods of Demonstrating Pharmaceutical Equivalence and Bioequivalence for Complex Drug Products

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Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration (FDA).
New Office of Research and Standards within OGD

• Division of Therapeutic Performance (DTP)
  - Facilitates pre-ANDA development of generic drugs
  - Conducts and promotes regulatory science research to establish standards to ensure therapeutic equivalence of generic versions of drug products.
  - Evaluates post-approval safety, product use and bioequivalence issues with approved generic drugs.

• Division of Quantitative Methods And Modeling (DQMM) –
  - Establishes predictive and physiological models of drug product performance, drug absorption, drug pharmacology, and other quantitative methods to ensure generic drug equivalence.
  - Develops new tools to analyze in vitro, pharmacokinetic, pharmacodynamics and clinical bioequivalence studies.
Office of Research and Standards Leadership Team

• Rob Lionberger, Acting Director ORS
• Wenlei Jiang, Acting Deputy Director ORS
• Larissa Lapteva, Acting Director DTP
• Rob Lionberger, Acting Director DQMM
• Thushi Amini, Research Coordinator
• Kris Andre, Scientific Coordinator
Office of Research and Standards Scientific Leaders

Transforming Research into Standards

• Lucy Fang
  – PK/PD models, NTI drugs
• Susie Zhang
  – Absorption models
• Jeff Jiang
  – Peptides and complex mixtures
• Sam Raney
  – Topical and transdermal products
• Bavna Saluja
  – Inhalation and nasal products, Abuse deterrent formulations
• Stephanie Choi
  – Complex drug products, Ophthalmic products
• Yih Chain Huang
  – Bioequivalence guidance development
What are Complex Generic Drugs?

• Complex Active Ingredients
  – LMWH, peptides, complex mixtures, natural source products

• Complex Formulations
  – Liposomes, iron colloids, nanomaterials

• Complex Route of Delivery
  – Locally acting drugs

• Complex Drug-Device Combinations
  – DPI, MDI, nasal spray, transdermal system
Complex Drugs ...

• Can have Generics (ANDA Approvals)
  – Enoxaparin (2011)
  – Sodium Ferric Gluconate (2011)
  – Doxorubicin HCl liposome injection (2013)
  – Acyclovir topical ointment (2013)

• Can be controversial
  – Citizen petitions on all of these
  – International differences (clinical studies for EMA)
  – Efforts to define non-biological complex drugs as a new category outside ANDA pathway

• Are more complex than other ANDA
  – More complex development
  – Longer reviews that impact GDUFA goals
  – One of the reasons for GDUFA support of regulatory science
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


• Post-market Evaluation of Generic Drugs
• Equivalence of Complex Products
• Equivalence of Locally Acting Products
• Therapeutic Equivalence Evaluation and Standards
• Computational and Analytical Tools
FY 2013 GDUFA Research Awards for Complex Products

- In vitro release tests for transdermal drug delivery systems
- In vitro-In vivo correlations of parenteral microsphere drug products
- Development of bio-relevant in-vitro assay to determine labile iron in the parenteral iron complex product
- Evaluation of dissolution methods for complex parenteral dosage forms (liposomes)
- In vitro release tests for topical dermatological products
- In vitro-In vivo correlations of ocular Implants

- Systematic evaluation of excipient effects on the efficacy of metered dose inhaler products
- Development of in vivo predictive dissolution method for orally inhaled drug products
- Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action
- Pharmacokinetics of locally acting orally inhaled drug products
FY 2014 GDUFA Research Awards for Complex Products

- Physiologically-Based Absorption and Pharmacokinetic Modeling and Simulation for Non-Gastrointestinally-Absorbed Drug Products in Humans
  - Dermal, Ocular, Nasal, Pulmonary, Liposomal
- Development of a Clinically Relevant In Vitro Performance Test for Generic Orally-Inhaled Drug Products
- Dissolution Methods for Suspension and Emulsion Ocular Drug Products
- Dissolution Methods for Semisolid Ocular Drug Products
- Dissolution Methods for Microsphere and Implant Drug Products
- Characterization of Critical Quality Attributes for Semisolid Topical Drug Products
- Evaluation of Plasma NTBI levels in Healthy Subjects Treated with Generic and Reference Sodium Ferric Gluconate
- Effect of Different Preparation Methods on the In Vitro and In Vivo Performance of Solid Dispersion Formulations
- Evaluation of In Vitro Release Methods for Liposomal Drug Products
- Development of an Integrated Mathematical Model for Comparative Characterization of Complex Molecules
Recent Guidance on Complex Generics

• Metered Dose Inhaler (April 2013)

• Dry Powder Inhaler (Sept 2013)

• Ophthalmic Emulsion (June 2013)

• Liposomal Injection (Feb 2010)
Q3 EQUIVALENCE
Why are Topical Products Complicated?

• Complexity
  - Semi-Solid dosage forms
  - Complex structure of skin
  - Product components affect skin
  - Disease state can change skin

• Failure Modes
  - Application
  - Formulation
  - Physiology

• Application
  - Different spreading on the skin
  - Different area/duration of exposure

• Formulation
  - Drug does not leave formulation
  - Thermodynamic activity is different (suspension v. dissolved drug)

• Physiology
  - Formulations have different effects on stratum corneum
  - One formulation prefers follicular pathway
Topical Product Performance Tests

- **In Vitro** Release Test
- **In Vitro** Permeation Test
- Tape Stripping
- TEWL / Exfoliation
- Vasoconstriction / Irritation
- Microdialysis
BE Approaches for Locally Acting Products

• FDA has begun to make different recommendation for Q1 and Q2 formulations for other locally acting drugs: Vancomycin and Acarbose approvals

• For other locally acting products (inhalation products, GI acting) 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)

• Q3 Physiochemical Properties
  – Appearance
  – pH
  – Globule Size Distribution
  – Rheological behavior
  – Drug Release (IVRT)
  – Drug Polymorphic Form
  – Drug particle size distribution
  – Specific Gravity
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)

• Potential Path Forward
  – In vitro tests are the best evaluation method for manufacturing process
    • Rheology
    • In vitro release (diffusion cell)
    • Particle Size (suspension)

• Precedent: Budesonide inhalation suspension (BE on particle size, no in vivo studies)
Application to Topical Products

• Acyclovir Ointment
  - In vitro approach for Q1 and Q2 formulations

• Lidocaine Topical Path
  - PK study for bioequivalence
  - Patch size (area) must be the same
  - Not a topical dermatological product
    • Local pain relief (different site of action)

• Cyclosporine Ophthalmic Emulsion
  - In vitro approach for Q1 and Q2 formulations
IVPT vs. IVRT

• IVPT (Permeation)
  – Human Skin
  – Unoccluded Dose
  – Finite Dose
  – Flux Profile (Jmax, etc.)
  – Physiological Media
  – pg to ng Range
  – Product stays ‘dry’
  – IVIV Correlation
  – Donor Variability

• IVRT (Release)
  – Synthetic Membrane
  – Occluded Dose
  – Infinite Dose
  – Release Rate (slope)
  – Alcoholic Media
  – μg to mg Range
  – Product-Media Interface
  – Specific to the Formulation
  – Relative Consistency
Future Steps for Q3

• Guidance on IVPT and IVRT
  – Best Practice and Method Validation
• Particle size comparisons for Q3
• Location of Drug in multiphasic formulations
• RTR Guidance on Q3 bioequivalence approaches
• Evaluate how failure modes for semisolid drug products with complex microstructures might be addressed during (A)NDA review.
• Evaluate alternatives to manage total quality risks for complex products.
• Evaluate complementary use of tools for topical product lifecycle management
NANOMATERIALS
Iron Complexes

- Five parenteral iron formulations
  - ferric carboxymaltose, ferumoxytol, iron sucrose, iron gluconate and iron dextran

  - Iron Sucrose: 10.1 nm, Iron gluconate 11.3 nm
Iron Complex BE Recommendations

• In vivo BE study
• In vitro BE study
  – Particle size equivalence

• Recommended Characterization
  – Iron core characterizations including but not limited to core size determination, iron oxide crystalline structure and iron environment.
  – Composition of carbohydrate shell and surface properties.
  – Particle morphology.
  – Labile iron determination under physiologically relevant conditions. The tests can be performed with in vitro haemodialysis system 1, the catalytic bleomycin assay of spiked human serum samples 1,2, the spectrophotometric measurement of Fe reduction, or other methods that are validated for accuracy and precision.

Example Guidance: Iron Sucrose:
Liposomes

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

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

• **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
Paclitaxel (Abraxane®)

- Albumin coated nanoparticles
- Improved tolerance over paclitaxel
Paclitaxel BE guidance

• In vivo BE study
  – Free and total drug

• In Vitro Particle Size Distribution

• Characterization
  – particle morphology,
  – particle size,
  – surface potential,
  – paclitaxel crystallinity,
  – fraction of free and bound paclitaxel or albumin in reconstituted suspension,
  – nature of bond between paclitaxel and albumin,
  – in vitro release kinetics
  – Albumin characterization

Generic Nanomaterials: General Principles

• Q1/Q2 cannot ensure supramolecular structure sameness

• Conventional plasma pharmacokinetics may not fully reflect rate and extent of drug available at target sites
  – Total drug alone insufficient to demonstrate BE

• All parenteral or topical ANDAs containing nanosize materials of less than 100 nm in diameter are generally recommended to demonstrate that the test and reference products have equivalent particle size distribution.

• Extensive characterization

• Other product specific critical attributes should also be equivalent
PRE-ANDA PROCESSES
New BE Guidance Process

• BE guidance requests are not treated as controlled correspondence
  – FDA cannot produce a guidance in the 2 month control timeline

• Formal OGD process for prioritization of BE guidance development
  – One priority list for all of OGD; managed by DTP

• Long term goal is to have BE guidance available before ANDA submission
  – We are using number of ANDA submissions without BE guidance as a metric
Formal BE Guidance Process*

• A new approach coordinated among divisions and offices within OGD

• Serves:
  • immediate need to capture BE standards for submitted applications, and
  • long-term goal to develop BE standards for future submissions

• Prioritizes BE guidance development based on:
  • Public health needs for generic development
  • Formulation features and predictability of in vivo performance
  • Precedent history with similar formulations
  • Industry demand for generic development (inquiries received by OGD, future expiration of marketing exclusivity)
  • Feasibility of different approaches to demonstration of bioequivalence (e.g., PK/PD studies, clinical studies, in vitro approach)

*is currently under development
Filing Review: Alternative BE Method

• Under current RTR guidance (Sept 2014), if you submit an alternative BE approach to a posted guidance without justification you can receive an RTR
  - What is a good justification?
  - References scientific data to support that the proposed method is as good or better than the current method at supporting equivalence

• If proposing an alternative approach to an existing guidance, we recommend that you first submit an inquiry or meeting request to genericdrugs@fda.hhs.gov

• Submit comments to the BE guidance docket
What if there is no Guidance?

• Does the General BE guidance apply?
• Request Guidance via GenericDrugs@fda.hhs.gov mailbox
  - Do this as soon as you think guidance will be needed.
  - Your request will be considered in our BE development process
  - You will be acknowledge as “not a control” but we are tracking requests

• Provide input to the GDUFA regulatory science prioritization process
  - This is where FDA will invest resources to establish or evaluate new approaches

• For complex products consider a pre-ANDA meeting request to discuss your proposed approach
  - Do this after you have done substantial homework work
FY 2015 Public Meeting on GDUFA Regulatory Science

- GDUFA Regulatory Science Page
  - Source for updates

- FY 2015 Meeting
  - Q3 of FY 2015 at White Oak
  - Docket will be open
  - We would value more input from the generic industry
Shared Vision of Regulatory Science
Success for Complex Drugs

• Both FDA and Generic Industry Have a Common Customer
  – Patients who want high quality generic products in all product categories

• Pre-ANDA Discussion Can Advance Regulatory Science

• Pre-ANDA Discussion Should Lead to Better ANDA Submissions