GDUFA Regulatory Science

Robert Lionberger, Ph.D.
Deputy Director for Science (acting)
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA

GPhA/FDA CMC Workshop
June 5, 2013
MISSION OF OGD

Make safe and effective generic drugs available to the American public
Make safe and effective generic drugs available to the American public by ensuring that OGD standards (as reflected in reviews, guidance and communications to sponsors and the public) continue to be based on the best currently available science and the results of regulatory science research

---MISSION OF OGD SCIENCE---
Use the Best Available Science to Make High Quality Generic Products Available

• Respond to Citizen Petitions that challenge OGD science and policy
• Develop new approaches for equivalence of complex and locally acting products
• Ensure approved generics are therapeutically equivalent
• Advance OGD modeling, simulation and data analysis
• Collaborate with external experts via contracts and grants
• Implement GDUFA Regulatory Science commitments
Market Failure for Innovation

• GDUFA is the only user fee to directly support regulatory science
  – Why? Market failure for innovation investments
• For new drugs, innovation rewarded by product exclusivity
• For generic drugs, innovation rewarded by market access for other generic firms
• GDUFA support for Regulatory Science indicates
  – There is a public benefit to innovative generics
  – There is a benefit to industry as a whole
    • Generics in all product categories
    • Better product evaluation
    • Improved public confidence in generic substitution
GDUFA Regulatory Science Agreement

• Final agreement letter – September 7, 2011
  – FDA committed that in the area of regulatory science it will continue, and for some topics begin undertaking various regulatory science initiatives.

  – FDA agreed to convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by CDER Director.
GDUFA Regulatory Science
Current Progress

• OGD hired a Research Coordinator for GDUFA Regulatory Science (Thushi Amini)
• Identified a chair for the internal GDUFA Regulatory Science Working Group (Robert Lionberger)
• An open public meeting for input into 2014 Regulatory Science Priorities is scheduled for June 21, 2013
  - Webcast link: https://collaboration.fda.gov/regscipart15/
• A docket is open for input
  - Docket No. FDA–2013–N–0402
• Research activities related to each 2013 topic are underway
FY 2013 Topics

1. BE of local acting orally inhaled drug products
2. BE of local acting topical dermatological drug products
3. BE of local acting gastro-intestinal drug products
4. Quality by design of generic drug products
5. Modeling and simulation
6. Pharmacokinetic studies and evaluation of anti-epileptic drugs
7. Excipient effects on permeability and absorption of BCS Class 3 Drugs
8. Product- and patient-related factors affecting switchability of drug-device combination products
9. Postmarketing surveillance of generic drug usage patterns and adverse events.
10. Evaluation of drug product physical attributes on patient acceptability
11. Postmarking assessment of generic drugs and their brand-name counterparts
12. Physicochemical characterization of complex drug substances
13. Develop a risk-based understanding of changes in API manufacturing and controls
GDUFA
Regulatory Science Themes

• Access to Generic Drugs
  – Topics: 1,2,5,7,12

• Therapeutic Equivalence of Approved Generics
  – Topics: 6,8,9,10,11

• Quality of Generic Drugs
  – Topics: 4,12,13
Bioequivalence of Local Acting Orally Inhaled Drug Products

• Complex dosage forms consisting of formulation and device components
  • Defining device similarity for generic dry powder inhalers
  • Demonstrating equivalent local drug delivery in the lung

• Results
  – Extensive research investments to open generic pathway for inhalation products
  – The first individual product guidance for a DPI has an FR notice in clearance.
  – The first individual product guidance for a MDI has posted
Bioequivalence of Local Acting Orally Inhaled Drug Products

Previous Research

- Asthma stability model
  - Pilot study results suggest a possible dose-response effect for ICSs
  - University of Iowa, Iowa City, IA (completed)
- Exhaled nitric oxide (eNO) model
  - Literature and published studies suggest a possible dose-response effect for ICSs
  - National Jewish Health, Denver, CO (completed)
- PK based approach
  - Relationships between PK and local drug delivery in the lung are still not understood
  - University of Florida, Gainesville, FL (expected to be completed in Sept 2014)
- In vitro DPI studies
  - Evaluation of formulation and device factors that can be modified to yield equivalent performance
  - Cirrus Pharmaceuticals, Durham, NC (Completed)
  - University of Bath, Bath, UK (Completed)
- Modified Chi-Square Ratio approach (completed)
- Modeling and simulations
  - Investigation of lung deposition for locally acting inhaled drugs by computational fluid dynamics
  - Virginia Commonwealth University, Richmond, VA (expected to be completed in Sept. 2014)
Bioequivalence of Local Acting Orally Inhaled Drug Products

New Research

• Development of in vivo predictive dissolution method for orally inhaled drug products
  – Open now: multiple awards

• Systematic evaluation of excipient effects on the efficacy of metered dose inhaler products
  – Open now

• Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action
  – Upcoming announcement in FY2013

• Pharmacokinetics of locally acting orally inhaled drug products
  – Upcoming announcement in FY2013
Bioequivalence of Local Acting Topical Dermatological Drug Products

• Results: New bioequivalence approaches in guidance and defended in citizen petitions
  – Lidoderm Patch:
    • PK based equivalence for a topical product
  – Acyclovir Ointment
    • Characterization based equivalence for formulations with same concentrations of same inactive ingredients

• Ongoing: Dermal Microdialysis
  – direct measure of drug in dermis, subject dosing complete, sample analysis underway

• New: In vitro release tests for topical dermatological products
  – Open now: multiple awards
Bioequivalence of Local Acting Gastro-intestinal Drug Products

• **Results**
  - 2012 vancomycin approvals based on in vitro dissolution
  - 2012 guidances for mesalamine (PK and dissolution for BE) posted

• **Ongoing**
  - Direct measurement of GI concentration and correlation with PK and dissolution(subjects are dosing)

• **Future**
  - Extension of in vitro approaches to products with lower solubility
Quality by Design of Generic Drug Products

• Results
  - QbD examples published in 2012
  - We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions.
  - Significant progress has been made by the generic industry to apply QbD principles in pharmaceutical development (~75% of ANDA submission embraced QbD, Day 1 presentation)

• Ongoing
  - Dosage form specific QbD for complex products (morning presentations)
    • Transdermal
    • Peptides
    • Liposomes
    • Topical
    • Nasal/Inhalation
Modeling and Simulation

• Results: Key publications of new product equivalence methods

• Ongoing: Internal Use
  - OGD access and training with modeling and simulation tools
  - Internal use of modeling and simulation in policy development and research

• New
  - Prediction of in vivo performance for oral solid dosage forms
    - Open now
      - https://www.fbo.gov/index?s=opportunity&mode=form&id=59bf29398a503c7be19f24baa233229f&tab=core&cview=0

• Future
  - Build OGD Computational/Informatics capability
  - IVIVC and Clinical trial simulation support of external research
Pharmacokinetic Studies and Evaluation of Anti-Epileptic Drugs

• Ongoing
  – AED Brand to Generic Switching (2010 award)
    • Are generic AED bioequivalent to the brand product in patients under clinical use conditions? Will complete dosing in 2013
  – AED Generic to Generic Switching (2011 award)
    • Are generic AED bioequivalent to another generic in patients under clinical use conditions?

• New
  – Pilot Study for Identification and Characterization of Generic Sensitive AED Patients
    • Under development
Example Study Design

- Patient population
- Product characterization
- Fully replicated, multiple dose, bioequivalence study design
- Product blinding via over-encapsulation
Excipient Effects on Permeability and Absorption of BCS Class 3 Drugs

• Ongoing
  – External research contract for in vivo studies of excipient effects

• New
  – Internal summary of PK and dissolution for approved BCS Class 3 drugs
Product and Patient-related Factors Affecting Switchability of Drug-device Combination Products

• Ongoing
  - Policy on patient use studies under development
  - Policy on human factors study under development
    • Auto-injector usability
  - Policy on device robustness studies under development
    • DPI
    • MDI dose counters

• New: In vitro release tests for transdermal drug delivery systems
Postmarketing Surveillance of Generic Drug Usage Patterns and Adverse Events.

• Ongoing
  - Initiated a pilot collaboration with Mini-Sentinel to evaluate this tool's application to generic drugs
  - Initiated a pilot collaboration with Uppsala Monitoring Centre

• New
  - Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns
Evaluation of Drug Product Physical Attributes on Patient Acceptability

• Results
  - Final guidance on tablet scoring
  - Final guidance on bead size for sprinkle

• New
  - Evaluation of generic oral tablet physical attributes on patient acceptability
    • Under development
Postmarking Assessment of Generic Drugs and Their Brand-name Counterparts

• **Immunosuppressants**
  - Ongoing: Immunosuppressant brand to generic 1 and 2 switching (2012 start)
    • Are brand and two generics equivalence in stable kidney and liver transplant patients under clinical use conditions?
  - New: Evaluation of Clinical and Safety Outcomes Associated with Conversion from Brand-Name to Generic Tacrolimus Products in High Risk Transplant Recipients
    • Upcoming announcement in FY2013

• **Iron Colloids**
  - New: Therapeutic Equivalence of Generic Iron Complex Product
    • Upcoming announcement in FY2013
Postmarking Assessment of Generic Drugs and Their Brand-name Counterparts

• Bupropion
  - Bioequivalence of Generic Bupropion (in patients)
  - Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns
    • Upcoming announcement in FY2013
  - Bupropion: In Vitro Metabolism Quantification
    • Upcoming announcement in FY2013
Physicochemical Characterization of Complex Drug Substances

• Results
  - Key Publication on Low Molecular Weight Heparin
      • http://www.nature.com/nbt/journal/v31/n3/abs/nbt.2528.html

• Ongoing
  - Collaboration with DPA (St Louis) on peptide characterization methods

• Future
  - Study designs to evaluate formulation and impurity impact on immunogenicity
Develop a Risk-based Understanding of Potential Adverse Impacts to Drug Product Quality

• Ongoing
  - Pilot: risk based review evaluations for IR tablets and aqueous based solution injectable dosage forms
  - Pilot: initial risk assessment of incoming submissions before they are assigned for review
  - Implementation of Question based Review (QbR) for DMF and Microbiology reviews
  - Revision of the CMC QbR

Topic 13
Equivalence of Narrow Therapeutic Index Drugs

• Impact: NTI drugs have clinical need for tight control of dosing/drug exposure
  – Available generic products should meet this need

• Results
  – Revision of BE recommendations for NTI
  – Replicate design, scaled BE limits, variability comparison
    • Posted as draft guidance on Warfarin Sodium:

• New
  – Collection of Dose Adjustment and Therapeutic Monitoring Data to Aid Narrow Therapeutic Index Drug Classification
Equivalence of Ophthalmic Drugs

- Results: Revision of BE recommendations for cyclosporine ophthalmic emulsion
  - Under development
- Ongoing: research study with U of Denver on IVIVC
- New: In vitro-In vivo Correlations of Ocular Implants
Equivalence of Complex Drug Products

- **Liposomes**
  - Result: ANDA to Doxil approved in 2013
  - New: Evaluation of Dissolution Methods for Complex Parenteral Dosage Forms

- **Iron Colloids**
  - Result: first ANDA approval in 2012
  - New: Development of Bio-relevant In-vitro Assay to Determine Labile Iron in the Parenteral Iron Complex Product

- **Sustained Release Parenterals**
  - New: In vitro-In vivo Correlations of Parenteral Microsphere Drug Products
Abuse Deterrent Formulations

• Impact: What are implications for generics?
  – Recent FDA guidance
  – Actions on Oxycontin and Opana ER

• New
  – Evaluation of drug product formulation and in-vitro performance characteristics related to abuse-deterrence for solid oral dosage forms of opioids
    • Upcoming announcement in FY2013
GDUFA Regulatory Science

• GDUFA Funds will support regulatory science focused on
  – Therapeutic Equivalence
  – Opening the ANDA pathway

• GDUFA mandates a new collaboration
  – FDA “will convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by CDER Director.”
Future Regulatory Science Input

• Current list of projects (FY 2013) was attached to the GDUFA letter
• The FY 2014 list is open for input
• June 21, 2013 public meeting
  – Webcast link: https://collaboration.fda.gov/regscipart15/
• A docket for public comment is open through July
• Meeting questions to
  – GDUFARegulatoryScience@fda.hhs.gov
• Encourage this group to provide input through the public process
Meeting Questions: June 21, 2013

• Identification of current regulatory science challenges that limit the availability of generic drug products
• Regulatory science approaches to improve the pre-approval evaluation of therapeutic equivalence of generic drug products
• Post-approval regulatory science approaches to ensure the therapeutic equivalence of approved generic drug products
• Prioritization of FY 2014 regulatory science research topics for generic drug products based on public health impact
• Areas where additional draft guidance is needed to clarify FDA recommendations on complex generic drug product development
Industry input is needed!

We welcome your comments to the docket at

DOCKET NO. FDA-2013-N-0402
http://www.regulations.gov/#!submitComment;D=FDA-2013-N-0402-0001

Questions?
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