Research initiatives in FDA's Office of Generic Drugs

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Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA

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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.*

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Make safe and effective generic drugs available to the American public

---MISSION OF OGD

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

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

GDUFA
Regulatory Science Emerging Areas

- Equivalence of Narrow Therapeutic Index Drugs
- Equivalence of Ophthalmic Drugs
- Equivalence of Complex Drug Products
- Abuse Deterrent Formulations

GDUFA
Regulatory Science Themes

- Post-market Evaluation of Generic Drugs
  - Topics: 6,8,9,10,11
- Equivalence of Complex Products
  - Topics: 8,12,E3
- Equivalence of Locally Acting Products
  - Topics: 1,2,3,E2
- Therapeutic Equivalence Evaluation and Standards
  - Topics: 4,7,13, E1,E4
- Crosscutting Computational and Analytical Tools
  - Topics: 5,12

Regulatory Science = Better Decisions

- For FDA
  - Pre-submission advice and policy
    - Guidance
    - Controlled Correspondence
  - Review
    - Consistency on complex review questions and citizen petitions
  - Post-approval
    - Question about generic substitution
- For Industry
  - Formulation and pharmaceutical development
  - Pass BE studies first time
  - Regulatory confidence

Both should align with patient needs

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Bioequivalence of Local Acting Orally Inhaled Drug Products

Topic 1

- 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 in clearance
  - The first individual product guidance for a MDI has posted
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf

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Bioequivalence of Local Acting Orally Inhaled Drug Products

Topic 1

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)

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Bioequivalence of Local Acting Orally Inhaled Drug Products

Topic 1

New Research

- Development of in vivo predictive dissolution method for orally inhaled drug products
  - Closed http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-014.html
- Systematic evaluation of excipient effects on the efficacy of metered dose inhaler products
  - Closed http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-013.html
- Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action
  - FY2013 Solicitation Number: FDA-SOL-1120918
- Pharmacokinetics of locally acting orally inhaled drug products

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Bioequivalence of Local Acting Topical Dermatological Drug Products

Topic 2

- 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
  - Closed http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-016.html

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Bioequivalence of Local Acting Gastro-intestinal Drug Products

Topic 3

- 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)
  - FY 2013: FDA-SOL-1120920
- Future
  - Extension of in vitro approaches to products with lower solubility

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Quality by Design of Generic Drug Products

Topic 4

- Results
  - QbD examples published in 2012
    - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM304305.pdf
    - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf
  - We encourage ANDA applicants to apply Quality by Design (QbD) principles to the pharmaceutical development in 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)
- Ongoing
  - Dosage form specific QbD for complex products
    - Transdermal
    - Peptides
    - Liposomes
    - Topical
    - Nasal/Inhalation

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Modeling and Simulation

Topic 5

- Results; Key publications of new product equivalence methods
  - *Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration.* Davit B, Chen M, Conner D, Haidar S, Kim S, Lee C, Lionberger R, Makhlouf F, Nwakama P, Patel D, Schuirmann D, Yu L. AAPS J. 2012 Dec;14(4):915-24.
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf
  - *A Stability Analysis of a Modified Version of the Chi-Square Ratio Statistic Used in Bioequivalence Testing of Locally Acting Drug Products with Highly Variable Particle Size Distribution.* Weber B, Hochhaus G, Adams W, Lionberger R, Li B, Tsong Y, Lee SL. AAPS J. 2013 Jan;15(1):1-9
  - *Use of partial AUC to demonstrate bioequivalence of Zolpidem Tartrate Extended Release formulations.* Lionberger RA, Raw AS, Kim SH, Zhang X, Yu LX. Pharm Res. 2012 Apr;29(4):1110-20.
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175029.pdf
- 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
    - closed
      - 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

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Pharmacokinetic Studies and Evaluation of Anti-Epileptic Drugs

Topic 6

- Ongoing
  - AED Brand to Generic Switching (FY2010 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 (FY2011 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

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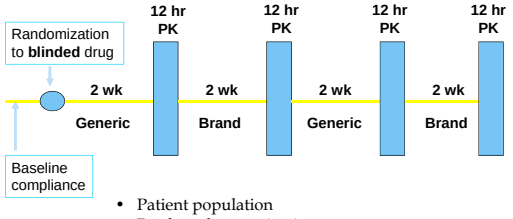
Example Study Design



- Patient population
- Product characterization
- Fully replicated, multiple dose, bioequivalence study design
- Product blinding via over-encapsulation

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Excipient Effects on Permeability and Absorption of BCS Class 3 Drugs

Topic 7

- Ongoing
  - External research contract for in vivo studies of excipient effects
- New
  - Internal summary of PK and dissolution for approved BCS Class 3 drugs

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Product and Patient-related Factors Affecting Switchability of Drug-device Combination Products

Topic 8

- 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
  - Closed: http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-015.html

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Postmarketing Surveillance of Generic Drug Usage Patterns and Adverse Events.

Topic 9

- 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
    - Closed: http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-022.html

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Evaluation of Drug Product Physical Attributes on Patient Acceptability

Topic 10

- Results
  - Final guidance on tablet scoring
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269921.pdf
  - Final guidance on bead size for sprinkle
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240243.pdf
- New
  - Evaluation of generic oral tablet physical attributes on patient acceptability
    - Under development for FY 2013

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Postmarking Assessment of Generic Drugs and Their Brand-name Counterparts

Topic 11

- Immunosuppressant
  - Ongoing: Immunosuppressant brand to generic 1 and 2 switching (FY2012 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
    - FY2013: Solicitation Number: 13-223-SOL-00102
- Iron Colloids
  - New: Therapeutic Equivalence of Generic Iron Complex Product
    - FY2013 Solicitation Number: FDA-SOL-1120929R

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Postmarking Assessment of Generic Drugs and Their Brand-name Counterparts

Topic 11

- Bupropion
  - Bioequivalence of Generic Bupropion (in patients)
    - Closed http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-021.html
  - Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns
  - Bupropion: In Vitro Metabolism Quantification

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Physicochemical Characterization of Complex Drug Substances

Topic 12

- Results
  - Key Publication on Low Molecular Weight Heparin
    - **Scientific considerations in the review and approval of generic enoxaparin in the United States**. Sau Lee, Andre Raw, Lawrence Yu, Robert Lionberger, Naiqi Ya, Daniela Verthelyi, Amy Rosenberg, Steve Kozlowski, Keith Webber & Janet Woodcock *Nature Biotechnology* **31**, 220–226 (2013):
    - 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

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Develop a Risk-based Understanding of Potential Adverse Impacts to Drug Product Quality

Topic 13

- 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

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Equivalence of Narrow Therapeutic Index Drugs

Emerging Topic

- 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:
      - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201283.pdf
- New
  - Collection of Dose Adjustment and Therapeutic Monitoring Data to Aid Narrow Therapeutic Index Drug Classification
    - Closed: http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-020.html

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Equivalence of Ophthalmic Drugs

Emerging Topic

- Results: Revision of BE recommendations for cyclosporine ophthalmic emulsion
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf
- Ongoing: research study with U of Denver on IVIVC
- New: In vitro-In vivo Correlations of Ocular Implants
  - Closed: http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-029.html

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Equivalence of Complex Drug Products

Emerging Topic

- Liposomes
  - Result: ANDA to Doxil approved in 2013
  - New: Evaluation of Dissolution Methods for Complex Parenteral Dosage Forms
    - Closed: http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-019.html
- 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
    - Closed http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-017.html
- Sustained Release Parenterals
  - New: In vitro-In vivo Correlations of Parenteral Microsphere Drug Products
    - Closed: http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-030.html

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Abuse Deterrent Formulations

Emerging Topic

- 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
    - FY2013 FDA-RFQ-1120913

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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

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U.S. Food and Drug Administration
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June 21, 2013 Public Meeting

- Questions
  - 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
- 17 speakers, 250 live and online attendees
- Docket FDA–2013–N–0402 was open for input
  - http://www.regulations.gov/#!submitComment;D=FDA-2013-N-0402-0001
- Slides, transcripts and video are available
  - http://www.fda.gov/Drugs/NewsEvents/ucm344710.htm
- 2014 Plans being drafted based on input

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