



U.S. Food and Drug Administration

Generic Drug User Fee Amendments of 2012

GDUFA Regulatory Science

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GDUFA Regulatory Science Commitments

- 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.*

FY 2013 GDUFA Regulatory Science 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. Postmarketing 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

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FY 2013 Regulatory Science Accomplishments

- New External Collaborations
 - 20 Grants, 8 Contracts for \$17 million in Regulatory Science
 - <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM386955.pdf>
- New Internal Collaborations
 - FDA lab (new equipment for Generic Drug Research: \$1 million)
 - 25 new GDUFA ORISE fellows for Generic Drug Research (10 to FDA lab)
- New Guidance for Industry
 - First MDI BE guidance (April), First Ophthalmic Emulsion BE guidance (June), First DPI BE guidance (Sept)
- New Plan for FY 2014 Regulatory Science
 - FY2013 Public Meeting and comments there and to the docket

June 2013 Public Meeting

- Slides, Transcripts, Video Available
 - <http://www.fda.gov/Drugs/NewsEvents/ucm344710.htm>
- Meeting Question on Complex Generics
 - Areas where additional draft guidance is needed to clarify FDA recommendations on complex generic drug product development
- Areas Identified
 - Statistical methodologies for in vitro equivalence and adhesion/irritation
 - Variability of dissolution for locally acting GI drugs
 - Acceptability of ANDAs for synthetic peptides

2013 Docket Comments: Summary

- QbD use cases for **complex products** (3 comments).
- Development of advanced in vitro dissolution methods, incorporating physiological factors and release models for **complex products** (2 comments).
- General and individual BE guidance for **complex dosage forms** (3 comments).
- BE standard for NTI drugs (2 comments).
- Post marketing surveillance (2 comments).
- Anti-epileptic drugs (3 comments).

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FY 2014 Regulatory Science Priorities

<http://www.fda.gov/Drugs/NewsEvents/ucm367997.htm>

1. Post-market Evaluation of Generic Drugs
2. Equivalence of Complex Products
3. Equivalence of Locally Acting Products
4. Therapeutic Equivalence Evaluation and Standards
5. Computational and Analytical Tools

1. Post-market Evaluation of Generic Drugs

- Because of the market penetration of generic drugs (84% of prescriptions in 2012) it is important that the generic drug program have a range of tools to monitor that these products are being successfully substituted and have the same safety and efficacy profile as their reference listed drug (RLD).

Post-market Evaluation of Generic Drugs (FY 2013)

- Bioequivalence of Generic Bupropion (steady state in patients)
- Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns
- Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns
- Investigation of inequivalence of bupropion hydrochloride extended release tablets: in vitro metabolism quantification
- Evaluation of Clinical and Safety Outcomes Associated with Conversion from Brand-Name to Generic Tacrolimus products in high risk Transplant Recipients

2. Equivalence of Complex Products

- Research to make generic versions available in all product categories and for all available RLDs, including products that have unique characteristics.
 - Drug-device combination human factors
 - Transdermal systems
 - Implants and parenteral microspheres
 - Liposomes
 - Iron colloids
 - Complex mixtures and peptides

Equivalence of Complex Products (FY 2013)

- 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)

3. Equivalence of Locally Acting Products

- The lack of efficient bioequivalence methods for locally acting drugs has limited the availability of generic drugs in this category. Research is focused on new bioequivalence approaches
 - Inhalation
 - Topical dermatological
 - Nasal
 - GI acting
 - Ophthalmic

Equivalence of Locally Acting Products (FY 2013)

- 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
- In vitro release tests for topical dermatological products
- In vitro-In vivo correlations of ocular Implants
- 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
- Correlation of mesalamine pharmacokinetics with local availability

4. Therapeutic Equivalence Evaluation and Standards

- Supports the evolution of equivalence and product quality standards to focus on ensuring therapeutic equivalence across all dosage forms and routes of delivery
 - Pathway for generic versions of abuse-deterrent formulations
 - Risk-based equivalence standards for narrow therapeutic index (NTI) drugs
 - Patient use and human factors
 - IVIVC/predictive dissolution for solid oral dosage forms.

Therapeutic Equivalence Evaluation and Standards (FY 2013)

- Collection of Dose Adjustment and Therapeutic Monitoring Data to Aid Narrow Therapeutic Index Drug Classification
- Evaluation of drug product formulation and in-vitro performance characteristics related to abuse-deterrence for solid oral dosage forms of opioids
- Prediction of In Vivo Performance for Oral Solid Dosage Forms

5. Computational and Analytical Tools

- Impact all four other priority areas and are essential to developing a modern ANDA review process that fully utilizes available computational and analytical tools.
 - PBPK/Absorption modeling for non-oral routes
 - PK/PD/Pharmacometrics models for generic drugs

Computational and Analytical Tools (FY 2013)

- FDA lab equipment
 - Particle size, rheology
- FDA lab ORISE
 - Formulation development and characterization
- OGD ORISE
 - Data analysis and modeling & simulation



COMPLEX GENERICS

Enabling Generics for Complex Products

- How to get scientific questions about complex drugs into the regulatory science research program
- How to apply for grants and contracts
- An update on our recent guidance on complex drugs
- How to submit a useful and successful pre-ANDA meeting requests for complex drugs
 - Note: Pre-ANDA meetings are not a GDUFA goal

What are Complex Generic Drugs?

- Complex Active Ingredients
 - LMWH, peptides, complex mixtures, natural source products
- Complex Formulations
 - Liposomes, iron colloids
- 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 many 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 review times that impact GDUFA goals
 - One of the reasons for GDUFA support of regulatory science

FY 2014 Public Meeting on GDUFA Regulatory Science

- Goal: Input for the FY 2015 Plan
- GDUFA Regulatory Science Page
 - Source for updates
 - <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm>
- FY 2014 Meeting
 - May 16, 2014 at White Oak
 - Docket will be open (FDA-2013-N-0402) until June 16, 2014
 - We would value more input from the generic industry
- Public input
 - Submit comments to the Docket

FY2014 Contract and Grant Process

- Contracts: Announced on www.fbo.gov
- Grants: Announced on www.grants.nih.gov
- BAA: Broad Agency Announcement
 - https://www.fbo.gov/index?s=opportunity&mode=form&id=281e9e6b5012b753dbec890ea2c5f1c4&tab=core&_cview=1
 - For unsolicited proposals



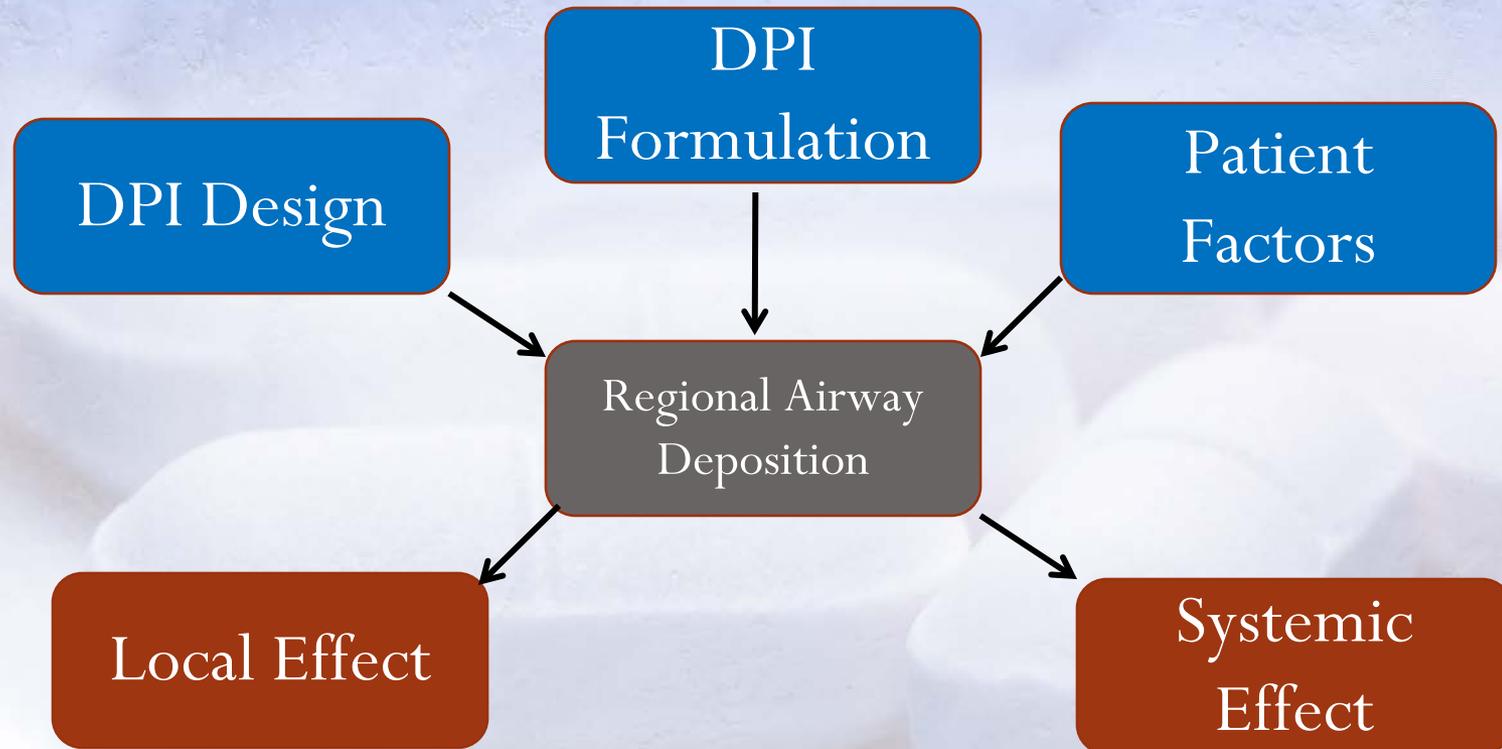
RECENT GUIDANCE

U.S. Food and Drug Administration
Generic Drug User Fee Amendments of 2012

Bioequivalence of Metered Dose Inhalers (MDI)

- The first individual product guidance for a MDI has posted (Albuterol Sulfate April 2013)
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf>
- Recommends in vitro, PK and PD equivalence studies
- Acceptance Limits on Dose Scale Confidence Intervals: 67-150%
 - Extensive simulation
 - For dose-scale analysis power for BE is driven by both within and between subject variability
 - For standard ABE we have methods for reference scaling on the within subject variability
 - These limits provide equivalent assurance of similarity as ABE limits of 80-125%

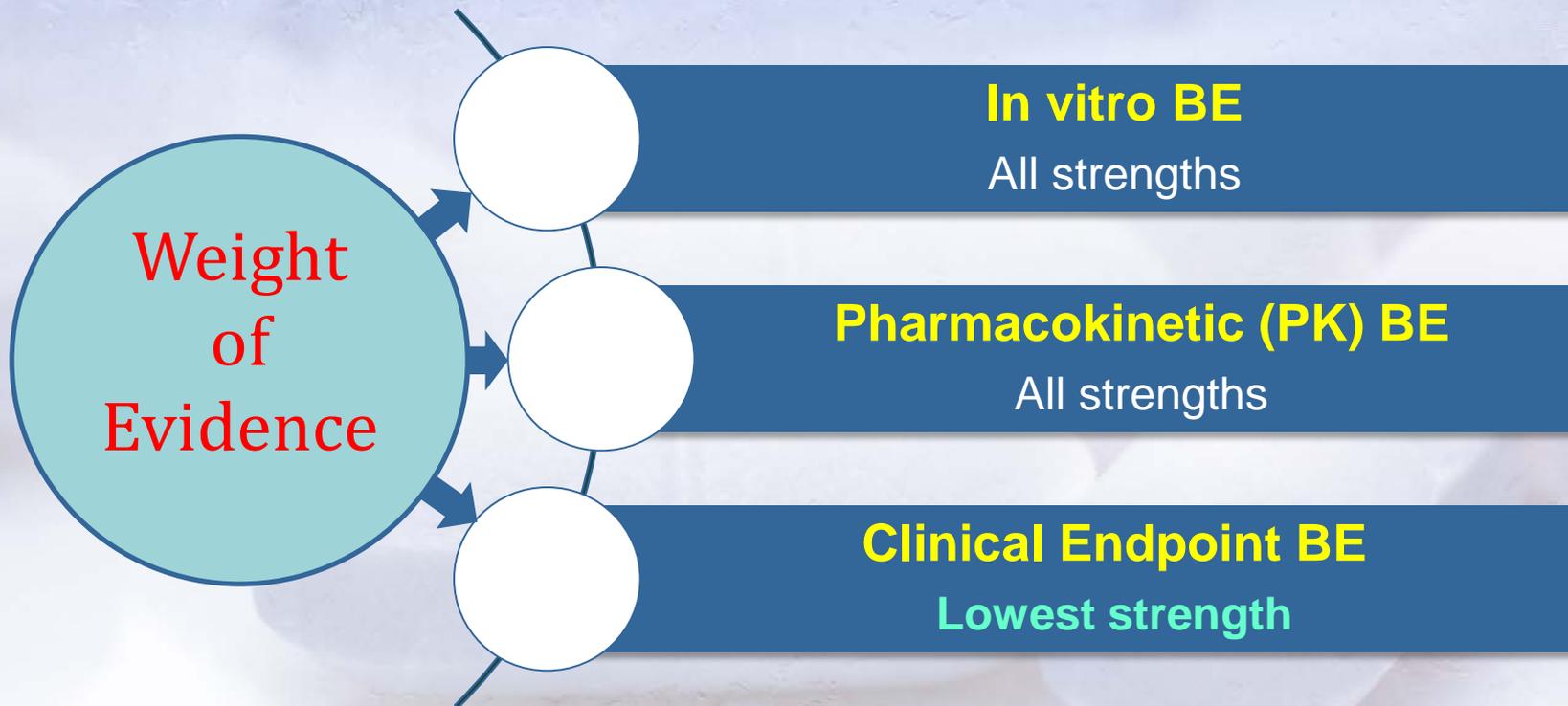
Bioequivalence of Dry Powder Inhaler (DPI)



First drug specific BE recommendation for DPI: Draft BE guidance for Fluticasone Propionate; Salmeterol Xinafoate (FP/SX) inhalation powder aerosol, published in September, 2013

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf>

BE Evaluation for Generic FP/SX DPI



Generic FP/SX DPI Device Recommendations

- Energy Source: Passive (breath actuated)
- Metering: Pre metered multi-dose format
- Number of Doses: 60
- External operating procedures: (1) Open, (2) Click, (3) Inhale, and (4) Close
- Similar size and shape to the RLD product
- Comparable device resistance to the RLD product
- Dose counter
- OGD recommends generic companies to send their working prototype for evaluation of device similarity



Bioequivalence of Local Acting Orally Inhaled Drug Products

New GDUFA Funded Research in FY 2013

- Development of in vivo predictive dissolution method for orally inhaled drug products
 - <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
 - <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

Other Guidance on Equivalence of Complex Drugs

- Doxorubicin Liposome
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf>
- Lidocaine Patch
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086293.pdf>
- Mesalamine (multiple forms)
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320004.pdf>
- Acyclovir Topical Ointment
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296733.pdf>
- Cyclosporine Ophthalmic Emulsion
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358114.pdf>



PRE-ANDA MEETING REQUESTS

Meeting Process: pre-ANDA Meeting on Complex Drugs

- Pre-ANDA Meetings are not covered by GDUFA
- Send pre-ANDA meeting request to OGD through
 - GenericDrugs@FDA.HHS.gov
 - Science Staff Scientific Coordinator: Kris Andre
- Evaluation
 - After assignment to a reviewer
 - Can we answer question via Control Correspondence process?
 - Request for more information, if necessary
- Response and Scheduling
 - Notification of meeting granted or denied
 - If meeting is denied, a Control Correspondence response to specific questions will be provided
- Meeting Preparation
 - Requester must provide final meeting package at least 4 weeks before scheduled meeting date
 - Internal pre-meeting held
 - Comments to requester a few days before
- Meeting Day
 - Some question may be answered in writing
 - Adjust agenda to focus on challenging questions
 - Use time wisely

Meeting Requests for Complex Drugs

- Pre-ANDA discussions were not part of OGD culture/process and are not part of GDUFA
- We want to work with industry on these issues
- pre-ANDA meetings help us meet the GDUFA ANDA goals by resolving complex issues before submission, improve submission quality, and reduce review cycles
- But we cannot grant them all
 - FY 2013 Statistics

Meeting Requests to OGD Science	Held or Scheduled	Denied or Withdrawn	Pending
21	5	6	10

What is in a Successful Meeting Request

- Impact
 - A product with no generics available
 - A product with unique regulatory science issues
- Clarity of Purpose
 - Clear and specific questions proposed
 - An proposed agenda must be included
- New Data
 - Data that is new to OGD
 - Pilot studies of an alternative approach

What is in an Unsuccessful Meeting Request

- Fishing for approaches
- Problems without proposed solutions
- Questions that can be answered in controlled correspondence
- Non-specific agenda
- Scope too broad
- No specific questions (get acquainted request)
- No data

Shared Vision of Regulatory Science Success for Complex Drugs

- Both FDA and Generic Industry Have a Common Customer
 - Patients and health care providers who want confidence and trust in high quality generic products in all product categories
- Identify Complex Regulatory Science Issues for the GDUFA Regulatory Science Priorities
- GDUFA Priorities Inform Research Awards and Guidance Development
- Pre-ANDA Discussion Can Advance Regulatory Science
- Pre-ANDA Discussion Should Lead to Better ANDA Submissions

Thanks! OGD Science Staff

- Thushi Amini (Research Coordinator)
 - GDUFA Regulatory Science Implementation
 - Grants and Contracts
- Kris Andre (Scientific Coordinator)
 - External Meetings
 - Workflow Management
 - Control Correspondence
- Staff: Wenlei Jiang, Yih-Chain Huang, Bavna Saluja, Stephanie Kim, Susie Zhang, Pradeep Sathe, Jeff Jiang
- Fellows: Nan Zheng, Renish Delvadia, Bryan Newman, Andrew Babiskin, Lei He, Denise Conti, Poonam Delvadia, Wendy Cai, Yan Wang, Kunyi Wu, Wen Qu, Priyanka Ghosh, Weixuan He