Complex Generic Drugs

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The views presented are those of the authors and do not necessarily reflect official views of the Food and Drug Administration.

GPhA Fall Technical Meeting

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Goals for Today

• How to get scientific questions about complex drugs into the regulatory science research program
• An update on our recent guidance on complex drugs
• How to submit a useful and successful pre-ANDA meeting requests for complex drugs
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 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 2013 Regulatory Science Accomplishments

• New External Collaborations
  – 20 Grants, 9 Contracts for $17 million in Regulatory Science

• New Internal Collaborations
  – FDA lab (new equipment for Generic Drug Research: $1 million)
  – 25 new 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
  – 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](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  - Areas where additional draft guidance is needed to clarify FDA recommendations on complex generic drug product development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).
GDUFA
FY 2014 Regulatory Science Priorities

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

- 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 2014 Public Meeting on GDUFA Regulatory Science

• GDUFA Regulatory Science Page
  - Source for updates

• FY 2014 Meeting
  - Q3 of FY 2014 at White Oak
  - Docket will be open
  - We would value more input from the generic industry
RECENT GUIDANCE
Bioequivalence of Metered Dose Inhalers (MDI)

• The first individual product guidance for a MDI has posted (Albuterol Sulfate April 2013)
• 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

BE Evaluation for Generic FP/SX DPI

Weight of Evidence

- **In vitro BE**
  - All strengths

- **Pharmacokinetic (PK) BE**
  - All strengths

- **Clinical Endpoint BE**
  - Lowest strength
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 firms 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

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

• 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**

• **Lidocaine Patch**

• **Mesalamine (multiple forms)**

• **Acyclovir Topical Ointment**

• **Cyclosporine Ophthalmic Emulsion**
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 grant more as resources increase
- 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

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<tr>
<th>Meeting Requests to OGD Science</th>
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<th>Denied or Withdrawn</th>
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<td>5</td>
<td>6</td>
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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 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
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