GDUFA Regulatory Science Update

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GPhA Annual Meeting

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Goals for Today

- Introduce Office of Research and Standards
- Research Update
- Standards Update
- Interactions with Industry

Office of Research and Standards

- **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.

GDUFA
FY 2014 Regulatory Science Accomplishments

- Continuing External Collaborations
  - 20 of 30 ongoing projects received additional resources
  - http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM420448.pdf
- New External Collaborations
  - 33 New Grants, 2 New Contracts for $20 million in Regulatory Science
  - http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM420446.pdf
  - ORS staff reviewed over 100 proposals in 2014
- 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

http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM417234.pdf

- 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 2015 Public Meeting on GDUFA Regulatory Science

- GDUFA Regulatory Science Page
  - Source for updates
  - http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm
- FY 2015 Meeting
  - Q2 of FY 2015 at White Oak
  - FR notice will be available
  - Docket will be open
  - We would value more input from the generic industry

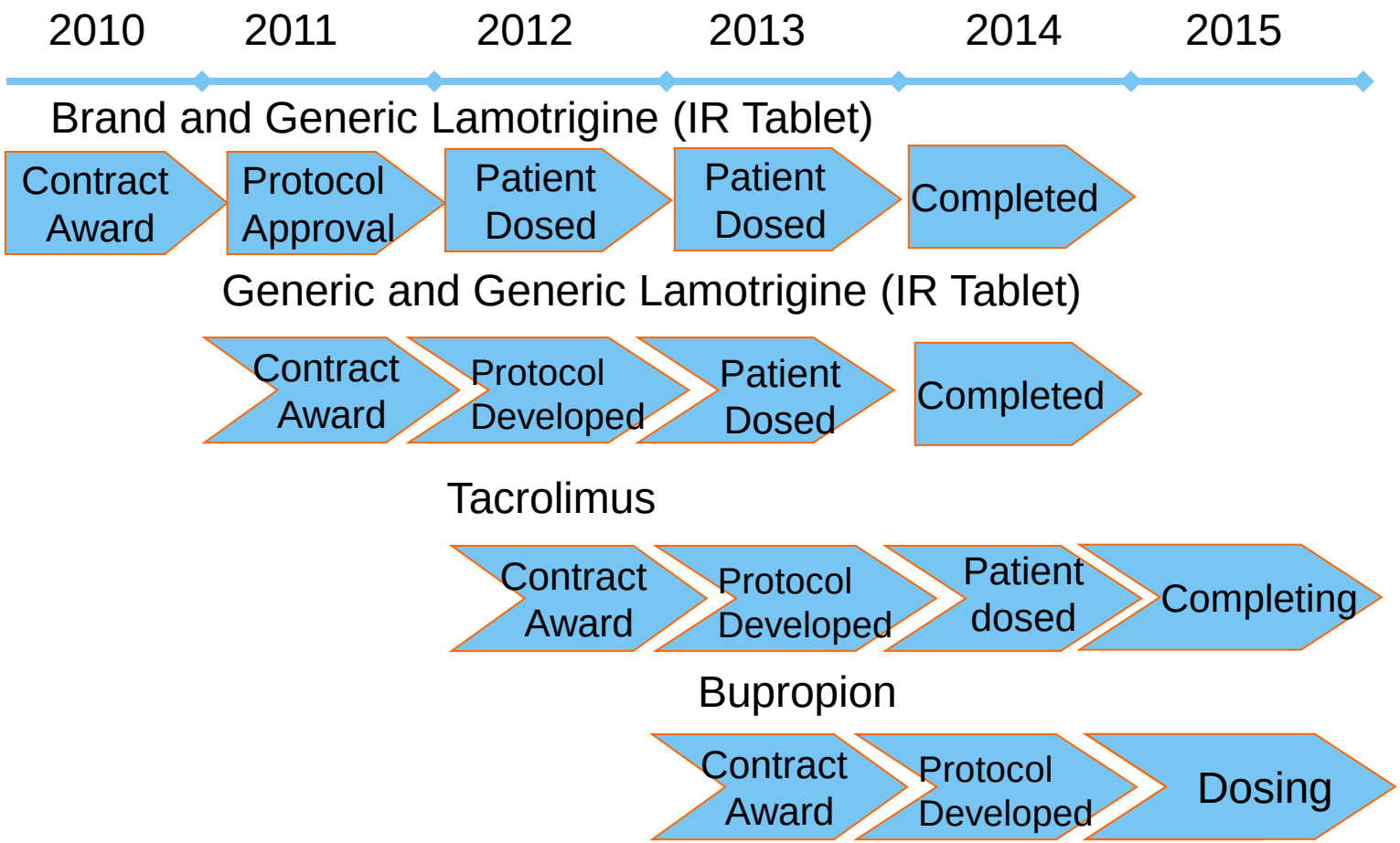
GDUFA
FY 2015 Regulatory Science Priorities
Distribution of Effort

1. Post-market Evaluation of Generic Drugs
   - FY 2014 30%
2. Equivalence of Complex Products
   - FY 2014 18%
3. Equivalence of Locally Acting Products
   - FY 2014 14%
4. Therapeutic Equivalence Evaluation and Standards
   - FY 2014 18%
5. Computational and Analytical Tools
   - FY 2014 20%

1. Post-market Evaluation of Generic Drugs

- **Post-market evaluation of generic drugs** includes researching monitoring methods, understanding patient perceptions of generic drug quality and effectiveness, and verifying therapeutic equivalence via patient brand-to-generic switching studies.
- These investigations provide additional data in therapeutic areas where concern exists about the substitutability of generic drugs and allow FDA to verify that generic drugs are fully interchangeable, safe, and effective in comparison to their reference listed drug (RLD).

From Anecdote to Evidence: Bioequivalence in Patients



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Top Line Results

- All completing studies confirm the conclusions of the studies submitted in the ANDA
- These study results were presented at a well-attended day long symposium at the 2014 AES meeting and provide evidence to support successful generic substitution of anti-epileptic drugs.

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.
- Office of Generic Drugs spends an increasing amount of time reviewing and developing policy for complex drug products, and future generic products will need to demonstrate equivalence to increasingly complex RLDs.

Highlights of Work in Progress

- Complex Active Ingredients
  - LMWH, peptides, complex mixtures, natural source products
  - Multivariate data analysis for complex mixtures in collaboration with FDA labs
- Advancing In Vitro Equivalence Methods for Complex Formulations
  - 7 grants on semi-solids for topical or ocular delivery
  - 6 grants on liposomes/sustained release implants
- Complex Drug-Device Combinations
  - DPI, MDI, nasal spray, transdermal system
  - Adhesion for transdermal systems

Results

- Draft Guidance on Conjugated Estrogens (CE) Tablets (Dec 2014)
  - Outlines detailed recommendations on how to establish the pharmaceutical equivalence of the drug substance and the bioequivalence of a proposed generic CE product. This guidance is the product of many years of collaborative work across CDER.
- Other Complex Product Guidance
  - Liposomal Injections: Verteporfin and Daunorubicin Citrate
  - Sublingual Film: Buprenorphine hydrochloride; Naloxone hydrochloride
  - Transdermal ER films: Buprenorphine and Estradiol
  - IUD: Levonorgestrel
  - Subq injection: Lanreotide acetate (nanomaterial injection)
  - Sevelamer Carbonate: Recommended characterization

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

Highlights of Work in Progress

- Topical Dermatological Products
  - Six coordinated grants (international: US, Europe, Australia) that include
    - New in vivo data
    - Manufacturing of semi-solid formulations
    - Characterization of semi-solid formulations
    - New PBPK modeling approaches
- Inhalation Products
  - Role of dissolution, particle size and PK studies
  - CFD modeling of deposition
- Ophthalmic Products
  - Seven coordinated grants on in vitro characterization, drug release, and drug delivery modeling
- Nasal Products
  - Use of PK studies alone for BE: in vitro, in vivo and modeling projects

Results

- Locally Acting Drug Guidance
  - Menthol Methyl Salicylate Topical Patch (PK bioequivalence)
  - Prednisolone Acetate Ophthalmic suspension
  - Brinzolamide Ophthalmic suspension
  - Mesalamine DR capsules
  - Sucralfate Oral Suspension
  - Budesonide Tablet Draft Guidance (PK bioequivalence)
  - Acyclovir Topical Cream
- Publication of Chi-squared ratio tests for cascade impactor profiles
  - Discussed at inhalation workshops
- pre-ANDA Meetings on Inhalation Product Development
- Citizen Petition Response on Cyclosporine Ophthalmic Emulation

4. Therapeutic Equivalence Evaluation and Standards

- Research supports the evolution of risk-based equivalence and product quality standards to ensure therapeutic equivalence across all dosage forms and routes of delivery.

Highlights of Work in Progress

- Pathway for generic versions of abuse-deterrent formulations
  - October 2014 Public Meeting
- Risk-based equivalence standards for narrow therapeutic index (NTI) drugs
  - Methods for identifying NTI drugs and ensuring risk-based BE and product quality standards
- Equivalence of modified release solid oral dosage forms
  - Value of replicate design BE studies, pAUC and IVIVC

Results

- Four new 2014 draft guidance recommended replicate design studies for narrow therapeutic index drugs
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    - tacrolimus ER, phenytoin, levothyroxine, carbamazepine
  - The movement from one size fits all to product specific standards is a sign of the maturation of the generic drug program
- Key Publication
  - *Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs*, LX Yu, W Jiang, X Zhang, R Lionberger, F Makhlouf, DJ Schuirmann, L Muldowney, M-L Chen, B Davit, D Conner and J Woodcock. Clinical Pharmacology & Therapeutics (2014)

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.

Highlights of Work in Progress

- FDA lab ORISE
  - Formulation development and characterization
  - CY 2014: 24 completed lab projects to support generic drug program
- OGD ORISE
  - Data analysis and modeling & simulation
- Modeling and simulation tools for the evaluation of generic drug equivalence
  - 7 grants on PBPK for non-oral delivery routes
  - 4 grants on pharmacometrics for generic drugs
- Clinical bioequivalence trial simulation

Advances in Standards

- Individual product guidance
  - OGD posted 157 new or revised individual product guidances in 2014
  - New internal processes
- Controlled Correspondence
  - ORS is responding to approximately 15 GDUFA controlled correspondence per month on complex scientific issues. We have completed the transition to a 60 day review process for GDUFA controlled correspondence.
- Pre-ANDA meeting requests
  - ORS spoke about our new process for these at GPhA Fall Tech meeting and reviewed 27 pre-ANDA meeting request in 2014.
  - Pre-ANDA meeting are not part of GDUFA commitments but provide an opportunity to discuss the most complex and critical issues face to face.
- Citizen petition responses
  - ORS consults contributed to 18 that were issued in 2014. The most significant discussed the bioequivalence standards for cyclosporine ophthalmic emulsion.

New Individual Product Guidance Process

- Individual Product 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 guidance development
  - One priority list for all of OGD; managed by DTP
- Long term goal is to have guidance available before ANDA submission
  - We are using number of ANDA submissions without individual product guidance as a metric

Formal 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)

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

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
  - ORS 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 reason 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

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

ORS Interaction Road Map

- Regulatory Science Yearly Public Meeting and Docket
  - Long term challenges
- Individual Product Guidance Requests
  - Before development begins
- Control Correspondence
  - Specific development questions
- Pre-ANDA Meeting Requests
  - Complex issues with data from significant development work

Shared Vision of Regulatory Science Success

- Both FDA and Generic Industry Have a Common Customer
  - Patients who want high quality generic products in all product categories
- Both FDA and Generic Industry Want a Strong Scientific Foundation for Product Development and Product Review
- Pre-ANDA Discussion Can Advance Regulatory Science
- Pre-ANDA Discussion Should Lead to Better ANDA Submissions