Regulatory Education for Industry (REdI):
GENERIC DRUGS FORUM

Hilton Hotel | Silver Spring, MD | April 13-14, 2016

Generic Drug User Fee Amendment (GDUFA) Regulatory Science Update

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Goals for Today

- **Introduction of Office of Research and Standards (ORS)**
- **Research Update**
- **Standards Update**
- **FDA-Industry Interactions**

Generic Drugs

- Generic drugs are copies of reference listed drug (RLD)
- Same in active ingredient, dosage form, safety, strength, routes of administration….

http://www.gphaonline.org/media/wysiwyg/PDF/GPhA_Savings_Report_2015.pdf

New Drug Application (NDA) vs. Abbreviated New Drug Application (ANDA)

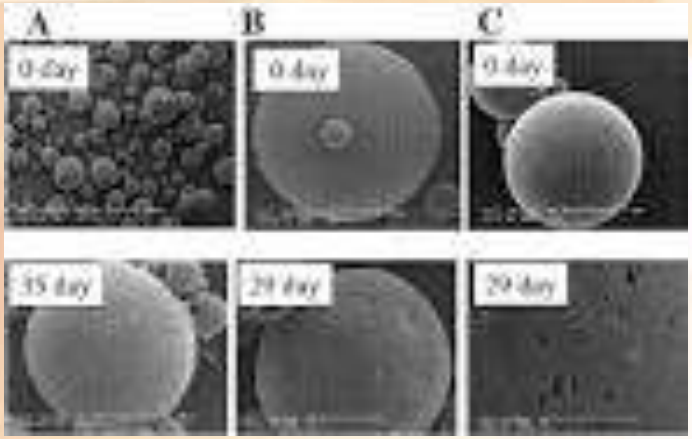
NDA

1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspection
6. Animal Studies
7. Clinical Studies
8. Bioavailability

ANDA

1. Chemistry
2. Manufacturing
3. Testing
4. Labeling
5. Inspection
6. Bioequivalence

Regulatory Science Needs for Generic Drugs



W. Jiang and S. P. Schwendeman. Stabilization and controlled release of bovine serum albumin encapsulated in poly(D, L-lactide) and poly(ethylene glycol) microsphere blends. Pharm Res 18: 878-885. 2001

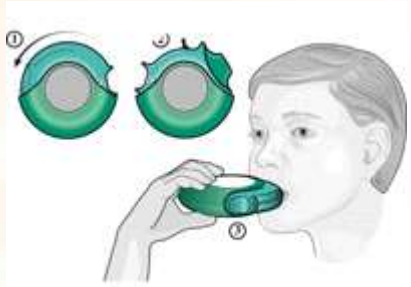


Figure 1: Diskus

https://my.clevelandclinic.org/health/medicaldevices/hic_How_to_Use_a_Metered_Dose_Inhaler/hic_How_to_Use_Your_Diskus_Dry_Powder_Inhaler_DPI

- Develop innovative equivalence approaches for complex drug products
- Set appropriate generic drug review standards
- Investigate questions of product substitutability

GDUFA Regulatory Science and ORS

The FDA **committed to employ regulatory science initiatives for generic drugs** based on 2012 GDUFA.

Office of Research and Standards (ORS) established in 2014

- Lead the implementation of the regulatory science commitments

- Translate research results into standards

ORS Mission Statement

The Office of Research and Standards is committed to make safe and effective generic drugs available to the American public by ensuring that the Office of Generic Drugs (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 the regulatory science research.

ORS Organization Structure

Office of Research and Standards

Immediate Office

- Research program management and oversight
- Outreach/budgeting
- Clinical research human subject protection
- Administrative support

Division of Therapeutic Performance (DTP)

- Facilitates pre-ANDA development of generic drugs
- Conducts and promotes regulatory science research to establish standards
- Evaluates post-approval safety with approved generic drugs.

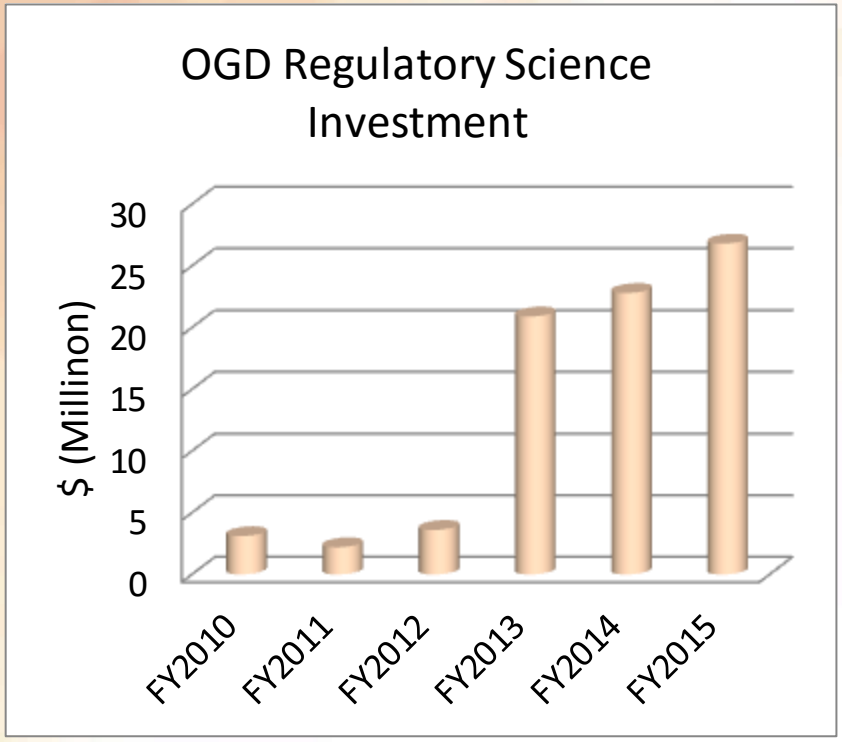
Division of Quantitative Methods and Modeling (DQMM)

- Establishes predictive and physiological models of drug product performance, and other quantitative methods to ensure generic drug equivalence.
- Develops new tools to analyze in vitro, pharmacokinetic, pharmacodynamics and clinical bioequivalence studies.

2015 Research Update

GDUFA Regulatory Science Page

http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm



2015 GDUFA Regulatory Science Statistics

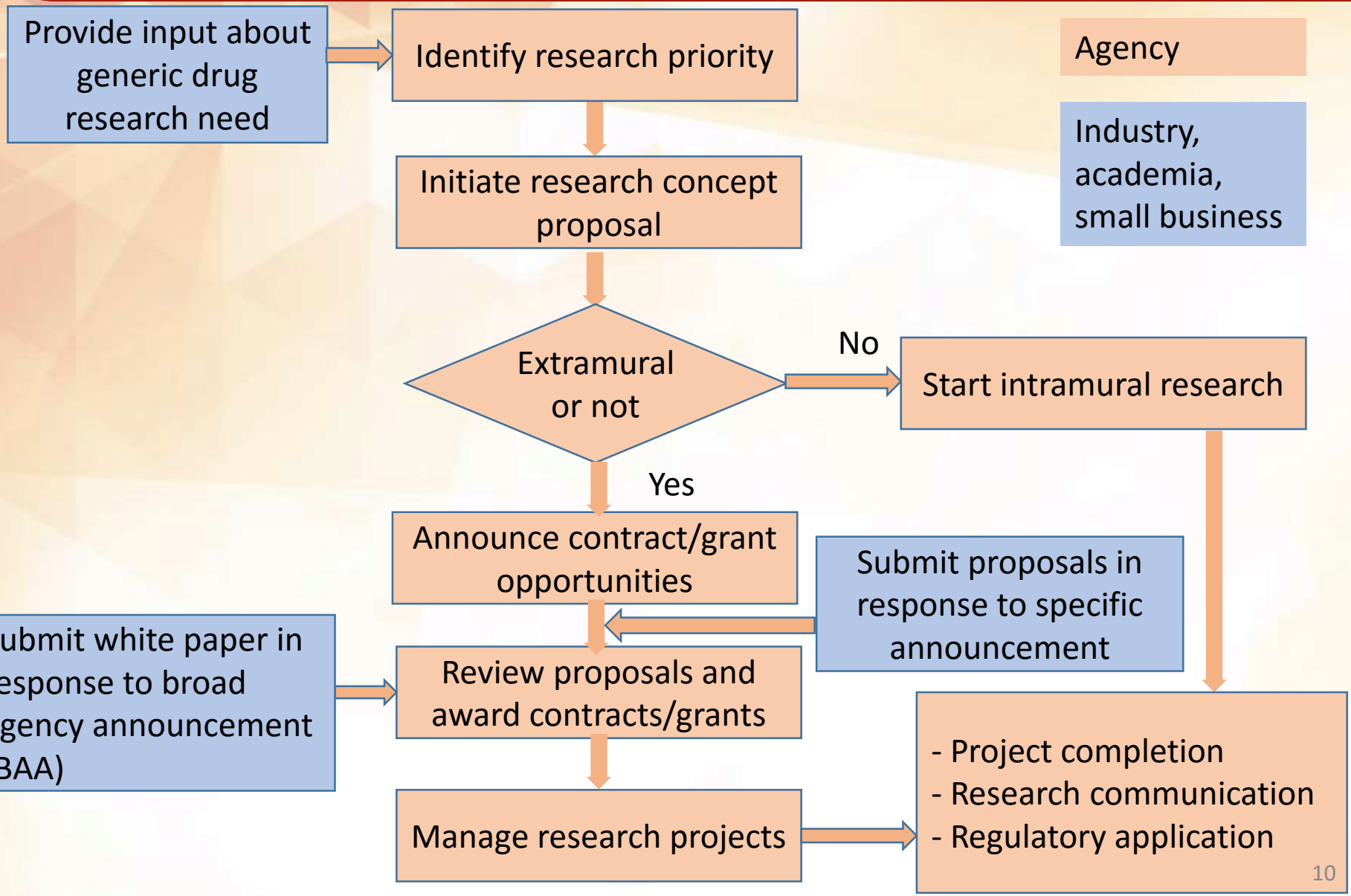
Extramural Projects
- 23 new
- About 90 ongoing

Intramural Projects
- 12 new
- Total 25 ongoing

Research Communication
- 30 publications
- 82 external posters
- 33 external presentations

Other Research Activities
- 37 external working group
- 9 workshops

Research Process Overview



Interaction about Research Program

- **FY 2016 Regulatory Science Initiative Part 15 Public Meeting**

http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm489572.htm

  - May 20, 2016 at FDA White Oak Campus
  - Email GDUFARegulatoryScience@fda.hhs.gov to register by April 29, 2016
  - Webcast available

- **FY 2016 GDUFA Regulatory Science Funding Announcements**

http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm391696.htm

- **FDA Broad Agency Announcement (BAA)**

http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm227223.htm

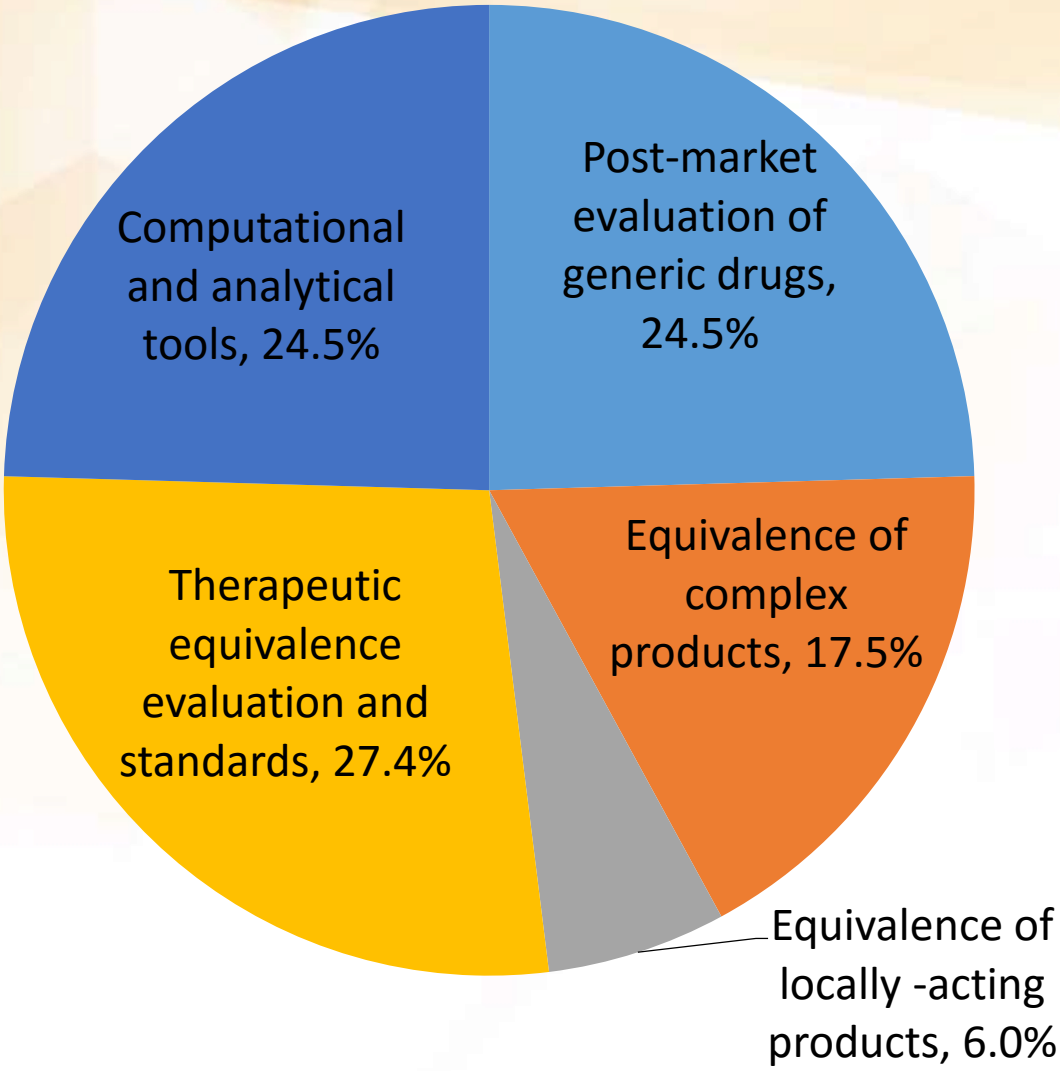
https://www.fbo.gov/index?tab=documents&tabmode=form&subtab=core&tabid=0245b334b899283bbd3d6329958af0bb

GDUFA Regulatory Science Priorities

http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM469453.pdf

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

GDUFA FY 2015 Regulatory Science Funding Distribution



1. Post-market Evaluation of Generic Drugs

Goal: Build public confidence about generic substitution

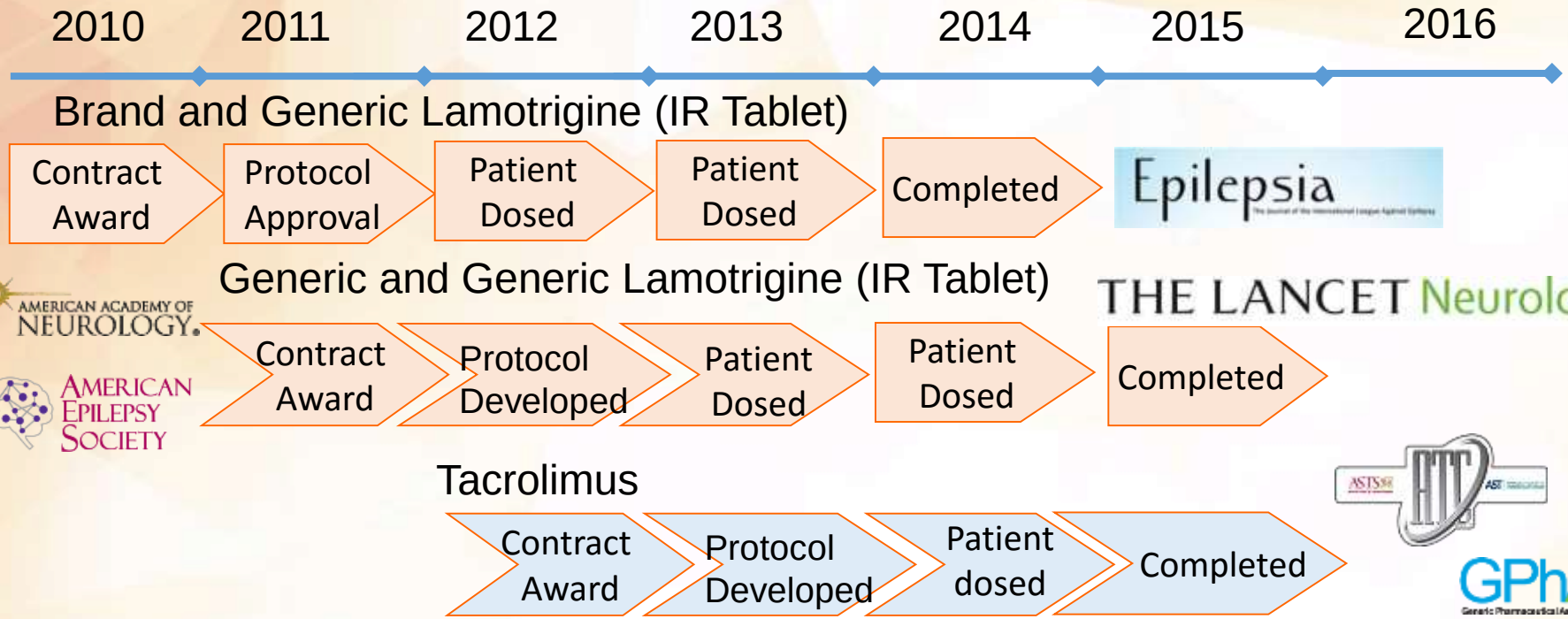
Verify therapeutic equivalence via patient brand-to-generic switching studies

Research monitoring methods

Understand patient perceptions of generic drug quality and effectiveness

Post-market Evaluation of Generic Drugs – highlighted results

- **All completing studies confirm the conclusions of the studies submitted in the ANDA**

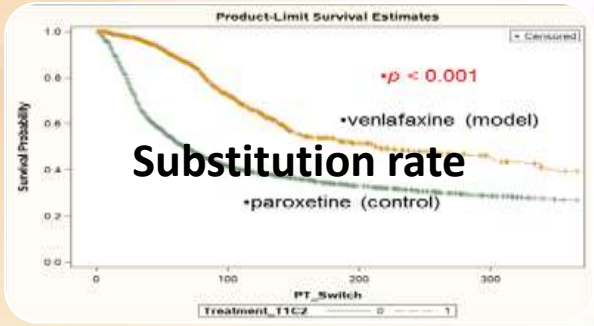


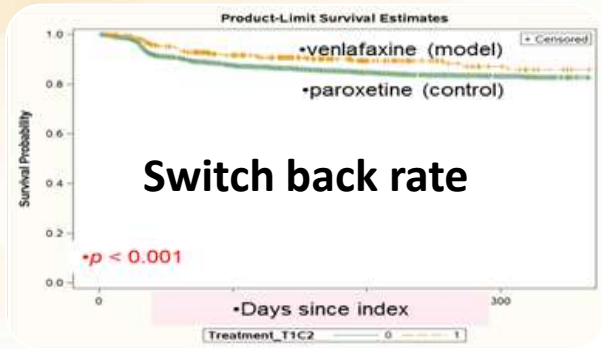
Ting et al. Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: A field test of the FDA bioequivalence standard. Epilepsia, 2015

Privitera et al. Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial. The Lancet Neurology. 2016

1. Post-market Evaluation of Generic Drugs – highlighted results

Exploration of different data sources and analysis method





Patient and physician survey

Widespread confidence in and acceptability of generic drugs

FDA's approval process ensured the safety and effectiveness of generic drugs

Greater education about generic drug approval process needed

Kesselheim AS, Gagne JJ, Eddings W, et al. Prevalence and Predictors of Generic Drug Skepticism among Physicians: Results of a National Survey. JAMA Internal Medicine. 2016 [in press]

Kesselheim AS, Gagne JJ, Franklin JM, et al. Variations in Patients' Perceptions and Use of Generic Drugs: Results of a National Survey. Journal of General Internal Medicine. 2016 [in press]

JAMA Internal Medicine

1. Post-market Evaluation of Generic Drugs – work in progress

Brand-generic switch studies	• Bupropion
Surveillance methodologies	• FDA's sentinel program • Machine learning • Application of case-control analysis
Perception and education	• Educating groups that influence generic drug use

2. Equivalence of Complex Products

Goal: Develop science-based policy and guidance to make generic versions available in all product categories

Complex active pharmaceutical ingredients (APIs)	Drug-device combinations	Transdermal systems	Implants and microspheres	Nanomaterials

2. Equivalence of Complex Products- Highlighted Results and Communication

- Used modern analytical techniques for comparative analysis of Glatiramer acetate (GA) and Copolymer-1 (as non-GA control)
- Accelerated in vitro release testing method for PLGA microspheres
- Characterized biodegradable polymer
- Evaluated cell uptake of iron colloids

Shen, J et al. A reproducible accelerated *in vitro* release testing method for PLGA microspheres. *Int J Pharm,* 2016.

Garner, J et al. A Protocol for Assay of Poly(lactide-co-glycolide) in Clinical Products. *Int J Pharm.* 2015.

Hao, J et al. Heat effects on drug delivery across human skin, Expert Opinion on Drug Delivery, 2016

Rogstad, S.M., et al. Modern analytics for synthetically derived complex drug substances: NMR, AFFF-MALLS and MS tests for glatiramer acetate. *Analytical and Bioanalytical Chemistry*, 2015.

2. Equivalence of Complex Products – work in progress

Complex API	• Impurity/immunogenicity characterization
Drug-Device Combinations	• Formulation effects on MDI pharmacokinetics • Dissolution methods for long-acting intrauterine system
Transdermal systems	• Adhesion • In vitro in vivo correlation of heated effects
Nanomaterials	• Liposomes dissolution • iron colloids biodistribution
Implants and microspheres	• Effect of raw materials manufacturing and storage on long-acting release microsphere products • Dissolution methods for long-acting periodontal drug products

3. Equivalence of Locally-Acting Products

Goal: Evaluate in-vitro alternatives or other efficient BE approaches to facilitate ANDA development and review

Topical dermato-logical drugs	Inhalation /nasal drugs	Ophthalmic drugs	Local gastro-intestinal acting drugs	Otic drugs

3. Equivalence of Locally-Acting Products : Highlights of work in progress

- **Gastrointestinal products**
  - **Wireless analysis device to measure in vivo drug dissolution in the GI tract**
- **Ophthalmic Products**
  - **Seven coordinated grants on in vitro characterization, drug release, and drug delivery modeling**
- **Nasal Products**
  - **Use of PK studies for BE: in vitro, in vivo and modeling projects**
- **Inhalation products**
  - **Formulation effects on Metered Dose Inhaler pharmacokinetics**

Lee, S. L., et al., (2015). Regulatory Considerations for Approval of Generic Inhalation Drug Products in the US, EU, Brazil, China, and India. *The AAPS Journal*, 17(5), 1285-1304

Raney, S. G., et al., (2015). Pharmacokinetics-Based Approaches for Bioequivalence Evaluation of Topical Dermatological Drug Products. *Clinical Pharmacokinetics*.

4. Therapeutic Equivalence Evaluation and Standards

Goal: Support the evolution of risk-based equivalence and quality standards to ensure product therapeutic equivalence

Generic versions of abuse-deterrent formulations	Risk-based equivalence standards for narrow therapeutic index (NTI) drugs	Equivalence of modified release solid oral dosage forms	Excipient safety

4. Therapeutic Equivalence Evaluation and Standards – work in progress

Abuse-deterrent formulations	• PK of opioid drug products following snorting of milled drug products
NTI drug classification	• Use exposure response analysis for identifying NTI drugs • Anti-epileptic drugs, immunosuppressants, and others
MR products	• pAUC • Fully replicated studies • IVIVC
Excipient safety	• Prediction and testing of excipient molecular targets • Interactions of excipients with intestinal transporters

5. Computational and Analytical Tools

Goal: Develop a modern ANDA review process that fully utilizes available computational and analytical tools

Advanced analytics	PBPK or absorption models	PD model or clinical trial simulation	Quantitative risk modeling

5. Computational and Analytical Tools – work in progress

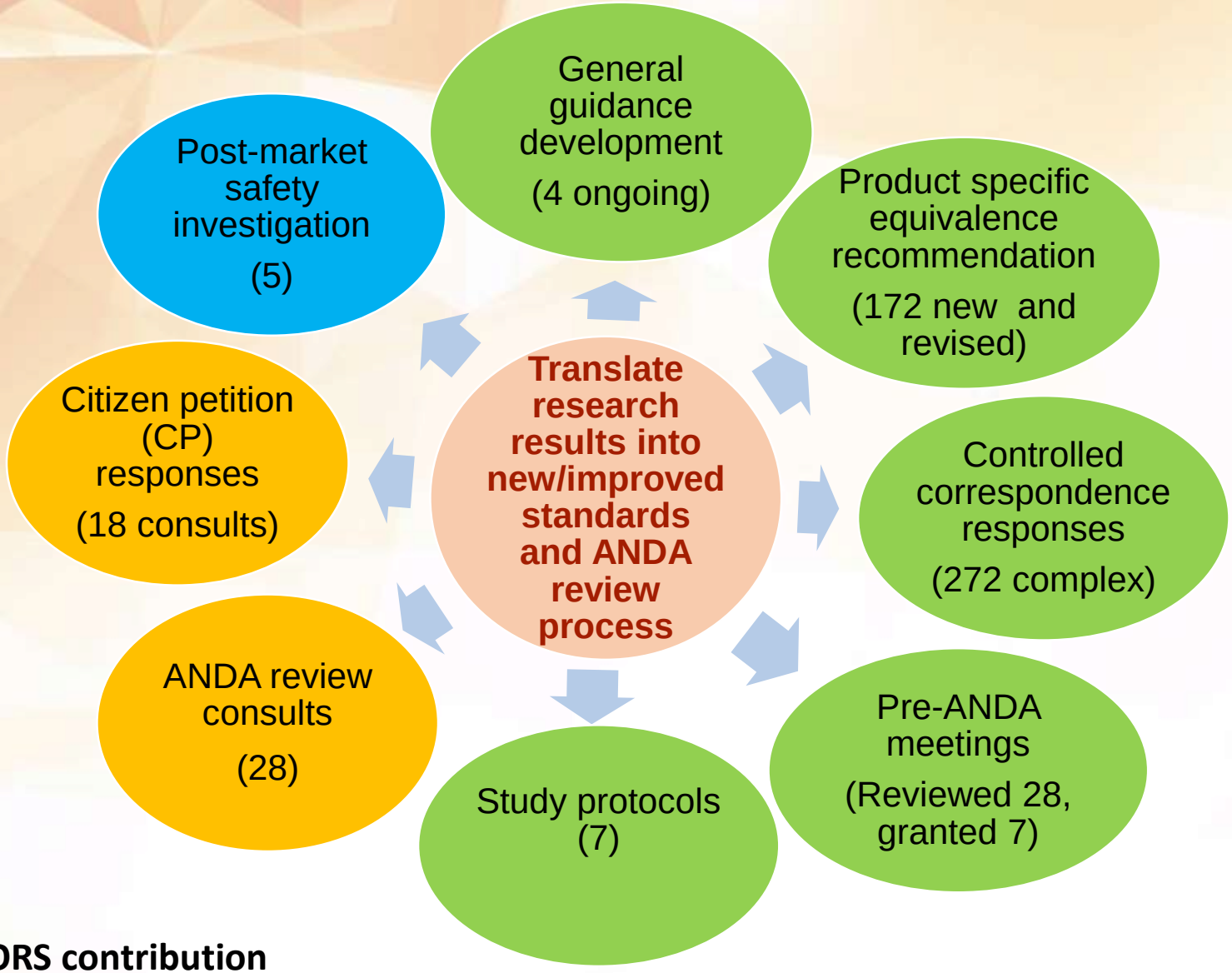
- **FDA ORISE fellows support API, formulation development and characterization, data analysis**

- **Modeling and Simulation**
  - Non-oral drug modeling, e.g., long acting injectable drugs
  - Modified-release solid oral dosage forms
  - Post-market risk assessment
  - Clinical bioequivalence trial simulation

W Jiang et al. *A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion*. AAPS Journal 2015

Andrew H. Babiskin and Xinyuan Zhang. Application of Physiologically Based Absorption Modeling for Amphetamine Salts Drug Products in Generic Drug Evaluation. J. Pharm Sci, May 2015

2015 Standards Update



Cited ORS contribution

Significant Product-specific Equivalence Recommendation

- **Complex drugs**
  - Sevelamer carbonate, Omega-3
  - Formoterol fumarate dry powder inhaler
  - Beclomethasone diproprionate metered dose inhaler
  - Fluticasone propionate nasal metered spray

- **Locally acting drugs**
  - Budesonide capsules
  - Ciprofloxacin/Dexamethasone otic suspension
  - Alprostadil urethral suppository
  - Minocycline HCl ER dental powder
  - Betamethasone dipropionate topical augmented lotion
  - Diflorasone diacetate topical cream

- **Others**
  - Methylphenidate ER tablet
  - Guidance revision for NTI drug products: Phenytoin, carbamazepine, levothyroxine
  - Dabigatran tablet

Significant General Guidance Development and ANDA Approval

- **General guidance**

General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf

- **Petition responses**

No pAUC for Naproxen/Esomeprazole

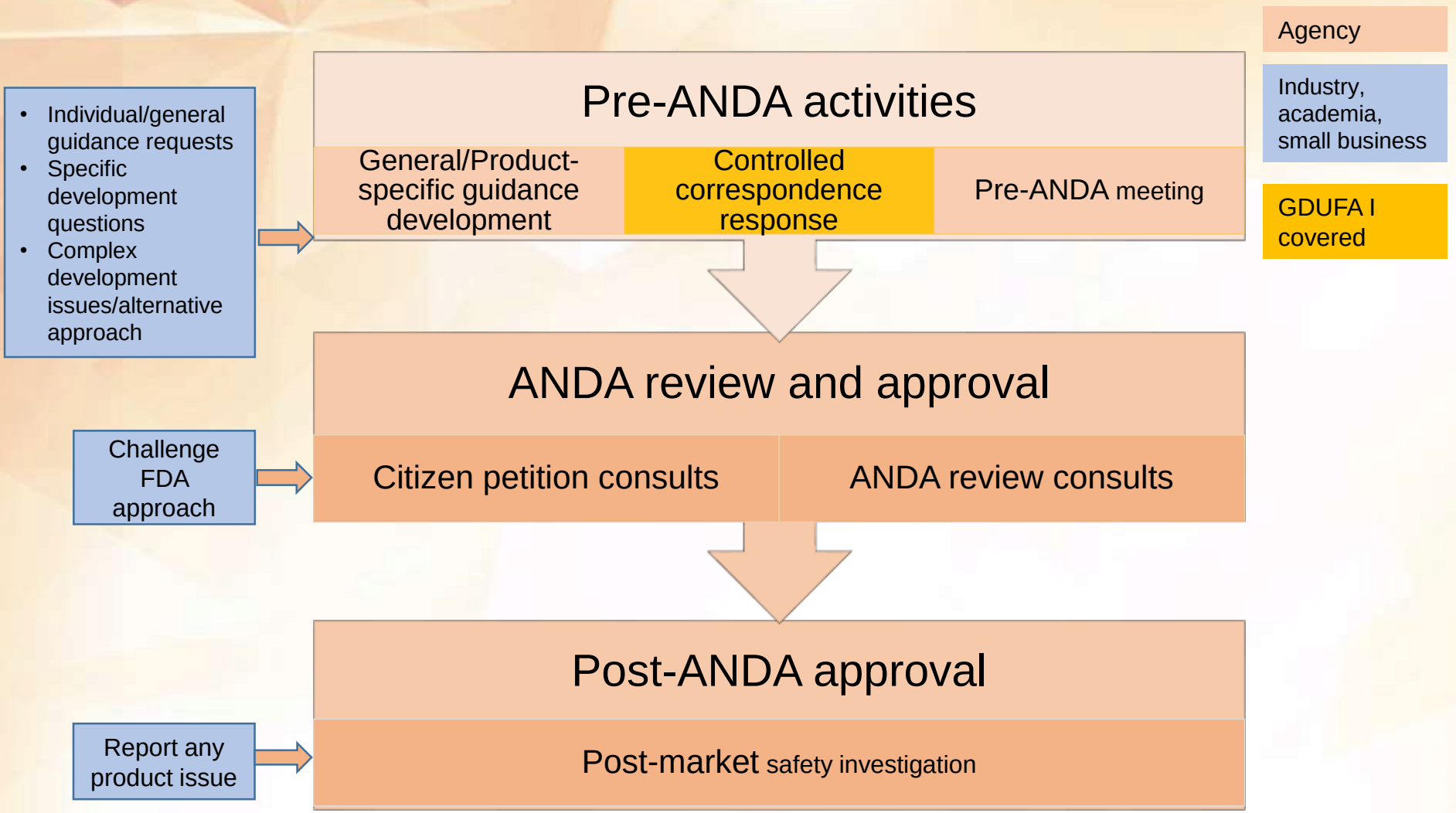
Dalfampridine not NTI

- **ANDA approval**

Glatiramer acetate injection

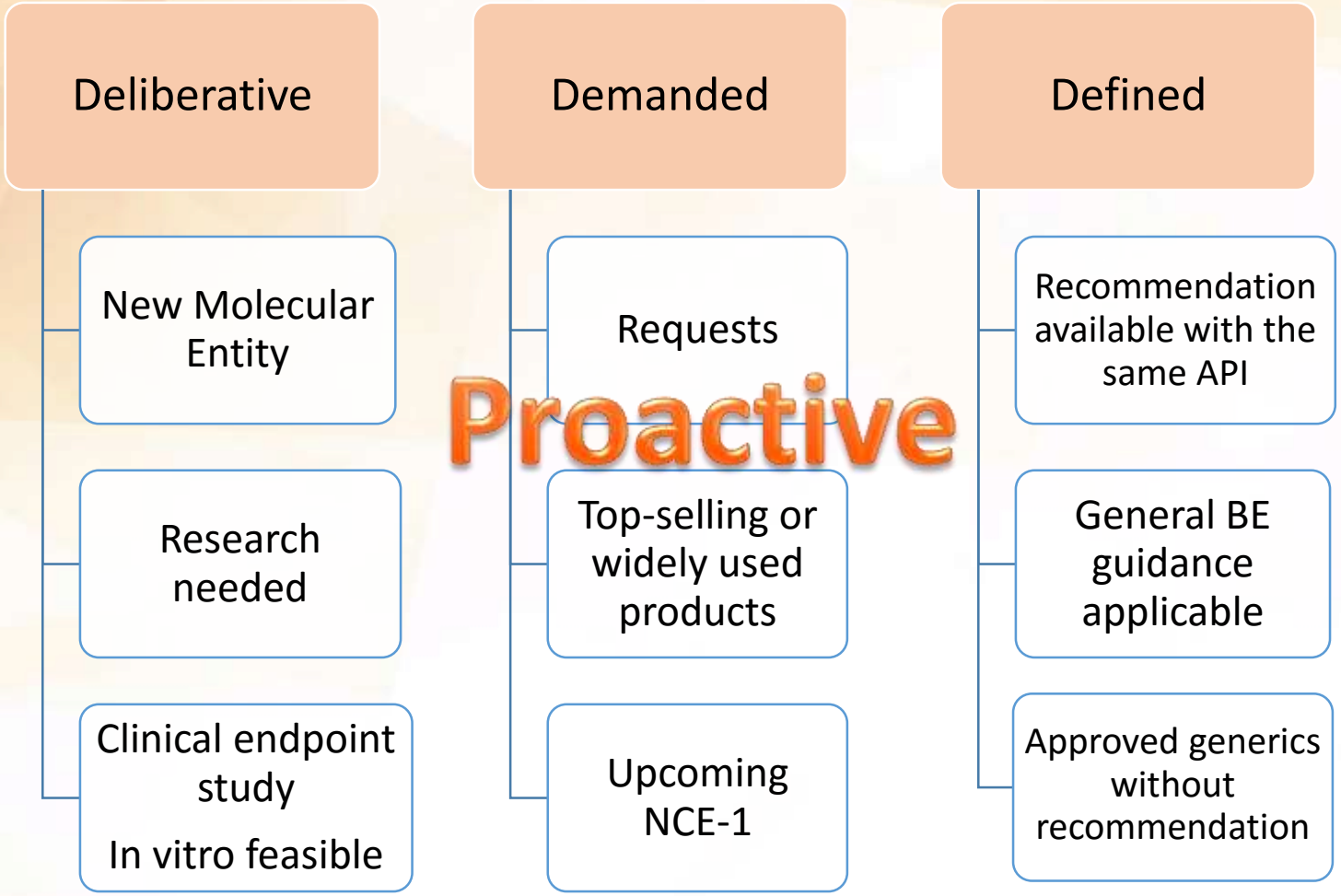
Mometasone furoate nasal spray suspension

Standards Development/ANDA Review/Post Approval Process



Product-Specific Equivalence Recommendation

- Recommendations on approaches to demonstrate equivalence
- 3D approach to prioritize recommendation development



http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

What if there is no equivalence recommendation for a specific product?

- Does the General BE guidance* apply?
- Request Guidance via GenericDrugs@fda.hhs.gov mailbox
- Provide input to the GDUFA regulatory science prioritization process
- Consider a pre-ANDA meeting (only after substantial development work)

* Draft Guidance for Industry: *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)-Dec 2013*

Controlled Correspondence

- **Specific questions about individual product development programs**
  - **Product composition**
  - **Advice on eligibility for BE study waivers**
  - **Study/device design issues**
- **Guidance for Industry: *Controlled Correspondence Related to Generic Drug Development***

  http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm411478.pdf

  - **Questions: GenericDrugs@fda.hhs.gov**
  - **GDUFA Y4: 60 day response time for each CC**

Pre-ANDA Meeting Requests for Complex Drugs

Goal

- Resolve complex scientific issues prior to submission
- Improve submission quality
- Reduce review cycle

Elements of a good meeting request

- Impact of the product
- Clarity of the purpose
- New development Data

Send meeting request to GenericDrugs@FDA.HHS.gov

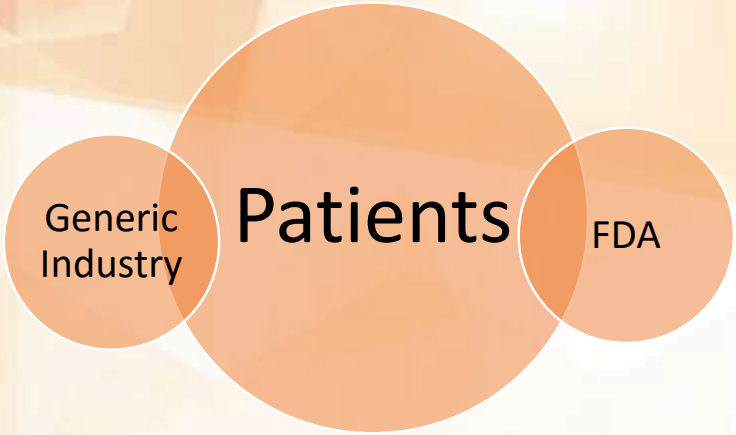
Pre-ANDA Meeting Process on Complex Drugs

- **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**

ORS Interaction Roadmap

Long-term challenges	• Provide input at GDUFA Regulatory Science yearly public meeting and Docket • Respond to solicitation or submit BAA proposals
Prior to development	• Request product-specific guidance development
Specific development question	• Submit control correspondence
Complex issues with significant development work	• Request Pre-ANDA meeting

Shared Vision of Regulatory Science Success



- **Engage with GDUFA regulatory science**
  - **Identify complex products with significant ANDA future interest**
- **Advance the Science of Equivalence**
  - **Generic Access in all Product Categories**
  - **Confidence in Generic Drug Substitution**
  - **Better Tools for Development and Review**

Thank you!

Questions?

surveymonkey.com/r/GDF-D1S2