U.S. FOOD & DRUG ADMINISTRATION

Public Workshop: New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products (OINDPs)

January 09, 2018

Opening Remarks

Lei Zhang, Ph.D.
Deputy Director
Office of Research and Standards
Office of Generic Drugs, CDER, FDA

Drug Competition Action Plan (DCAP)-

- Reducing gaming by branded companies…
- Resolving scientific and regulatory obstacles…
- Improving the efficiency and predictability of the FDA's generic review process…

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm564725.htm

Reducing the Hurdles for Complex Generic Drug Development

Posted on **October 2, 2017** by **FDA Voice**

By: Scott Gottlieb, M.D.

Earlier this year, I announced our Drug Competition Action Plan to advance new policies aimed at bringing more competition to the drug market. My goal was to improve access consumers have to the medicines that they need. I consider access to medicine a matter of public health. If consumers are priced out of the drugs they need, that's a public health concern that FDA should address, within the scope of its mandate and authorities.

While FDA doesn't control drug pricing, our policies do affect competition in the market. This is the nexus of our current efforts on drug pricing.

Our plan has a number of different domains. Among them is a compilation of efforts to improve the efficiency of the generic drug approval process; and another is a group of

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FDA Statement

Statement from FDA Commissioner Scott Gottlieb, M.D. on new steps to facilitate efficient generic drug review to enhance competition, promote access and lower drug prices

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For Immediate Release January 3, 2018

Statement

The FDA today announced additional steps to encourage generic competition as part of our continued implementation of the Drug Competition Action Plan. This plan has three main components: reducing gaming by branded companies that can delay generic drug entry; resolving scientific and regulatory obstacles that can make it difficult to win approval of generic versions of certain complex drugs; and improving the efficiency and predictability of the FDA's generic review process to reduce the time it takes to get a new generic drug approved and lessen the number of review cycles undergone by generic applications before they can be approved. The new steps we're announcing today go toward achievement of this third goal. We expect to take additional steps this year to promote competition; to help reduce drug prices and improve access to medicine for Americans.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm591184.htm

Complex Generic Products -Cornerstones of GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables and implantables, transdermals, MDIs
- Complex drug-device combinations
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

GDUFA: Generic Drug User Fee Act
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Enhanced Pre-ANDA Process in GDUFA II

- **Improve access and approvals**
- **Decrease cycles to approval**

Complex Products

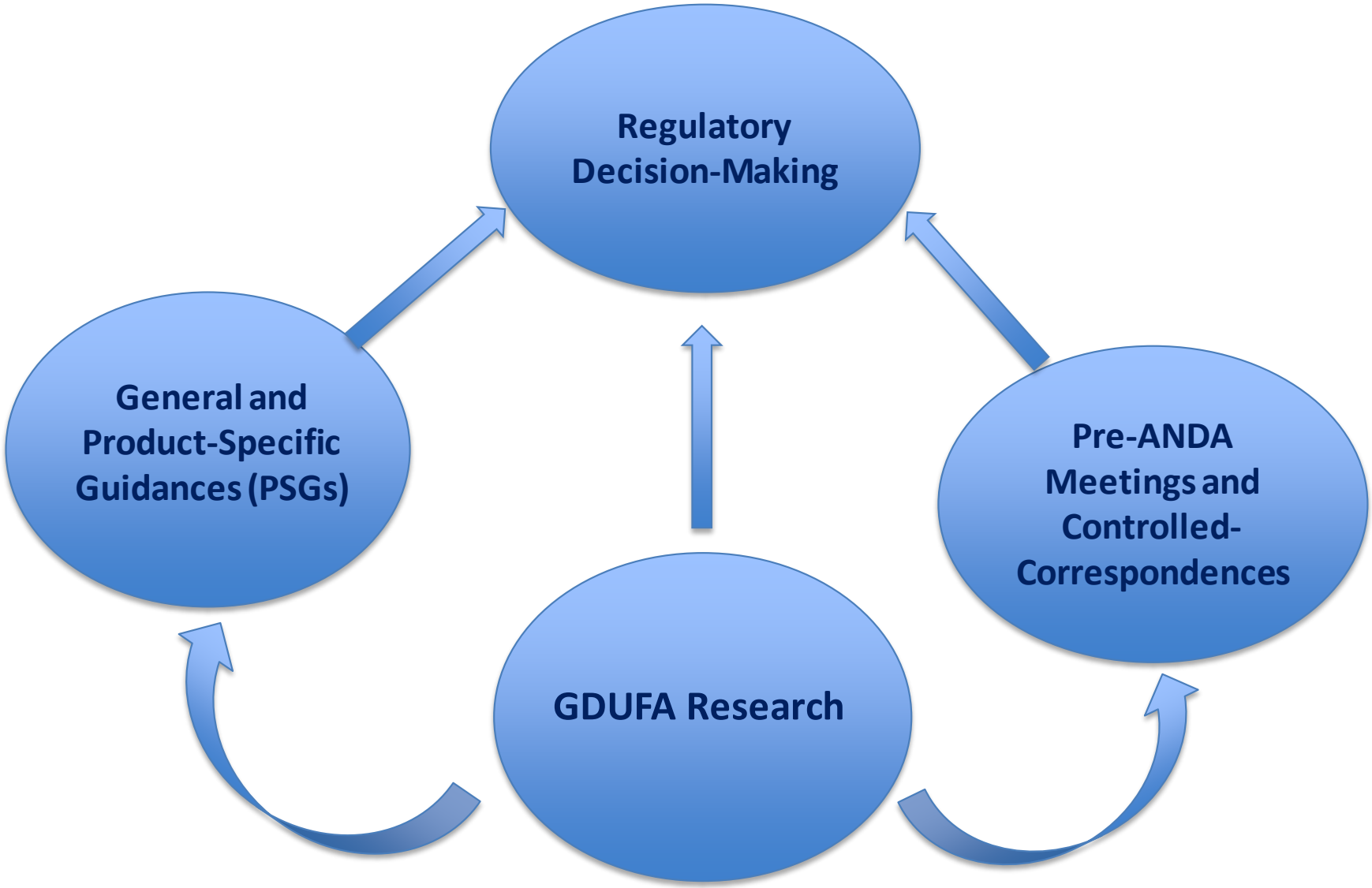
- **Early Stage**
  - GUDFA research
  - Pre-ANDA meetings with goals
- **Mid-stage**
  - Product-specific guidance (PSG) when available
  - Pre-ANDA product development meetings with goals for alternatives to PSG (difference class)
  - 120 day controls for alternatives to PSG (same class)
- **Submission and Review**
  - Pre-ANDA pre-submission meetings with goals
  - Mid-cycle meetings

Non-complex Products

- **Early Stage**
  - GDUFA research
  - Goals on product-specific guidance (PSGs) for NME (2 years after NDA approval)
- **Mid-stage**
  - 60 day controls
  - 120 day controls for alternatives to product-specific guidance
  - IID enhancements
- **Submission and Review**
  - Shorter review goals for eligible priority applications with complete and accurate PFC.

NME: new molecular entity; IID: inactive ingredient database; PFC: pre-submission facility correspondence

Science-Informed Regulatory Policy and Decision-Making



GDUFA II Complex Product Workshops

- Oct 6th, 2017: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations

- Oct 20th, 2017: Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access

- **Jan 9th, 2018: New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products**

Future workshops in 2018 and 2019:

  - Combination products
  - PBPK modeling for locally-acting products

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Generic Drug Product Substitutability

In relation to the Reference Listed Drug, generic products are expected to be:

Pharmaceutically Equivalent (PE)

- The same active ingredient, dosage form, strength, route of administration and meet the same compendial standards (strength, quality, purity, and identity)

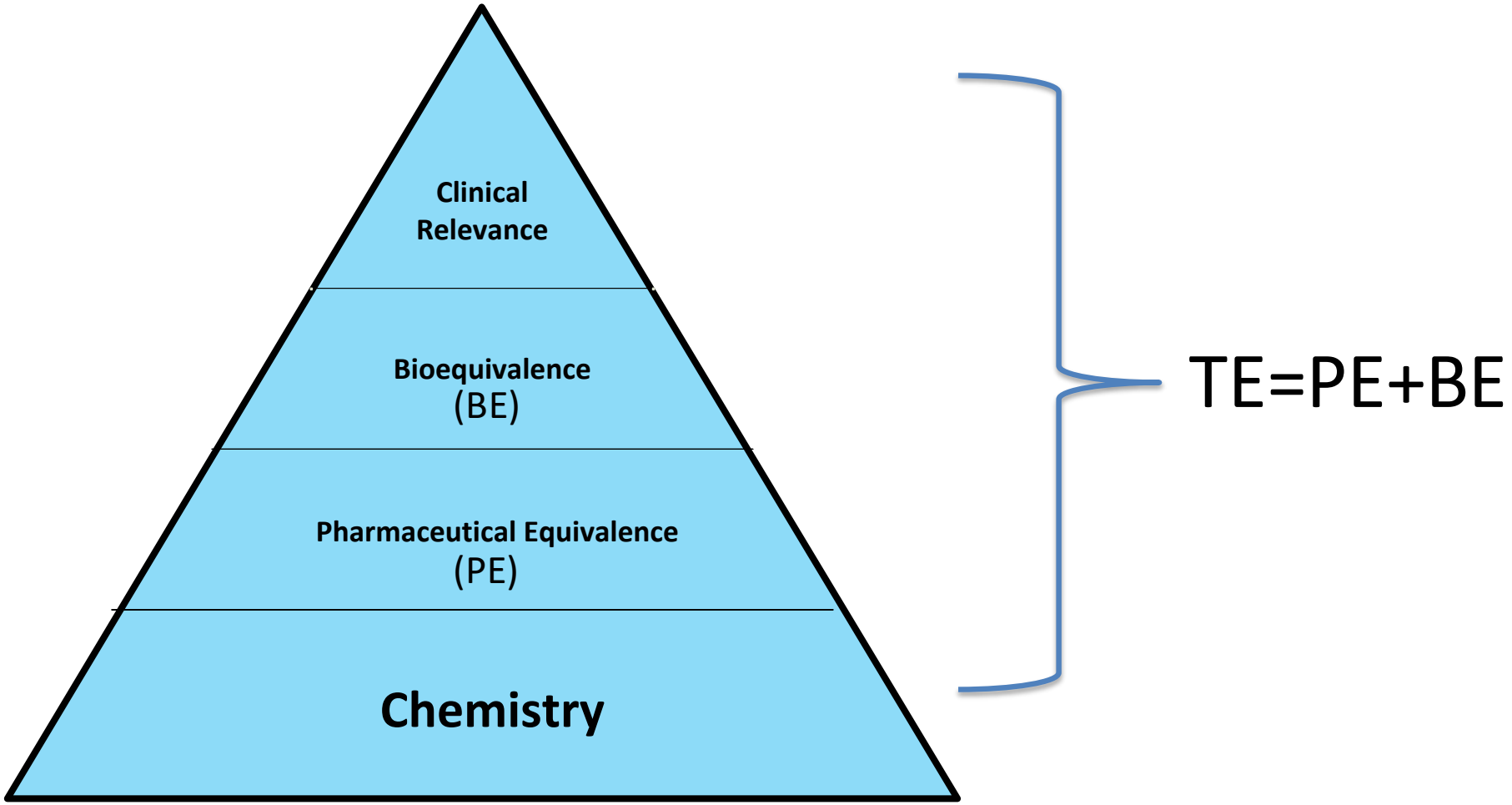
Bioequivalent (BE)

- No significant difference in the rate and extent of absorption of the active ingredient

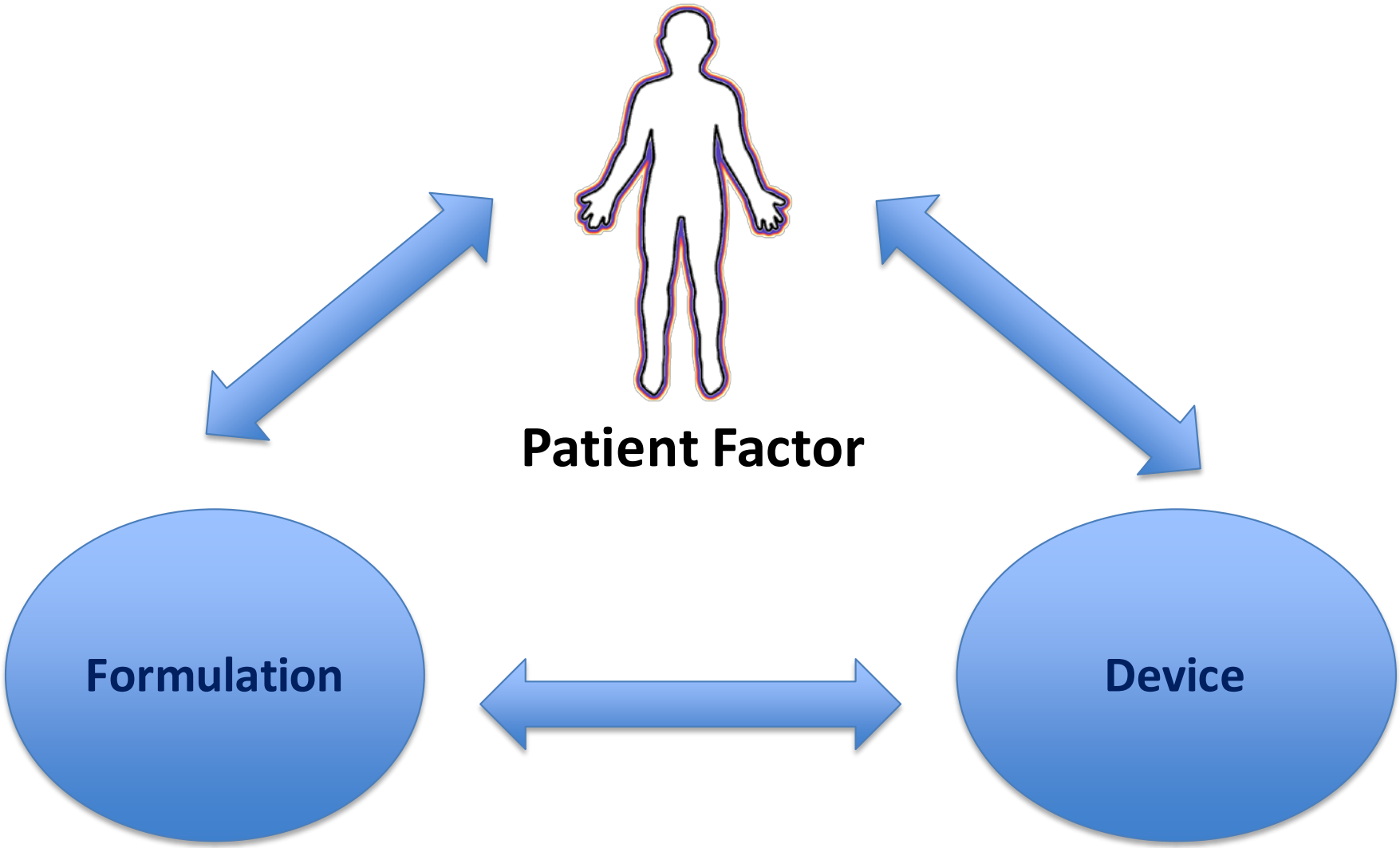
Therapeutically Equivalent (TE)

- The same safety and efficacy when used in the indicated population according to the labeling recommendations

Evaluations of Generic Drugs



Complexity for Orally-Inhaled and Nasal Drug Products



Challenges with Demonstration of TE of Locally Acting Generic OINDPs

- Drug delivery is local to the site of action (e.g., lung tissue), not systemic
  - Intended target effect does not rely primarily on systemic absorption
  - Challenges to measuring local effect
- Device is integral part of the delivered dose
- Several factors influencing drug local and systemic bioavailability include:
  - Patient-device interactions
  - Device-formulation interactions
  - Regional drug distribution
  - Local dissolution/permeability/clearance

TE: therapeutic equivalent

Current Generic Landscape of OINDP

- 68 approved OINDPs
  - ~50 generic nasal products approved (~15 reference listed products)
  - No generics approved for orally-inhaled products
- 39 PSGs were issued since 2013
  - 57% of the approved OINDPs
  - Both in vitro BE only option and a weight of evidence approaches were recommended based on product-specific attributes

13 PSGs (Nasal)	**Current PSGs have in vitro only BE option (for Q1/Q2 the same products)**
26 PSGs (Nasal and Inhaled)	**Current PSGs recommend weight of evidence approach**

Source: Orange Book
PSG: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

GUDFA Research to Address Public Health Needs

Need for approval pathways for these complex products that lack generic competition:

- **Patient need:** To ensure affordable high quality generics are available.
- **Industry need:** To provide a clear, cost- and time-saving ANDA submission path.
  - Alternative BE approaches to avoid costly but insensitive comparative clinical endpoint studies
- **Agency need:** To ensure confidence in the approval pathway and the equivalence of any approved products.

Collaborations is Key to Future Success

Parekh et al, Clin Pharmacol Ther, March 2015

Objectives of Today's Workshop

- Present the outcomes from the research projects initiated under the GDUFA Regulatory Science Research Program;
- Discuss how regulatory science initiatives have helped address regulatory science knowledge gaps by providing insights on factors that influence the performance of generic OINDPs;
- Share the Agency's experience on the utility of novel analytical tools and methods developed under the regulatory science initiative for generic OINDP product development and bioequivalence assessments; and
- Obtain input from the public on what, when, where, and how analytical methods and procedures should be applied in the development and review of abbreviated new drug applications (ANDAs) for complex OINDPs.

FY2018 GDUFA Priority Areas

- Complex active ingredients, formulations, or dosage forms
- Complex routes of delivery
- Complex drug-device combinations
- Tools and methodologies for BE and substitutability evaluation

Save the date: FY 2018 Generic Drug Research Public Workshop

- May 24, 2018, 8:30-4:30 PM
- FDA White Oak Campus

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Thank You!

- Presenters and panelists
- Audience and participants
- Organizers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