

# **LEVERAGING QUANTITATIVE METHODS & MODELING TO MODERNIZE GENERIC DRUG DEVELOPMENT & REVIEW**

## ***INTRODUCTION & WORKSHOP OBJECTIVES***

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# THANK YOU

- Presenters and Panelists
- Audience and participants
- Organizers in OGD

Thank You!

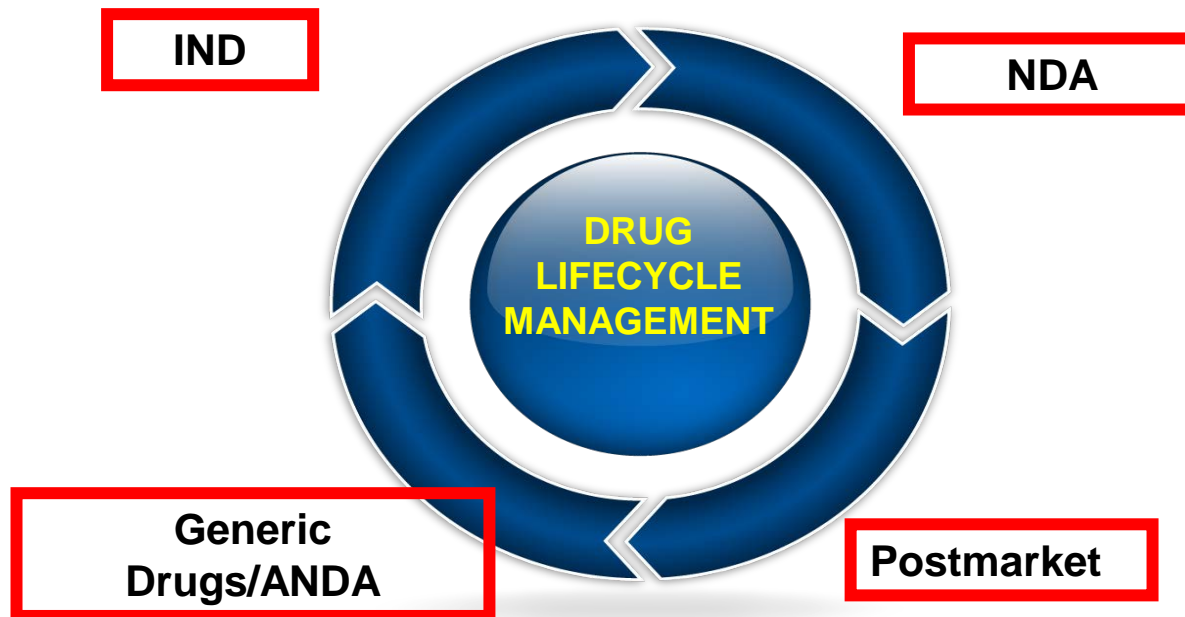
# PURPOSE OF WORKSHOP

1. Engage stakeholders in a discussion of current and emerging approaches and applications of quantitative methods, modeling and simulation (QMM).
2. Gain input regarding opportunities and knowledge gaps related to QMM to inform regulatory decision making through the drug product lifecycle, *with a focus on generic drugs.*



# QUANTITATIVE METHODS (QMM)

*USED IN ALL PHASES OF THE DRUG PRODUCT LIFECYCLE*



- 1. Address scientific and regulatory issues and uncertainties*
- 2. Provide the framework for synthesizing information and extrapolating beyond what has been studied/submitted in application*



# QMM: PKPD and PBPK Modeling for NEW Drugs *Current Uses*

1. Drug-drug Interactions (DDI) – most experienced area
2. Dosing recommendations in labeling
3. Dose extrapolation (peds or other populations)
4. Dose determination for patients with organ dysfunction
5. Justification for prioritizing studies (“when”)
6. Supporting a particular study design (“how”)



# Model-Informed NEW Drug Development

- Tools used to improve NEW drug development strategy and decision making
- “Development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making” (Lalonde)
- FDA identified MIDD as an important pathway for lowering drug attrition and dealing with regulatory uncertainty with NDAs

Indication	MBDD approach adopted	Efficiencies gained over historical designs and analysis
Thromboembolism <sup>a</sup>	Omit phase IIa, model-based dose–response relationship, adaptive phase IIb design	2,750 Fewer patients, 1 year shorter study duration
Hot flashes	Model-based dose–response relationship	1,000 Fewer patients
Fibromyalgia	Prior data supplementation, model-based dose–response relationship, sequential design	760 Fewer patients, 1 year shorter study duration
Type 2 diabetes	Prior data supplementation, model-based dose–response relationship	120 Fewer patients, 1 year shorter study duration
Gastroesophageal reflux	Model-based dose–response relationship	1,025 Fewer patients
Rheumatoid arthritis	Model-based dose–response relationship	437 Fewer patients, increased probability of success
Global anxiety disorder	Omit phase IIb	260 Fewer patients, 1 year shorter study duration
Lower urinary tract symptoms	Meta-analysis	Increased probability of success
Urinary incontinence	Meta-analysis	Increased probability of success

MBDD, model-based drug development.

# QMM OPPORTUNITIES FOR GENERICS

- 1. LEVERAGE knowledge and experience in new drug space for generic drug development, review and regulatory decision making
- 2. Identify BEST PRACTICES to improve the use and acceptance of QMM for generic drug development, review and regulatory decision making

**MODERNIZE**  
**INNOVATE**  
**INTEGRATE**

# **WHY GENERIC DRUGS AND WHY NOW??**





# IMPACT OF GENERIC DRUGS

## *VALUE PROPOSITION*

- ~90% of drugs dispensed in the US are generics
- Only ~27% of drug spending
- Generic drugs saved the US healthcare system **\$1.67 Trillion** in last 10 years



# FDA's GENERIC DRUG PROGRAM

- ~1,000 Abbreviated New Drug Applications (ANDA's) submitted annually
- 855 ANDA approvals in FY2017 (11 months)
  - 693 Full Approvals; 162 Tentative Approvals
- ~10,000 currently approved ANDAs
- ~25% of all ANDAs currently approved were approved since GDUFA I, i.e., in the last 5 years



**HUGE VOLUME OF APPLICATIONS TRANSLATES INTO NUMEROUS OPPORTUNITIES FOR QMM**

# WHY NOW?

- *July 2014 – OGD SuperOffice established*
  - “new” Division of Quantitative Methods & Modeling (DQMM)
- *May 19, 2016 OGD public workshop*
  - Mechanistic Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation
- *March 15, 2017 Advisory Committee*
  - Pharmaceutical Science & Clinical Pharmacology AC in conjunction with ASCPT annual meeting
  - Model-informed drug development (MIDD) for new and generic drugs discussions focused on approaches and evidentiary information needed

# WHY NOW?

- **9/11/2017 to the Regulatory Affairs Professionals Society (RAPS) 2017 Regulatory Conference:**

<https://www.fda.gov/NewsEvents/Speeches/ucm575400.htm>

*These tools are especially important to our use of modeling and simulation as part of drug review...across our review program...*

*...making more advanced use of these and similar tools....to make our review process more efficient and scientifically sound...*

*...to make the drug development process more scientifically modern and efficient...*

- **7/7/2017 Blog:**

<https://blogs.fda.gov/fdavoices/index.php/2017/07/how-fda-plans-to-help-consumers-capitalize-on-advances-in-science/>

*Modeling and simulation play a critical role in organizing diverse data sets and exploring alternate study designs...*

*These computing capabilities are becoming a key requirement to the ability of our review staff to manipulate the large data sets that are now a common feature of drug applications.....*

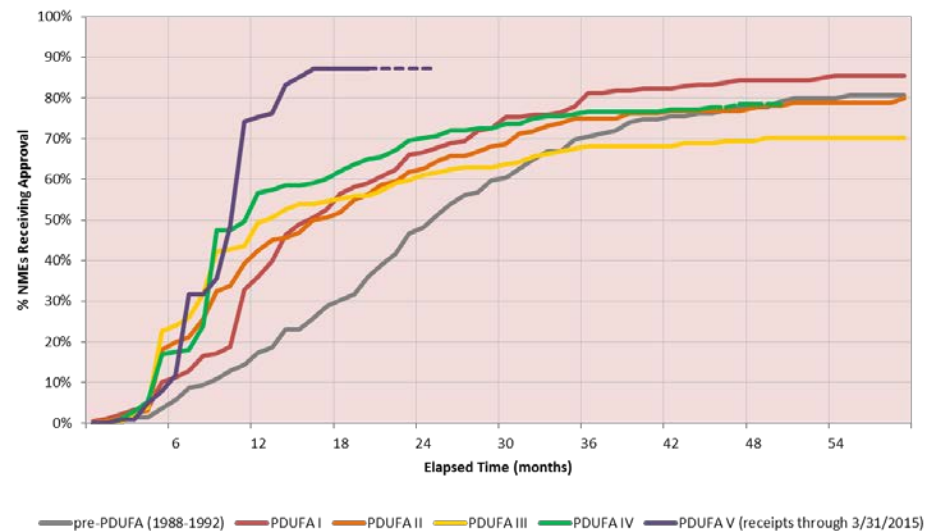
*We're at the beginning of a transformative era in science and medical technology....*



# WHY NOW?

- GDUFA II –
  - Pre-ANDA for complex drug products
  - Need to increase:
    - Access to generic drugs
    - 1<sup>st</sup> cycle approvals
  - Need to decrease:
    - Number of review cycles
    - Time to approval

CDER New Molecular Entity Approval Rates by PDUFA Cohort

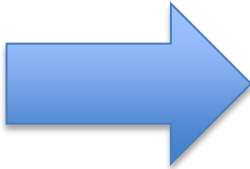


\* PDUFA V estimates based on 77 NMEs submitted in FY 2013 – mid FY 2015 (it is too early to estimate performance for later submissions)  
 Projection estimates account for actions to date and elapsed time to date for non-approvals  
 Data as of 9/30/16

# GDUFA II “PRE-ANDA”

## *Predicting untested clinical situations*

- Complex drug products (defined in GDUFA II)
  - Complex active ingredients, complex formulations, routes of delivery or dosage forms, complex drug-device combinations, and others
  
- Use of mechanism-informed modeling based on knowledge of:
 

<ol style="list-style-type: none"> <li>1. Drug substance property</li> <li>2. Formulation characteristics</li> <li>3. In-vitro release profiles</li> <li>4. Physiologic variables</li> </ol>		<p>PBPK Models Hypothesis Testing Risk Assessment</p>
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- Plenty of “priors” and real world experiences to improve assumptions and to build robust models/conduct simulations that answer important questions
  - Translates into opportunities for more efficient development of drug products with limited generic competition
    - Dermal, inhalant, ophthalmic, nasal, transdermal complex generic drug products

# ANDA requirements:



$$PE + BE = TE$$

## Pharmaceutical Equivalence (PE)

- Same active ingredient as the RLD
- Same route of administration
- Same dosage form
- Same strength

## Bioequivalence (BE)

- Same rate and extent of absorption from RLD
- Do *not* show a significant difference

## Therapeutic Equivalence (TE)

- Same PD effects
- Same efficacy and safety profiles
- Substitutable

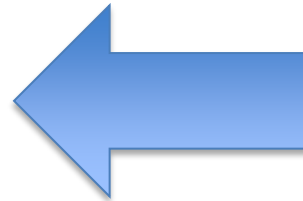


# ANDA requirements:

$$PE + BE = TE$$

## Pharmaceutical Equivalence (PE)

- Same active ingredient as the RLD
- Same route of administration
- Same dosage form
- Same strength



- Formulation strategies
- Dissolution specifications
- Identification of critical quality attributes for BE assessment of locally acting drug product
- In vitro-in vivo correlation for formulation design (IVIC)
- Computational toxicology molecule based-modeling
- Physiologic based PK models (PBPK)
- Quantitative risk models

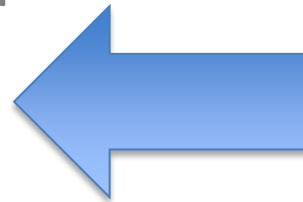


# ANDA requirements:

$$PE + BE = TE$$

## Bioequivalence (BE)

- Same rate and extent of absorption from RLD
- Do *not* show a significant difference



- Food effect predictions
- BE risk assessment
- Improve/modernize BE study design and assessment
- Develop regulatory standards
  - Product-specific guidance
- ADME properties
- Population PK – model-based for drugs with sparse PK
- Virtual BE study
- Exposure-response relationship for S&E
- NTI drugs
- PK/PD & PBPK models
- Quantitative risk models

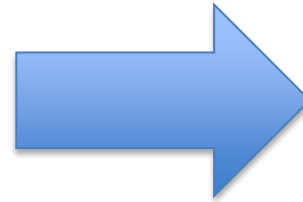


# ANDA requirements:



$$PE + BE = TE$$

- Use of “big” data
- Systems pharmacology
- Postmarket signal detection/evaluation
- Pharmacoeconomic drivers
- ANDA workload predictions
  - Capacity analytics
  - Staffing models
- Quantitative risk models



## Therapeutic Equivalence (TE)

- Same PD effects
- Same efficacy and safety profiles
- Substitutable



# GDUFA II and “PRE-ANDA”/Complex Products

- Translates into LOTS of opportunities for:
  - GENERIC drug industry to conduct and submit QMM (MIDD/PBPK data/analyses) to optimize and streamline generic drug product development
  - FDA to modernize, innovate and integrate regulatory decision making

# GLOBAL FOCUS

- Drug access and affordability is a global public health need
- Drug development is a global enterprise
- FDA frequently viewed as the “Gold Standard” for Global Drug Regulation
- Application to US FDA has become the first choice for international business strategy
- US FDA has the opportunity to lead and collaborate on how to apply these tools more globally:
  - Frequently used, well recognized and accepted for new drug development and regulatory decision making
  - Clinically and scientifically relevant, measurable and reproducible QMM
  - Leverage that experience, knowledge and apply to generic drug development, review and regulatory decision making



# TRANSFORMATIVE POTENTIAL FOR GENERICS

- For generic drug development
- For generic drug regulatory decision making
  - Move beyond the oral absorption model
  - Apply to other locally acting drugs and complex drug products
- For GDUFA II
  - Improve access and approvals
  - Decrease cycles to approval
- Abundant Opportunities

# PLEASE SUBMIT YOUR COMMENTS TO THE DOCKET

- Opportune areas
- Risk-based alternative BE approaches/standards for complex and locally acting
- Emerging QMM methods
- Post-approval evaluation of substitutability/signal detection



