# Model Integrated Evidence as Pivotal Information for Drug Regulatory Decision Making: When, Where, and Why From Generic Drug Perspective

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# Quantitative Methods and Modeling in New and Generic Drug Approvals

- The use of advanced quantitative methods and computational modeling has become part of modern drug development and assessment

- New Drug: Model Informed Drug Development

- Generic Drug: MIDD + MIE?

MIDD: Model informed drug development
MIE: Model integrated evidence

# What is Model Informed Drug Development?

- A powerful tool to guide drug development and can support development and review decision making
- Its scope of application is closely related to data sufficiency and the extent of existing knowledge that can be used to interpret data and extrapolate results
- Modeling and simulation generated data cannot always substitute for the required basic level of clinical evidence in the new drug application (NDA) stage

https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program

Jain et al. CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 5–8

# What is Model Integrated Evidence?

- Using MIE such as the VBE study results not just to plan a pivotal study but to serve as pivotal evidence
  - product approval
  - in combination with relevant *in vitro* BE testings, support alternatives to otherwise recommended conventional *in vivo* studies
- An integration of knowledge and predictive performance of the model for the intended modeling purpose
- Only information that is a combination of science and knowledge, and is sufficiently supported, validated, and verified by prior data, can be classified as MIE for regulatory decision making

Zhao et al. Clin Pharmacol Ther. 2019 Feb;105(2):338-349

# What is a Virtual BE Study?

- Use of model to compare test and reference formulations
- Model must have a formulation variable that can be adjusted to represent the difference between T and R
- Model generates a population for BE study, compares T and R in that population
  - Simulate many studies to estimate probability of success or failure

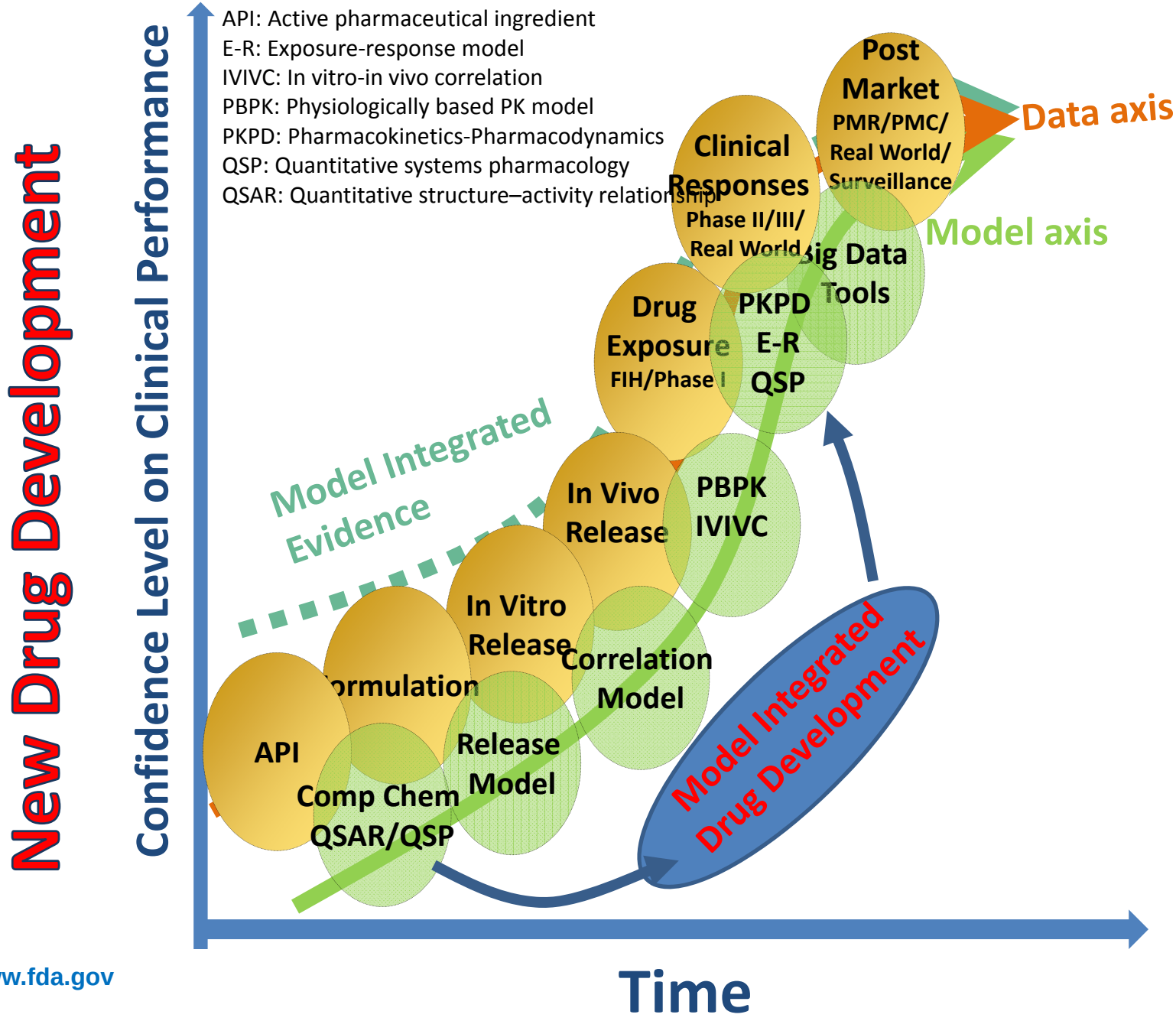
BE: bioequivalence; T: test product; R: reference product

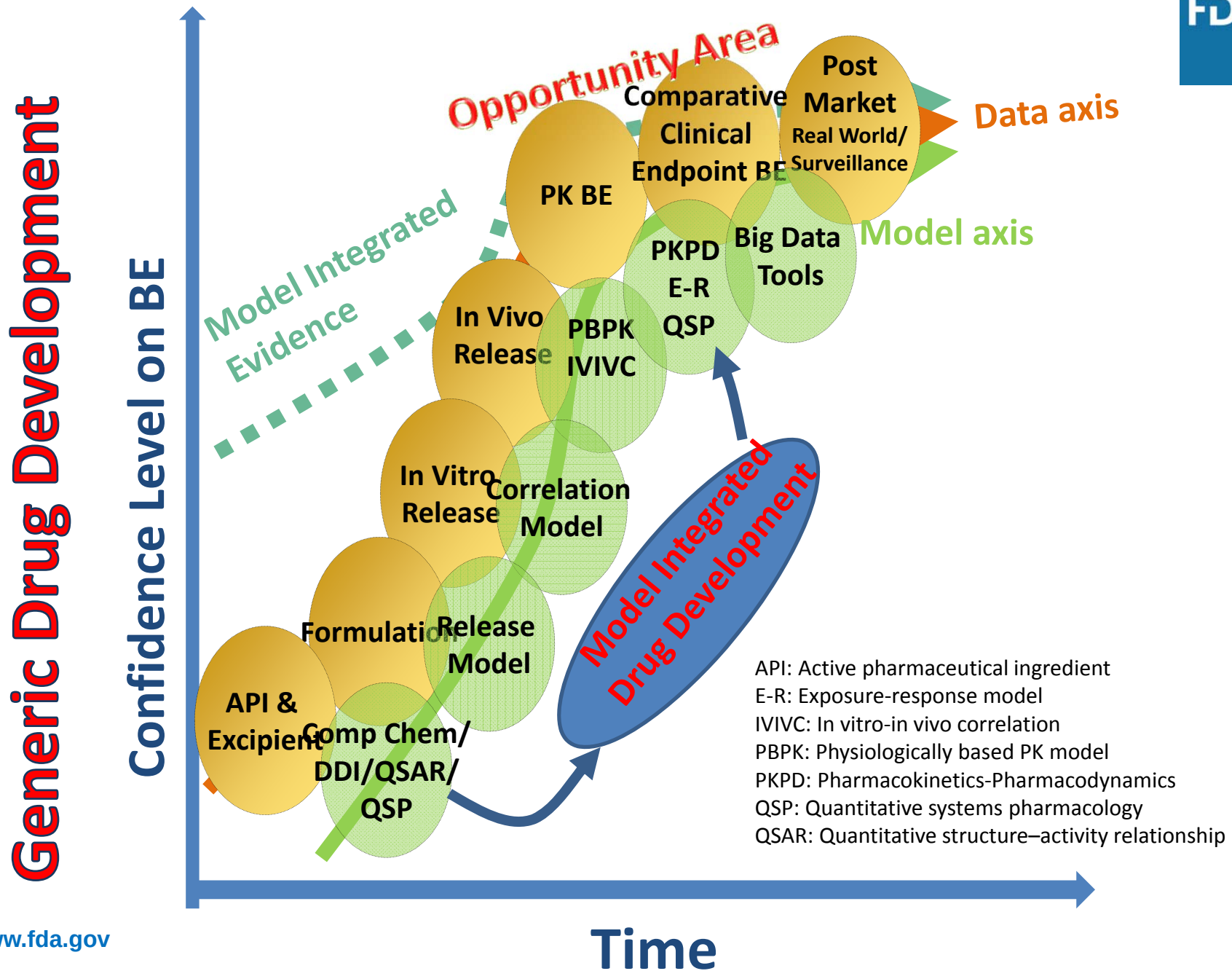
# Modernize ANDA Program to Ensure Timely Availability of High Quality Generic Products via Modeling and Simulation

- Increase first cycle approval rate; decrease number of review cycles
- Shorten drug development timeline
- Develop sensitive and efficient bioequivalence methods
- Reduce exposure of human subjects to unnecessary studies

- ***All of the above are especially important for locally acting, complex, and modified release products.***

ANDA: Abbreviated new drug application
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm631710.htm


New Drug Development
Confidence Level on Clinical Performance
API: Active pharmaceutical ingredient
E-R: Exposure-response model
IVIVC: In vitro-in vivo correlation
PBPK: Physiologically based PK model
PKPD: Pharmacokinetics-Pharmacodynamics
QSP: Quantitative systems pharmacology
QSAR: Quantitative structure–activity relationship
Post Market
PMR/PMC/
Real World/
Surveillance
Data axis
Clinical Responses
Phase II/III/
Real World
Model axis
ig Data
Tools
Drug Exposure
FIH/Phase I
PKPD
E-R
QSP
Model Integrated Evidence
In Vivo Release
PBPK
IVIVC
In Vitro Release
Correlation Model
ormulation
API
Comp Chem
QSAR/QSP
Release Model
Model Integrated Drug Development
Time


Generic Drug Development
Confidence Level on BE
Time
Opportunity Area
Model Integrated Evidence
Data axis
Model axis
Post Market
Real World/ Surveillance
Comparative Clinical Endpoint BE
PK BE
PKPD E-R QSP
Big Data Tools
In Vivo Release
PBPK IVIVC
In Vitro Release
Correlation Model
Formulation
Release Model
API & Excipient
Comp Chem/ DDI/QSAR/ QSP
Model Integrated Drug Development
API: Active pharmaceutical ingredient
E-R: Exposure-response model
IVIVC: In vitro-in vivo correlation
PBPK: Physiologically based PK model
PKPD: Pharmacokinetics-Pharmacodynamics
QSP: Quantitative systems pharmacology
QSAR: Quantitative structure–activity relationship

# Scope of Quantitative Method and Modeling (QMM) Activities

| | Category |
|---|---|
| Regulatory Activities | ANDA Review Consults |
| | Pre-ANDA Meetings |
| | Controlled Correspondence |
| | Guidance Development and Revision |
| | Citizen Petitions |
| Research Activities | GDUFA Grants/Contracts |
| | Internal Regulatory Research Projects |

# Quantitative Clinical Pharmacology (QCP)

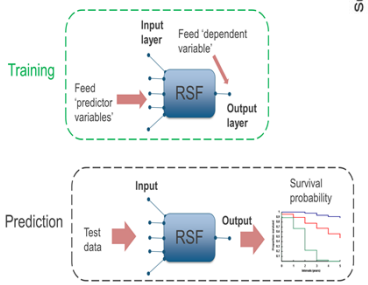
- BE study design and data analysis
  - Pharmacokinetic (PK) endpoints
    - Sparse PK sampling: model-informed optimal BE study design and model-based BE analysis
    - Endogenous baseline correction: appropriate BE metrics and criteria
    - Patient PK study: long-acting injectables
  - Pharmacodynamic (PD) endpoints
    - Dose-scale analysis
    - Endpoint sensitivity assessment
    - Alternative study design
  - Clinical endpoints
    - Clinical trial simulation platform
- PK/PD analysis to support BE recommendations and analysis
    - Narrow therapeutic index (NTI) classification and BE criteria
    - Partial AUC as additional BE metric
    - Model-based BE assessment

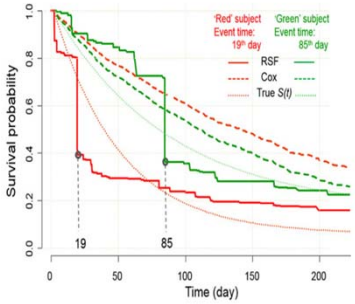
# PBPK for Systemically and Locally Acting Products

- Identification of critical quality attribute and bio-predictive dissolution method
- Determine appropriate systemic PK BE metrics to ensure equivalence on local drug delivery at the site of action
- Justify differences in quality attributes and in vitro testing results from reference listed drug (RLD)
- Simulate virtual BE studies to evaluate effects of formulation difference on systemic and action site drug exposure
  - For locally acting products, PBPK modeling package can potentially be used to support not conducting comparative clinical endpoint (CE) or PD endpoint studies as currently recommended in PSGs
- Advance in vitro approaches to BE for locally-acting products
  - Guide selection of clinically-relevant in vitro tests for BE

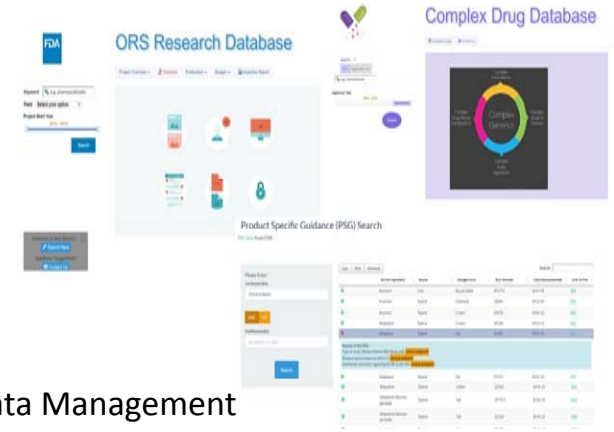
# Data Analytics/Big Data

***Natural Language Processing***



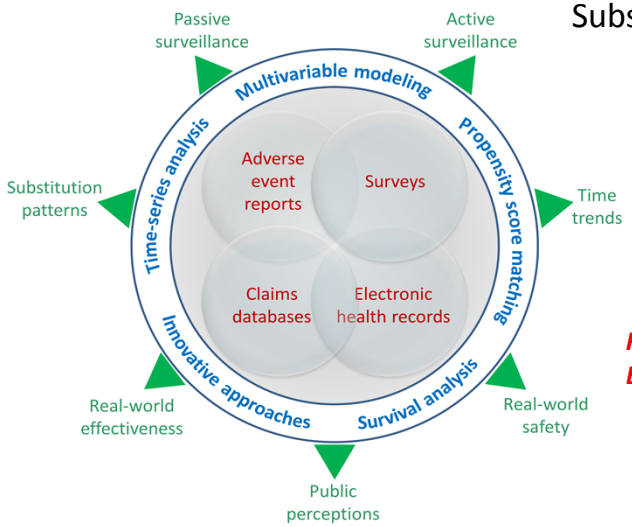




Big Data Analytics

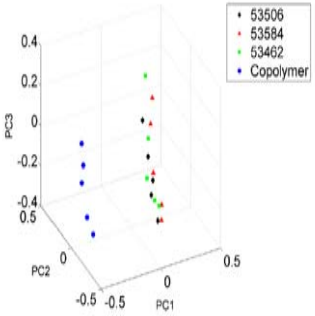


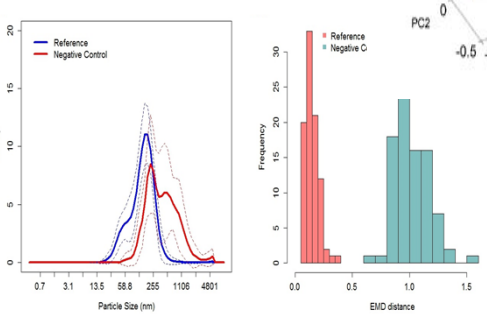

Data Management

Generic Drug Substitution




**In Vitro Bioequivalence**




***Real World Evidence***

# Cases Today

- PK/PK-PD based virtual BE studies for study design and alternative BE pathways
- PBPK models to support not conducting comparative clinical endpoint or PD endpoint studies
- Will not cover new in vitro BE methods and methods for assessing CE/PD endpoints in this talk

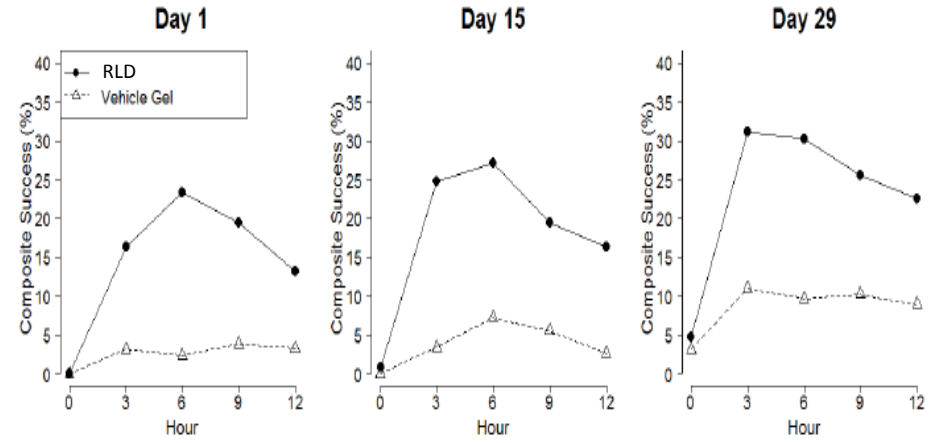
# PK/PD Analysis to Bridge Study Design Gap in BE Assessment

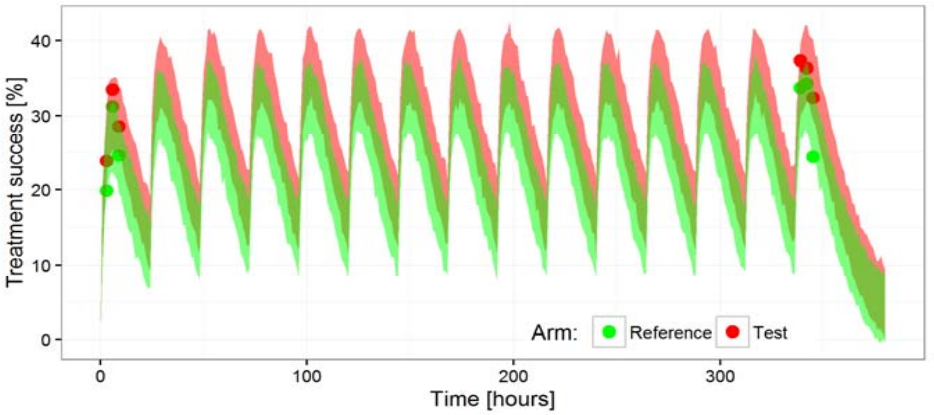
Topical gel for dermatological topical application

**Background**: Comparative clinical endpoint BE study was conducted by the ANDA applicant prior to the issuance of Product-Specific Guidance (PSG), applicant did not assess clinical endpoints on all recommended time points in PSG

**Question:** Any concern for not meeting the BE criteria for those time points not studied?

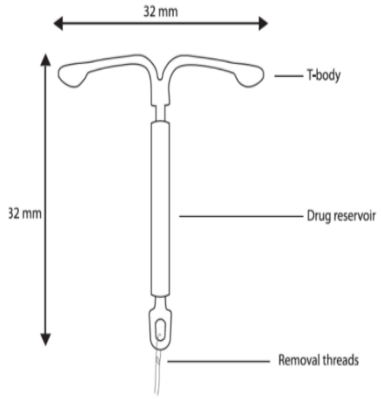
**Impact:** FDA's trial simulations with the validated PD model predicted similar treatment response and supported the tentative approval decision of the ANDA.



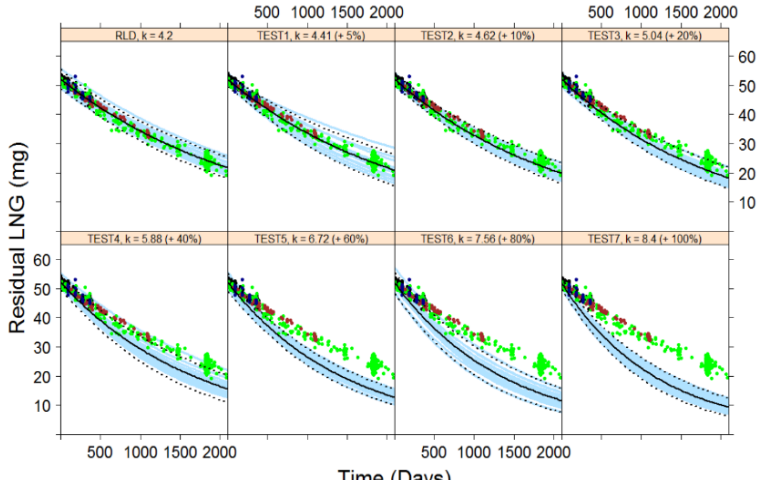
# PK/PD Analysis: Alternate Study Design and BE metrics

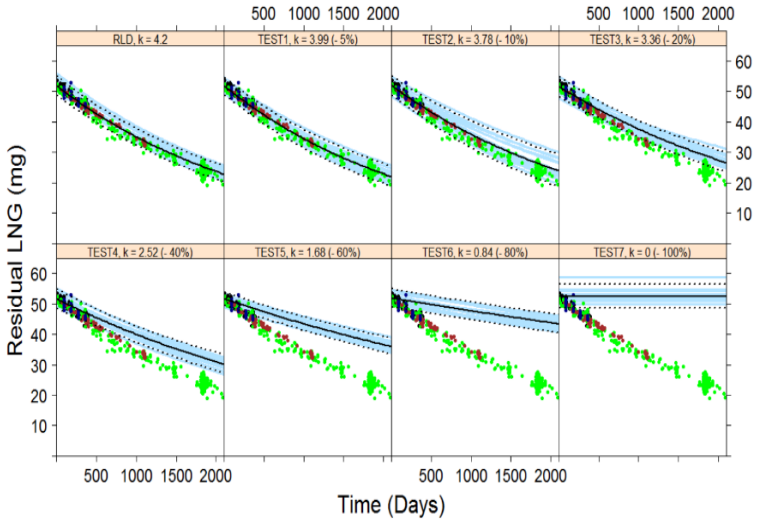
**Background:** Levonorgestrel (LNG) Intrauterine System is indicated for 5 years for prevention of pregnancy.




**Question:** Can Modeling & Simulation (M&S) inform alternative BE metrics and statistical criteria to facilitate generic development?

**Impact:** FDA's M&S analysis suggests that a one-year in vivo BE study and 90% CI within 95.00-105.26% for residual LNG at Month 12 would ensure therapeutic equivalence. A one-year BE study would significantly shorten product development time and could potentially encourage generic competition.



# Current Utilities in PK-PD Model Based Virtual BE Study Simulations

- Study sample size determination
  - Highly variable product
  - Parallel design
  - Sequential/adaptive study design
    - Cost/benefit analysis
- Methodology development
  - Chances to allow a bad product to pass
  - Chances to allow a good product to fail

# PBPK Analysis Supports Alternative BE Approaches

Product X, metered aerosol

**Background:** An alternative BE approach was proposed, including the in vitro tests and PK studies, but no comparative clinical endpoint study. The firm provided predictions from computational fluid dynamics (CFD) and PBPK models, along with data from additional in vitro tests to justify their approach.

**Question:** Is the proposal to eliminate the PD study acceptable, in light of additional PK study and modeling results?

**Impact:** With sufficient model verification, (1) in vitro and in vivo PK BE studies in combination with (2) the PBPK modeling approach can be a viable regulatory pathway to infer locally delivery equivalence.

# PBPK Modeling Supports Alternative BE Approaches

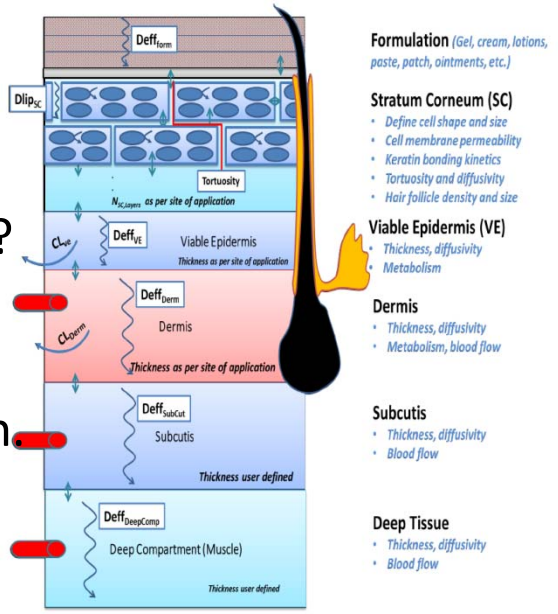
Product Y, Topical Gel  for a topical treatment.

**Background**: The applicant proposed an alternate approach for the BE evaluation which includes Dermal PBPK as part of support of not conducting a comparative clinical endpoint study with a Q1/Q2/Q3 formulation.

**Question**: Is the proposed alternate BE approach acceptable?

**Impact:**

- The PBPK model helped us understand the systemic to local link and supported the propose alternative approach
- (1) A suitably verified PBPK model that can predict both systemic and local PK for test and reference products and (2) in vivo PK BE study supported the BE assessment without conducting a PSG recommended comparative clinical endpoint BE study.



# FDA Expectations for Submitting Modeling Results

- Quantitative Clinical Pharmacology (QCP) models: Following the general practice for empirical based model evaluation approaches

- PBPK models:
  - FDA PBPK guidance: Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry
    - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf
  - PBPK applications to support not conducting comparative CE/PD studies
    - In infancy stage
    - Current additional expectation for model verification that can expedite review

# Current Expectations for PBPK Model Verification

- Proper documentation of the entire model development process
  - A list and justification of model assumptions needs to be provided
- Literature and other data sources utilized for model development and verification need to be properly and accurately cited
- The rationale behind the various decisions made during model development need to be clearly stated and supported by scientific evidence
- Verification standards need to be stated at the initiation of the model verification process and applied throughout
- Incorporation of quality attributes for the drug products of interest is an important component of the model structure
  - when these are not available, the selection of parameter values needs to be justified
- For locally acting products
  - Comparing model-predicted drug concentrations in the local tissues with experimentally obtained values when available in addition to assessing model performance at the systemic exposure level
  - Incorporation of compounds with local, in addition to systemic, experimental data into the verification plan is desirable

# Conclusions

- M & S critical impact on generic drug review and approval
  - Generating Model Integrated Evidence for Generic Drug Development and Assessment (Clin Pharmacol Ther. 2019 Feb;105(2):338-349)

- Model verification serves as a key step in using model to inform regulatory and drug development decisions
  - ASCPT preconference on PBPK for locally acting drug products in March 2019
  - February 2019 CPT theme issue for “Generic Drugs”

- Looking into the future
  - More collaborations between the agency and generic industry are key to the successful value creations for generic and new drug development and approval via quantitative methods and modeling

# Acknowledgment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- Office of Biostatistics

## Office of Product Quality

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  - Paul Seo


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ADMINISTRATION

# What is Model Integrated Evidence?

- Quantitative methods and modeling (QMM) have been increasingly applied by the FDA to facilitate generic drug development and review
  - Playing a critical role in the modernization of bioequivalence (BE) assessment
  - Aiding the development of novel BE methods, in vitro-only BE approaches, and risk-based evaluations
- QMM can critically guide drug development
- QMM can provide information about generic drug equivalence in groups or situations that are not studied directly
- Model integrated evidence or virtual BE studies to potentially provide pivotal information for generic drug approval

Zhao et al. Clin Pharmacol Ther. 2019 Feb;105(2):338-349

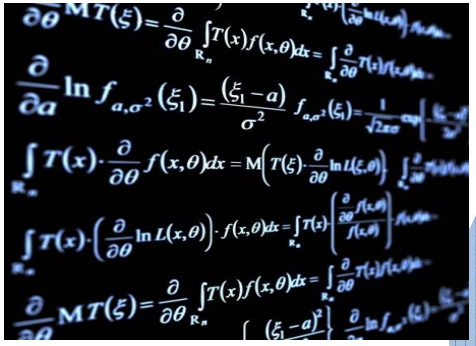
# Core Tool Sets to Aid Generic Drug Development and Approval

## Our Goal is to facilitate

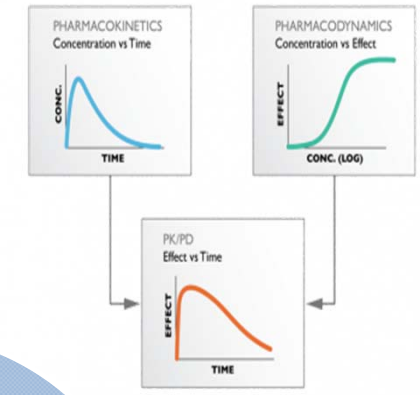
- Generic drug development/review
- Policy development
- Regulatory decisions

Non-Oral Drug

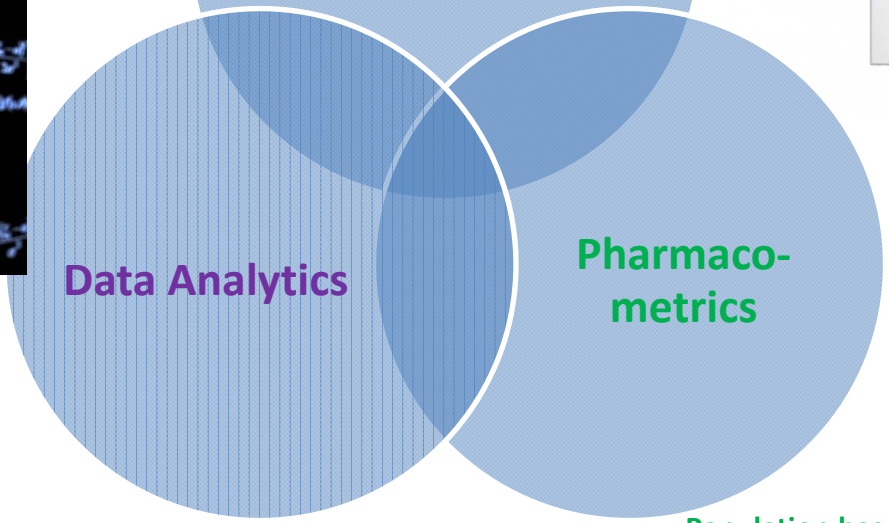
Oral Drug

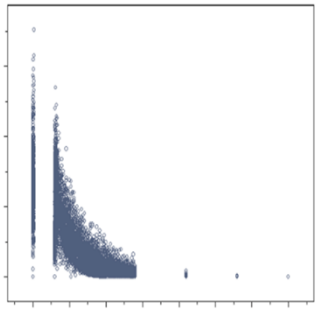


Machine learning toolsets
Analytics for complex mixtures
Systems pharmacology
Risk-based models
Business process models




PK-PD model



Population based model

# 18 Topic Areas with Various Levels of M&S Involvement during GDUFA I (FY2013-2017)

- Complex Mixtures and Peptides
- Database and Knowledge Management
- Drug-Device Combinations
- Drug Products that Incorporate Nanotechnology
- Generic Drug Utilization and Substitution
- Locally-Acting Gastrointestinal Drugs
- Locally-Acting Orally Inhaled and Nasal Drug Products
- Long-Acting Injectables and Implants
- Modified Release Drug Products
- Ophthalmic Products
- Oral Abuse-deterrent Opioid Products
- Patient Substitution Studies
- Perceptions of Generic Drugs
- Pharmacokinetic/Pharmacodynamic Models and Pharmacometrics
- Physiologically-Based Absorption and Pharmacokinetic Models for Non-Oral Routes
- Predictive Dissolution and Physiological Models of Oral Absorption
- Topical Dermatological Drug Products
- Transdermal Drug Products

# PK/PD Analysis to Evaluate Clinical Impact of PK Differences

Naproxen sodium extended-release tablets: treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, acute gout, primary dysmenorrhea, and the relief of mild to moderate pain

**Background**: Generic product was observed to have a delayed Tmax but similar concentrations compared to the RLD.

**Question:** Does Tmax differences observed between generic and RLD have any clinical implications for acute analgesic effect?

**Impact:** PD simulations predicted that generic and RLD had similar onset of action for acute effect in spite of Tmax difference. ANDA supplement was approved.