Quantitative Methods and Modeling in Regulatory Science

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Office of Research and Standards

Office of Generic Drugs

Center for Drug Evaluation and Research

Food & Drug Administration

Friday, March 6th, 2020, The Ohio State University

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

My Memorable Moments at OSU

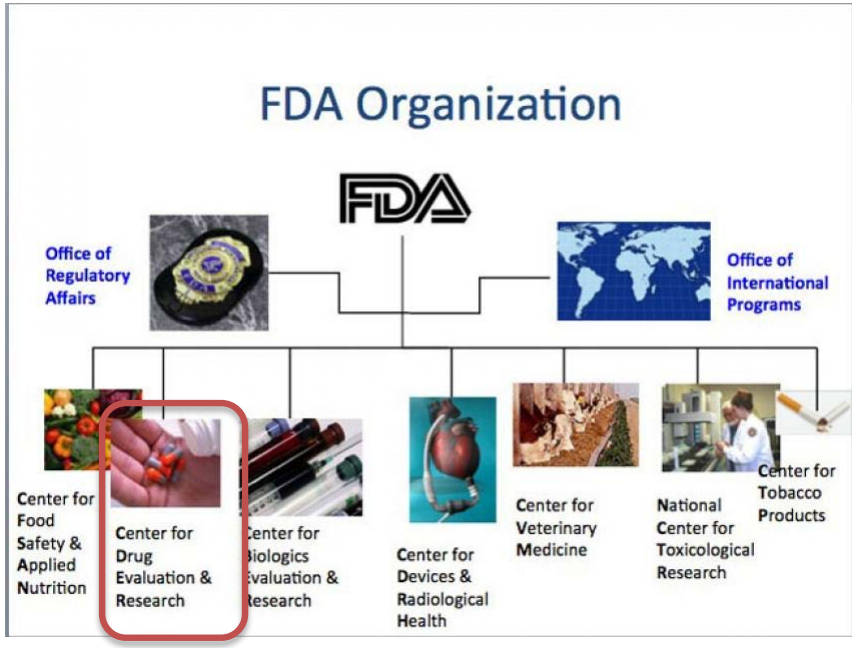
- A PhD student in Pharmaceutical Sciences in 9/1998
- The birth of my daughter (Sally Zhao) in 9/2001
- 2002 Ohio State University (OSU) Football- National Championship!!!
- The birth of my son (Philip Zhao) in 9/2003
- PhD degree in 12/2003
- Master degree in Applied Statistics 3/2004

Agenda Today

- Introduction to the regulatory science program under Office of Generic Drugs

- Use of Modeling and Simulation to Support New Bioequivalence (BE) Approaches

FDA Campus



www.fda.gov

Office of Generic Drugs (OGD)

- Located in the Center for Drug Evaluation and Research
- Four Sub-Offices: Bioequivalence, Regulatory Operations, Generic Drug Policy, Research and Standards
- Office of Research and Standards (ORS) – leads the implementation of regulatory science commitments and translates research results into standards for safe, effective, and equivalent generic drugs.

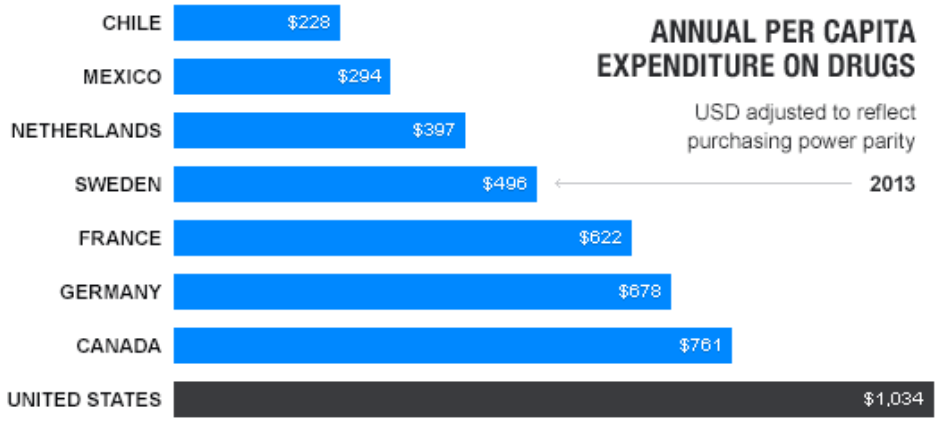
Generic Drugs:

- Are duplicates of brand-name drugs
- Are the same as those brand name drugs in active ingredients, dosage form, strength, route of administration, quality, performance characteristics, safety, efficacy, and intended use.

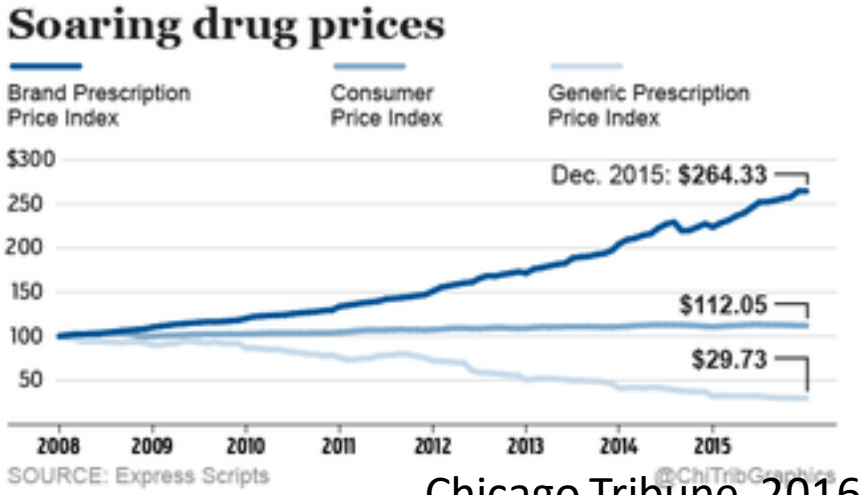
From FDA website – Understanding Generic Drugs
https://www.fda.gov/drugs/buying-using-medicine-safely/generic-drugs

Introduction to Generic Drugs

- Each Abbreviated New Drug Application (ANDA) relies on a reference listed drug (RLD)
- Generic drugs cost less to develop because applicants do not repeat the safety and efficacy studies conducted for RLD approval
- An ANDA generally demonstrates
  - It is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences)
  - It is bioequivalent to the RLD



Fortune, 2015



Chicago Tribune, 2016

Overview of Work at Office of Research and Standards

- Core expertise
- Scope of work: Regulatory-related activities + Research projects
  - Review consults in ANDA submissions
  - Pre-ANDA questions
  - Controlled correspondence
  - Citizen petitions
  - Product-specific guidance development
  - Research projects

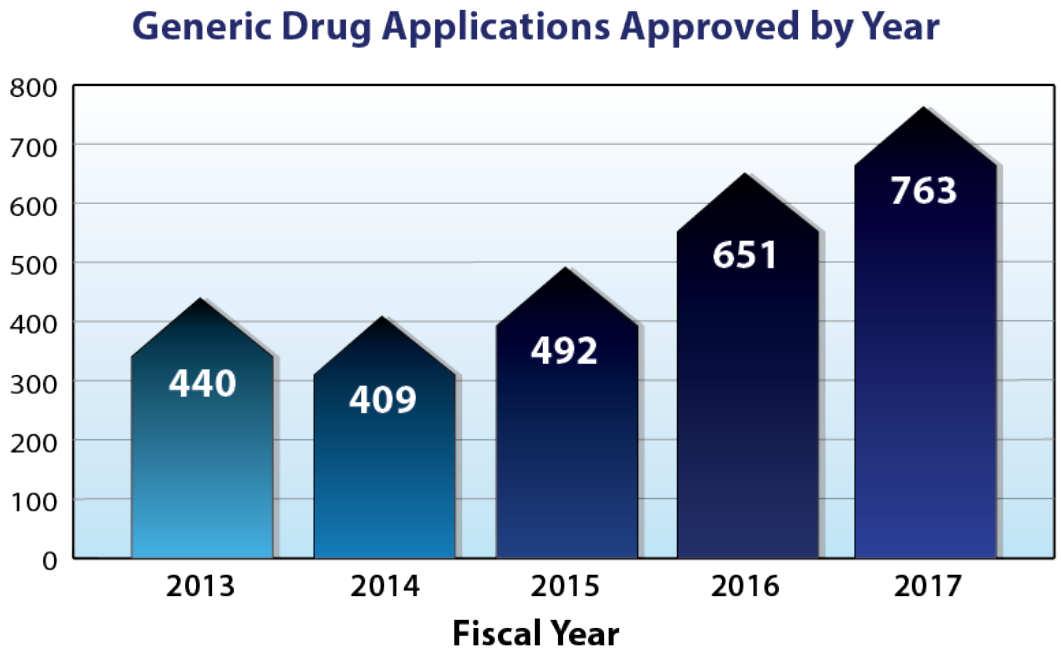
Complex Generic Products in Generic Drug User Fee Amendments (GDUFA) II

- Complex active ingredients
  - Complex mixtures of active pharmaceutical ingredients (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, metered-dose inhalers
- Complex drug-device combination products
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement (e.g., opioid abuse-deterrent formulations)

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

GDUFA Regulatory Science

- FDA has a role in advancing drug science and pharmacologic knowledge helps increase drug access by providing science-based methods and standards for determining equivalence.
- ~$25 million per year on stakeholder-driven generic drug regulatory science
  - Goal: Access to generics in all product categories
  - 90+ ongoing projects
  - Recent focus on complex products



Generic Drug Science & Research Website:
https://www.fda.gov/drugs/generic-drugs/science-research

ORISE Positions

- Post-doctoral fellowship opportunities are available in CDER/OGD/ORS – multiple positions available – fellowship program is administered by Oak Ridge Institute for Science and Education (ORISE) and established via interagency agreement
- Specific areas of scientific expertise
  - Locally acting products including oral inhalation/nasal drug products
  - Solid oral dosage forms
  - Modeling and simulation

OAK RIDGE INSTITUTE FOR SCIENCE AND EDUCATION

Full-time Employment/Post Doc Fellowships

- Looking for a career in regulatory pharmacology and modeling?
- If you are an experienced pharmacologist, scientist, mathematical modeler or physician with interest in drug development, send CV/resume for consideration

  Markham.Luke@FDA.HHS.GOV

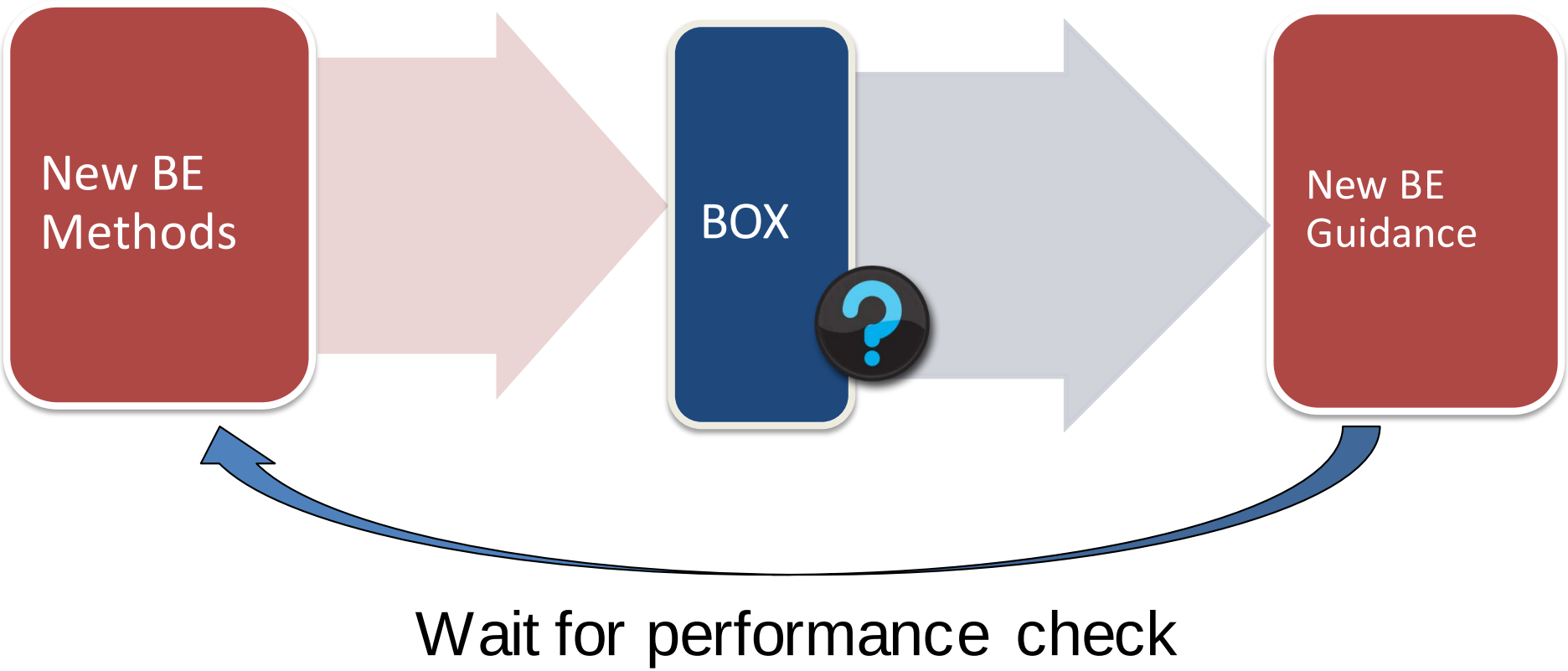
  Liang.Zhao@FDA.HHS.GOV

Extramural Collaborative Funding Opportunities

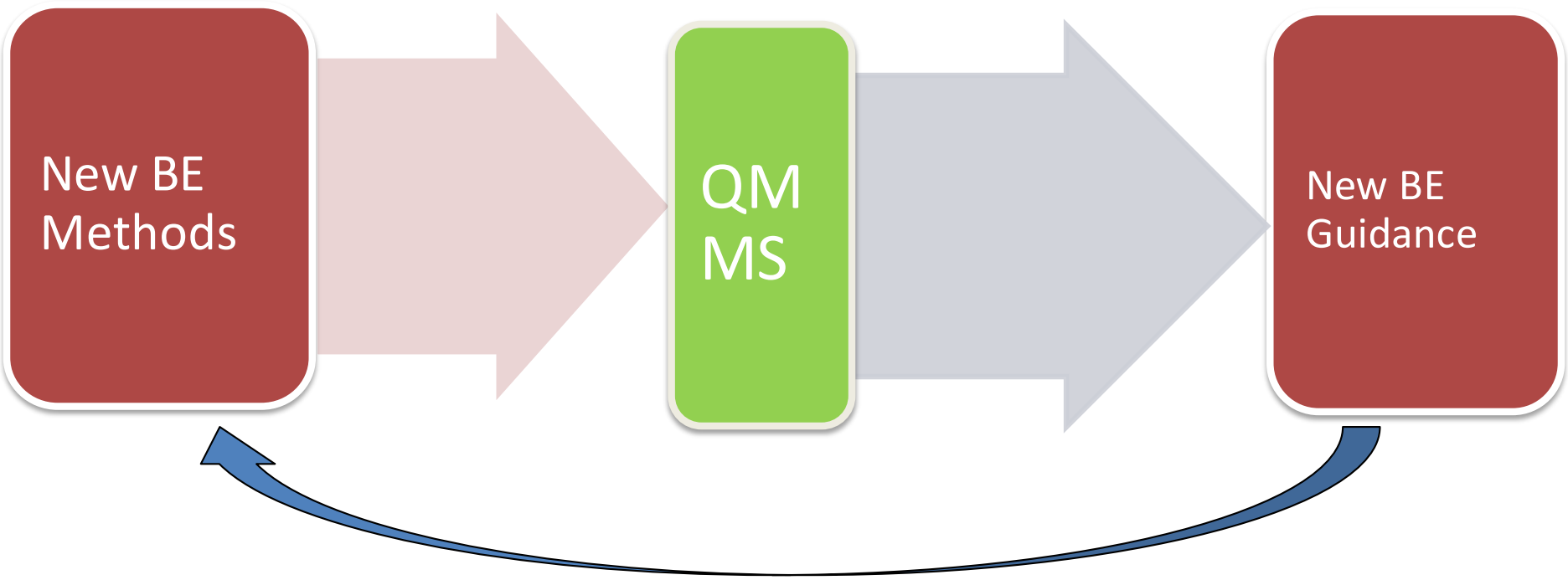
- Contracts (Broad Agency Agreements)
- Collaborative Grants

https://www.fda.gov/drugs/generic-drugs/generic-drugs-collaboration-opportunities

Evaluation of Feasibility of a BE Standard



Evaluation of Feasibility of a BE Standard



QMM: Quantitative Methods and Modeling

- To assess potential factors impacting exposure and/or clinical performance
- To identify appropriate pharmacokinetic (PK) metric to assure therapeutic equivalence
- To calculate the power to conclude BE or Bioinequivalence (BIN) for the associated BE standards ahead of BE guidance implementation

U.S. FOOD & DRUG ADMINISTRATION

Use of Modeling and Simulation to Support New BE Approaches

Modernize ANDA Program to Ensure Timely Availability of High Quality Generic Products

- 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.***

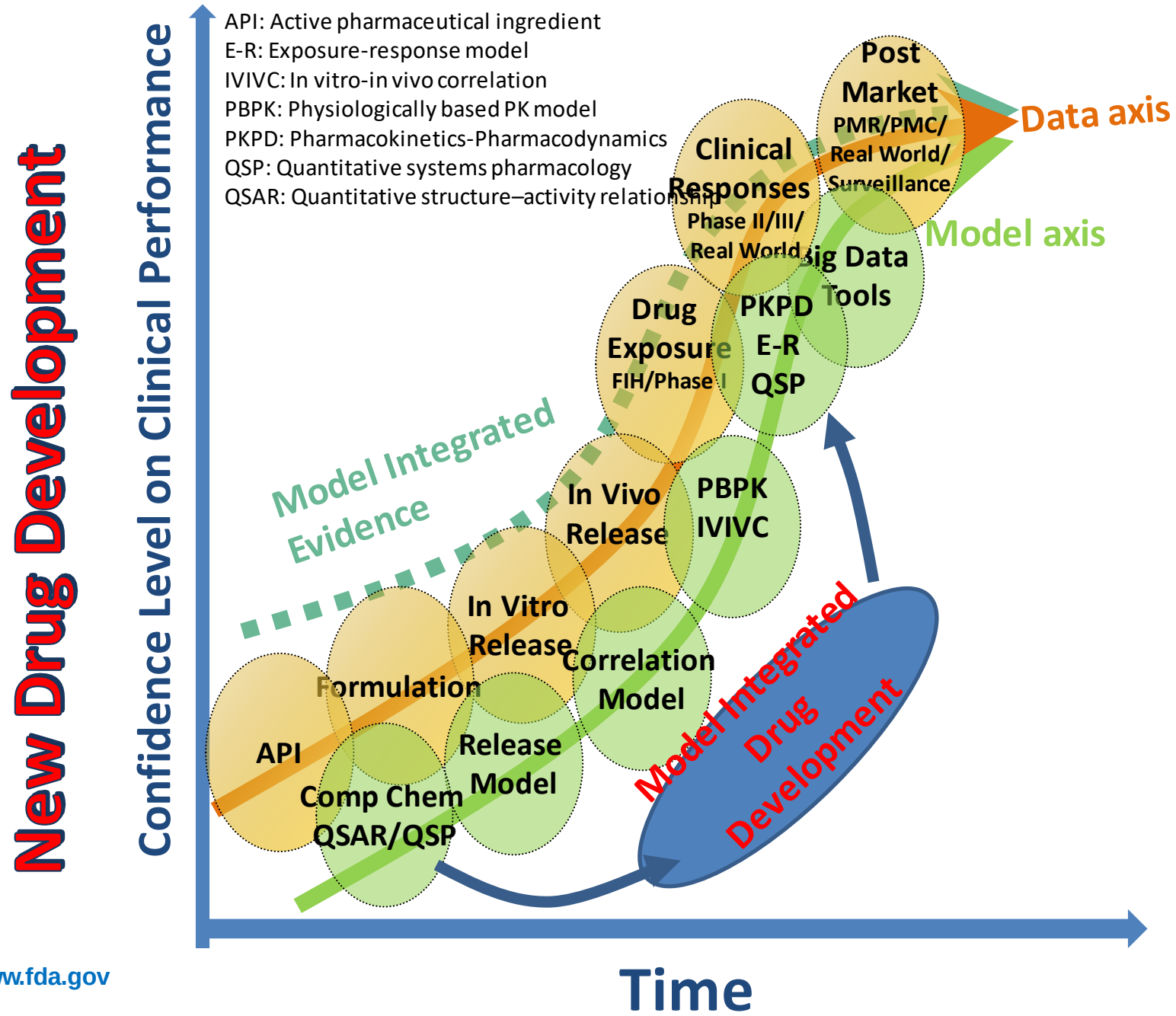
Generating Model Integrated Evidence for Generic Drug Development and Assessment

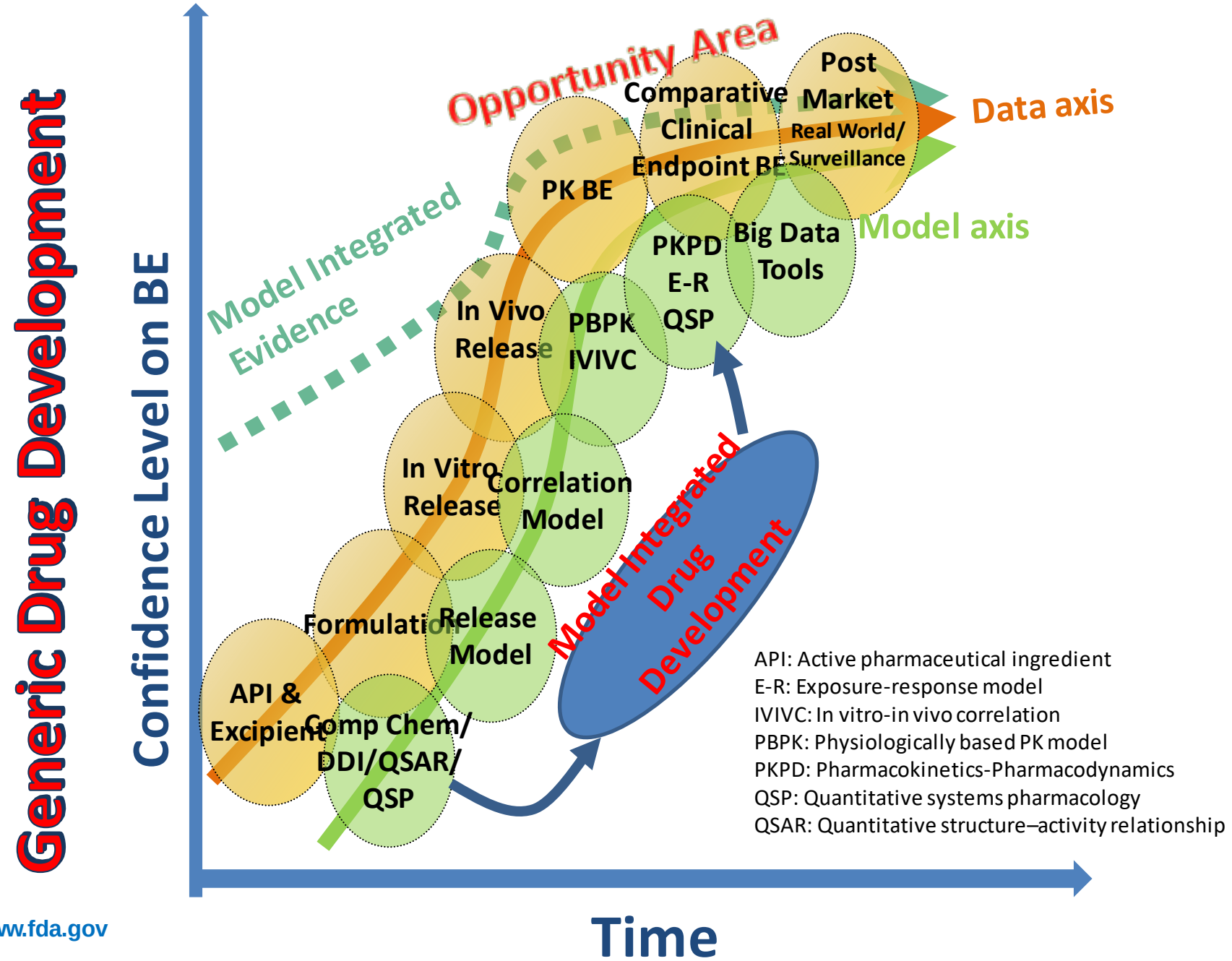
- Quantitative methods and modeling (QMM) has been increasingly applied by FDA to facilitate generic drug development and review
  - Playing a critical role in the modernization of BE assessment

- QMM has aided the development of novel BE methods, in vitro-only BE approaches, and risk-based evaluations

- The future of QMM is model integrated evidence or virtual BE studies that can potentially provide pivotal information for generic drug approval

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


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
New Drug Development
Confidence Level on Clinical Performance
Time
Data axis
Model axis
Post Market
PMR/PMC/
Real World/
Surveillance
Clinical Responses
Phase II/III/
Real World
Big Data Tools
Drug Exposure
FIH/Phase I
PKPD
E-R
QSP
Model Integrated Evidence
In Vivo Release
PBPK
IVIVC
In Vitro Release
Correlation Model
Formulation
API
Comp Chem
QSAR/QSP
Release Model
Model Integrated Drug Development


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
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PKPD: Pharmacokinetics-Pharmacodynamics
QSP: Quantitative systems pharmacology
QSAR: Quantitative structure–activity relationship

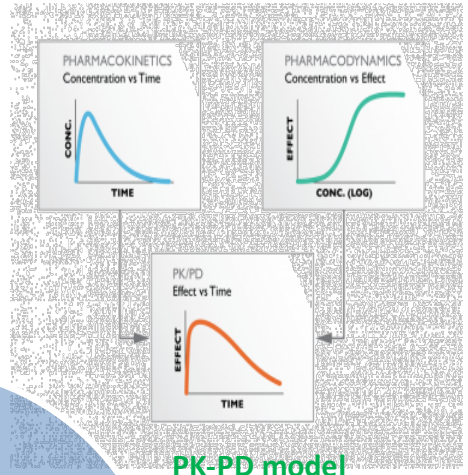
Core Tool Sets to Aid Generic Drug Development and Approval

Our goal is to facilitate

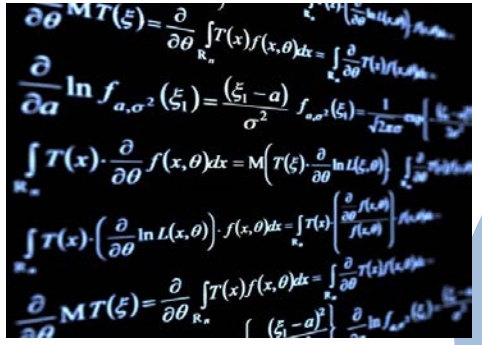
- Generic drug development/review
- Policy development
- Regulatory decisions

Non-Oral Drug

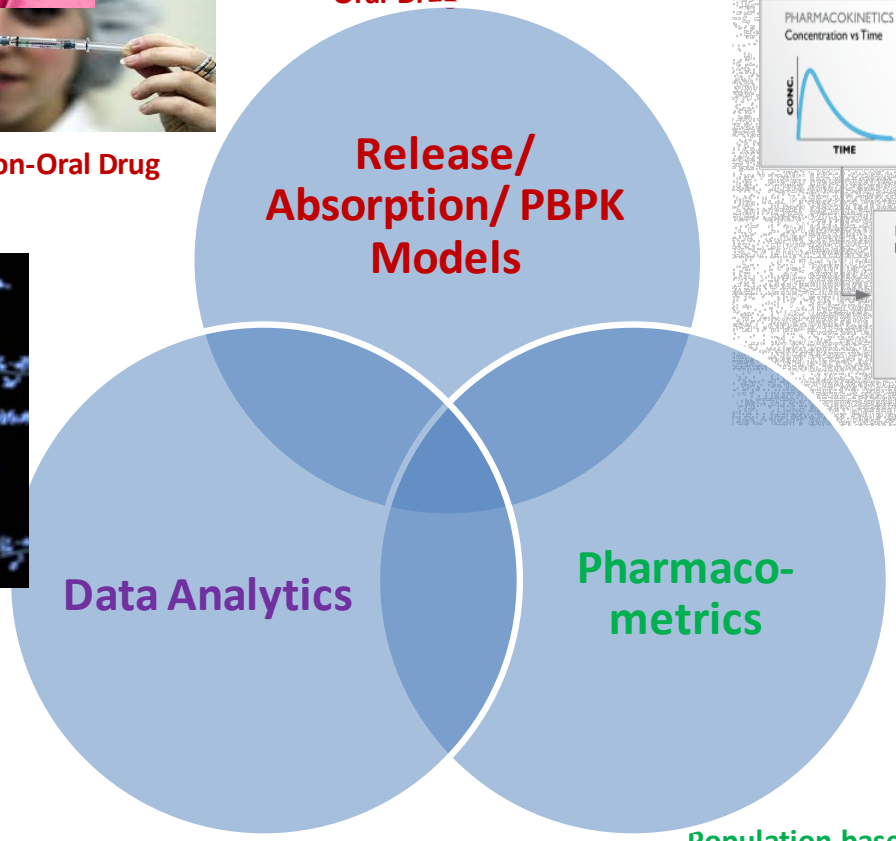
Oral Drug

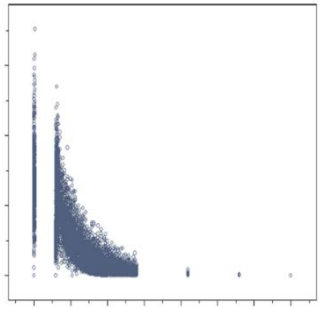


PK-PD model



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





Population based model

18 Topic Areas with Various Levels of QMM 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

GDUFA: Generic Drug User Fee Amendments

21

Scope of Quantitative Method and Modeling (QMM) Activities

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

Quantitative Clinical Pharmacology (QCP)

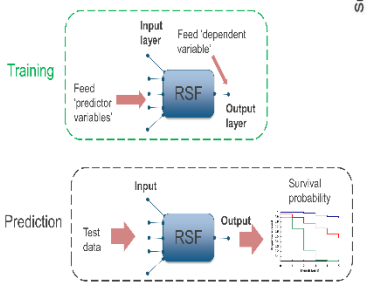
- BE study design and data analysis
  - Pharmacokinetic (PK) endpoints
    - Sparse PK sampling: model-informed optimal BE study design and model-based BE analysis
    - Endogenous baseline correction: appropriate BE metrics and criteria
    - Patient PK study: long-acting injectables
  - Pharmacodynamic (PD) endpoints
    - Dose-scale analysis
    - Endpoint sensitivity assessment
    - Alternative study design
  - Comparative 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

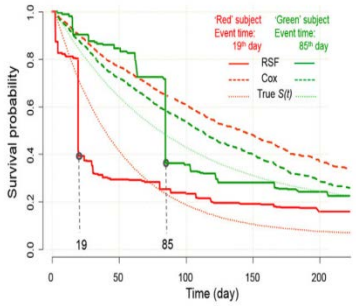
Physiologically Based Pharmacokinetic (PBPK) for Systemically and Locally Acting Products

- Use of PBPK modeling to applicants to support drug product development
  - E.g., Pre-ANDA /ANDA to use PBPK modeling package to support not conducting comparative clinical endpoint (CE) or PD endpoint BE studies
  - Review of regulatory submissions containing PBPK and/or computational fluid dynamic modeling – pre-ANDA meetings and ANDA consults
  - Identification of critical quality attribute and bio-predictive dissolution method
- Advance in vitro approaches to BE for locally acting products (i.e., product-specific guidances) in lieu of conducting a comparative PD/CE BE study
  - Determine appropriate BE metrics on systemic PK to ensure local equivalence
  - Simulate virtual BE studies on local PK based directly on formulation inputs
  - Identification of quality attributes with clinical relevance
  - Justify differences in quality attributes from RLD
  - Guide selection of clinically relevant in vitro tests for BE

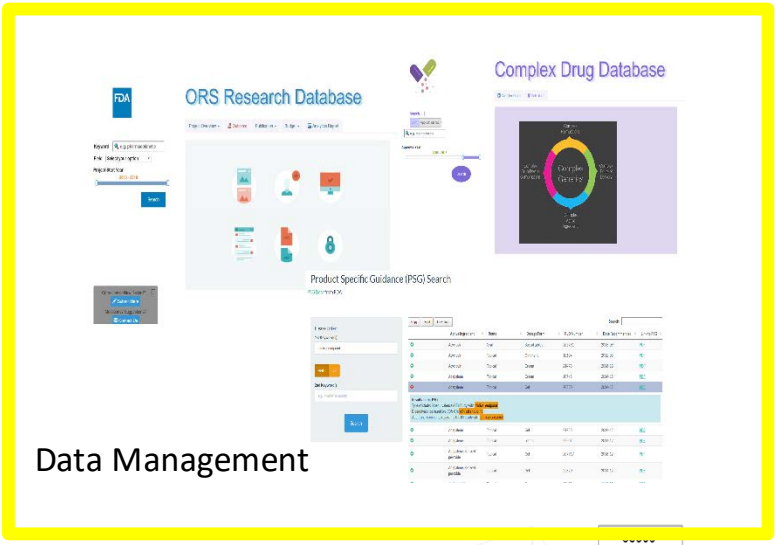
Data Analytics/Big Data

Nature Language Processing



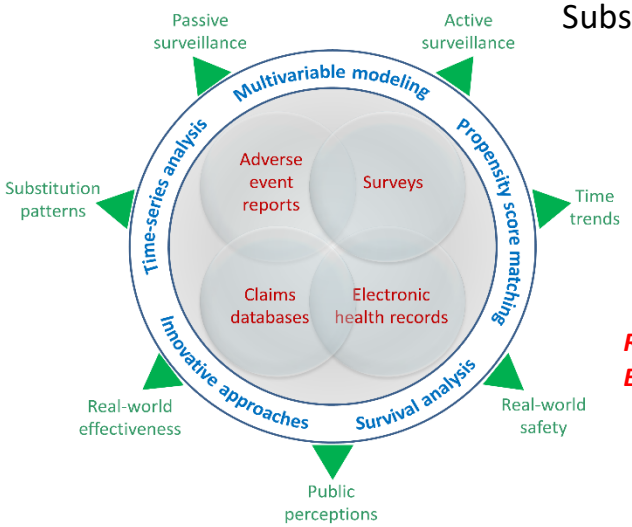


Big Data Analytics



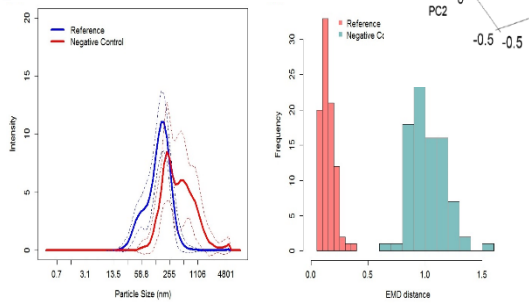
Data Management

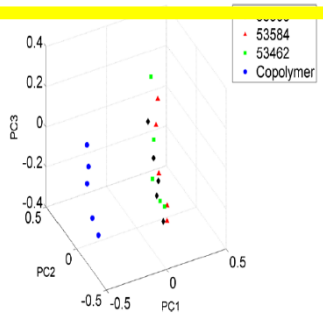
Generic Drug Substitution



Real World Evidence

In Vitro Bioequivalence





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 BE studies

Note: Will not cover new in vitro BE methods and methods for assessing PD/CE endpoints in this talk

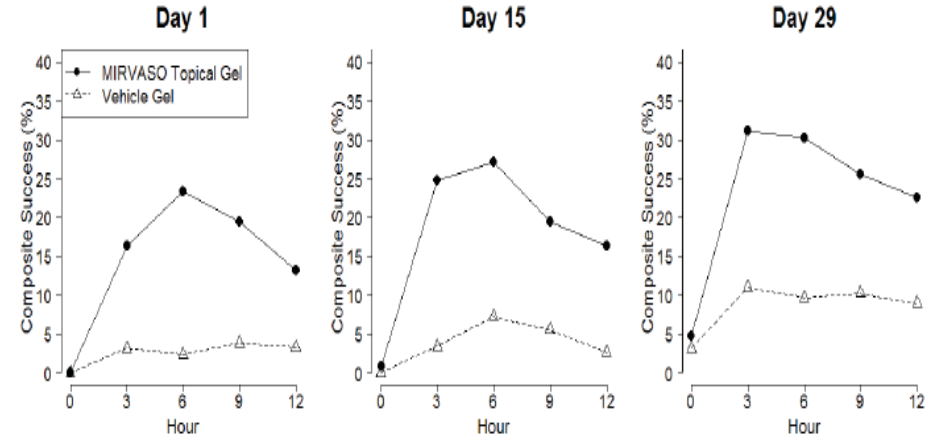
PK/PD Analysis to Bridge Study Design Gap in BE Assessment

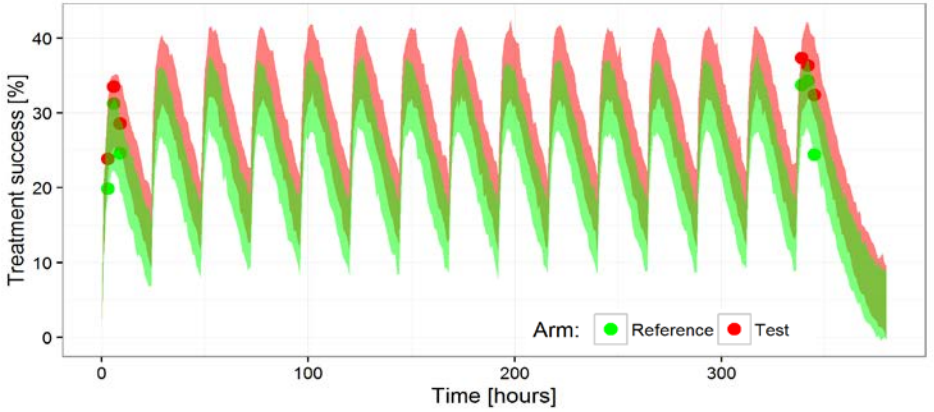
Brimonidine topical gel: for topical treatment of persistent (non-transient) facial erythema of rosacea in adults 18 years of age or older

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 comparative 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.





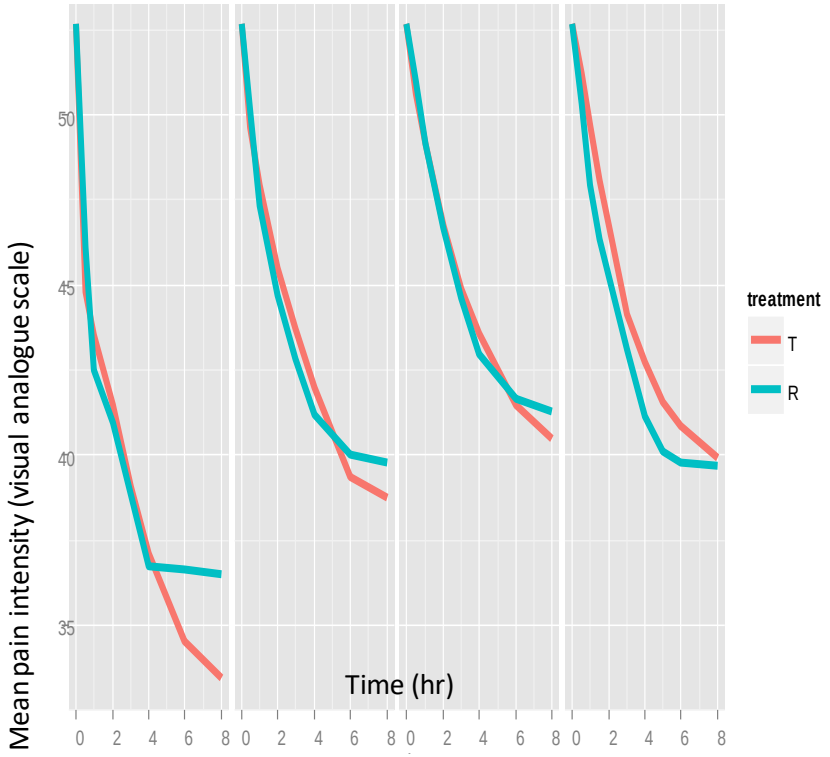
PK/PD Analysis to Evaluate Clinical Impact of PK Differences

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.

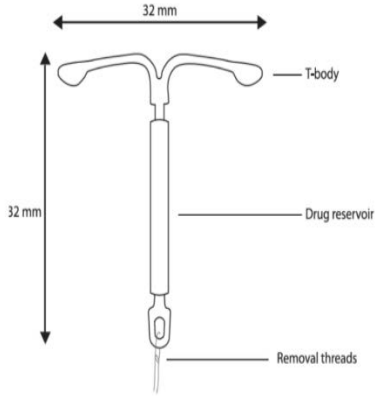
Question: Does Tmax differences observed between generic and RLD have any clinical implications for acute analgesic effect?

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.



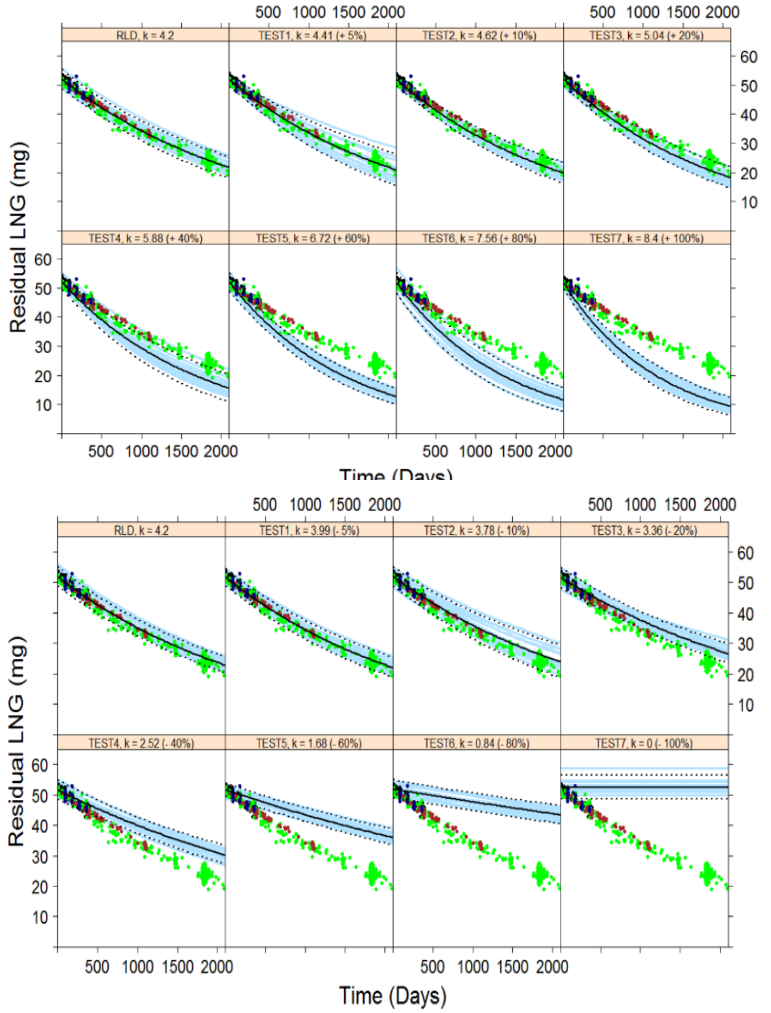
PK/PD Analysis: Alternate Study Design and BE metrics

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 as reflected in our recently published guidance 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 study design
    - Cost/benefit analysis
- Methodology development
  - Minimize chances to allow a bad product to pass
  - Maximize chances to allow a good product to fail

PBPK Analysis Supports Alternative BE Approaches

Product X, metered aerosol: maintenance treatment of asthma as prophylactic therapy

Background: An alternative BE approach was proposed, including the in vitro tests and PK studies, but no comparative clinical endpoint BE study. The applicant 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: The models show promise, particularly the CFD model, in evaluating regional dose while considering device differences. However, the model used to support regulatory decision making should be sufficiently verified.

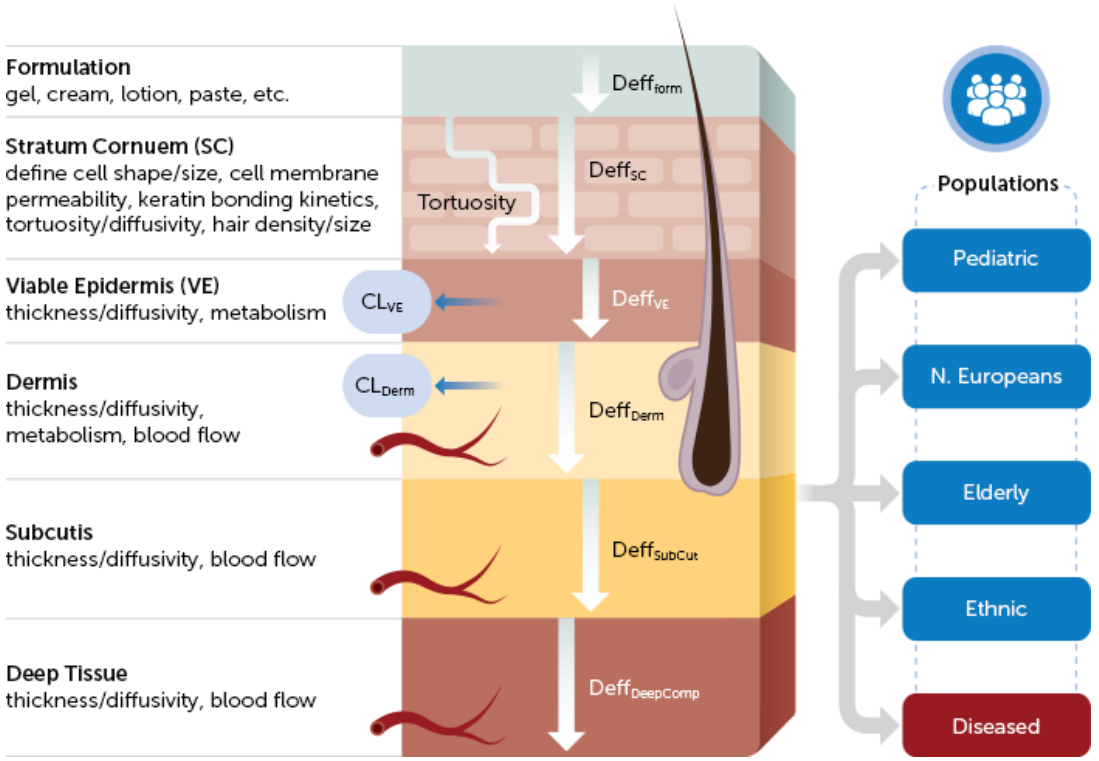
PBPK Modeling Supports Alternative BE Approaches

Product Y, Topical Gel, 1%: a drug indicated for the relief of the pain amenable to 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 study with a Q1/Q2/Q3 formulation.

Question: Is the proposed alternate BE approach acceptable?

Impact: A suitably verified PBPK model can be used to predict both systemic and local PK for this product and support the BE assessment.



https://www.certara.com/2018/03/02/skin-in-the-game-mechanistic-modeling-of-dermal-drug-absorption/?ap=PBPK

FDA Expectations for Modeling Result Submissions

- 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 BE studies
    - In an early stage
    - Currently, additional expectations exist for model verification that can facilitate review

Current Considerations for PBPK Model Verification and Validation

- 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 should to be properly and accurately cited
- The rationale behind the various decisions made during model development should to be clearly stated and supported by scientific evidence
- Verification standards should 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 should 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 drugs with local, in addition to systemic, experimental data into the verification plan is desirable

Conclusions

- M&S critically 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 for PBPK models 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 Clinical Pharmacology Therapeutics theme issue for "Generic Drugs" (https://ascpt.onlinelibrary.wiley.com/toc/15326535/2019/105/2)
  - Current scientific considerations to verify physiologically-based pharmacokinetic models and their implications for locally acting products (CPT Pharmacometrics Syst Pharmacol. 2019 Jun;8(6):347-351)
- Looking to the future
  - More collaborations among agency, academia, and generic industry are key to the successful value creations for generic and new drug development and approval via quantitative methods and modeling

Acknowledgment

Office of Generic Drugs

- Office of Research and Standards (ORS)
  - Robert Lionberger
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  - Andrew Babiskin
  - Sue-chih Lee
  - Meng Hu
  - All Scientists in DQMM
- ORS/Division of Therapeutic Performance
- Office of Bioequivalence

Office of Translational Sciences

- Office of Clinical Pharmacology
  - Shiew-Mei Huang
  - Colleen Kuemmel
  - Issam Zineh
- Office of Biostatistics

Office of Product Quality

- Division of Biopharmaceutics, Office of New Drug Products
  - Paul Seo


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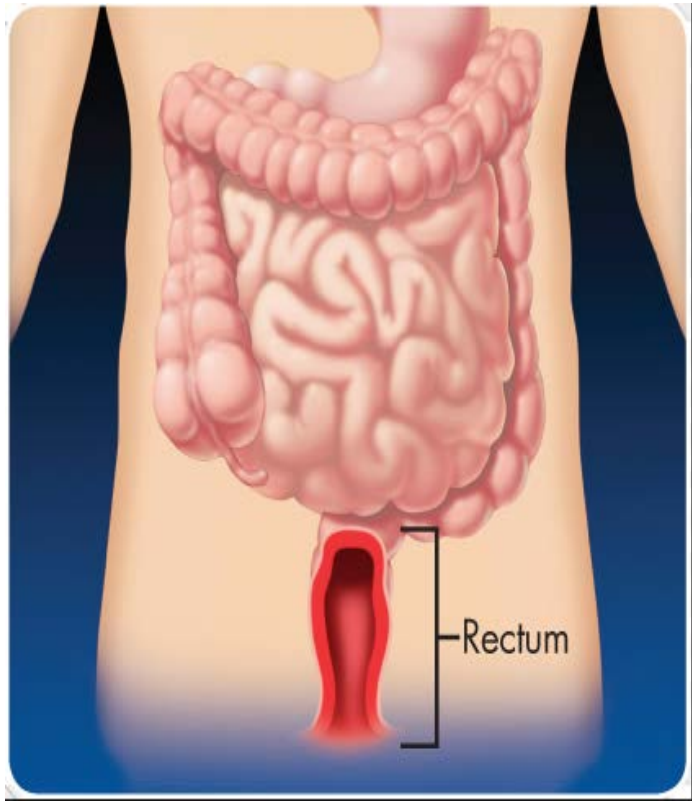
PBPK Analysis Supports Mesalamine Rectal Suppository BE Evaluation

Mesalamine suppositories: for the treatment of mild to moderate active ulcerative proctitis

Background: The 90% confidence intervals (CIs) of $AUC_{0-\infty}$ did not meet the 80.00-125.00% limit for the test product.

Question: What is the clinically relevant BE limit for $AUC_{0-\infty}$ in assessing BE of mesalamine suppository products?

Impact: PBPK modeling and simulation suggested $AUC_{0-\infty}$ may be evaluated as a supporting not a pivotal BE metric for this ANDA and supported the tentative approval decision of the ANDA.



PK/PD Analysis: pAUC Recommendation for Abuse-Deterrent Opioids

Background: Oral and nasal PK studies are recommended to evaluate the abuse deterrence of the test abuse-deterrent opioid products in comparison with the RLD when physically manipulated or chewed.

Question: What's the clinically relevant PK metrics in assessing human abuse potentials?

Impact: FDA's PK/PD analysis supports partial AUC (pAUC) recommendation for seven product-specific guidances of abuse-deterrent opioids.

NDA #	API	Trade Name	Dosage Form	In vivo PK AD studies	pAUC recommendation
022272	Oxycodone HCl	**OxyContin**	ER Tablet	IN	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
022321	Morphine Sulfate; Naltrexone HCl	**Embeda**	ER Capsule	IN, Oral (crushing)	$pAUC_{0\text{-}2hr}$
206627	Hydrocodone Bitartrate	**Hysingla ER**	ER Tablet	IN, Oral (chewing)	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
206544	Morphine Sulfate	**MorphaBond ER**	ER Tablet	IN	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
208090	Oxycodone	**Xtampza ER**	ER Capsule	IN, Oral (chewing and/or crushing)	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
208603	Morphine Sulfate	**Arymo ER***	ER Tablet	IN	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$
209777	Oxycodone HCl	**RoxyBond**	Tablet	IN	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$

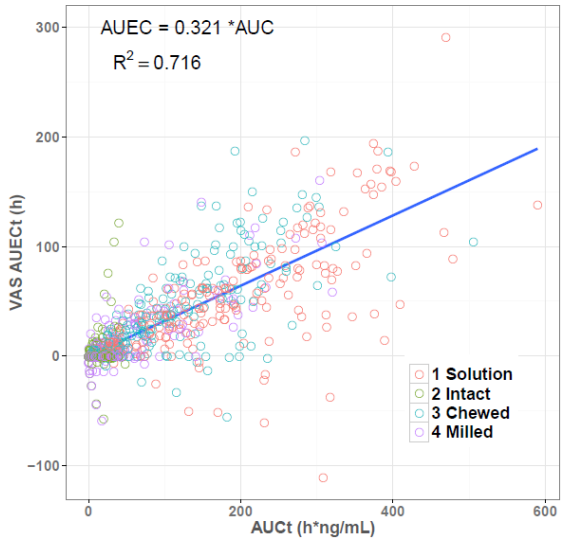
IV: intravenous; IN: intranasal
* The intranasal route is not approved until 2018 due to market exclusivity of MorphaBond

PK metrics of opioids assessing comparative abuse deterrence:

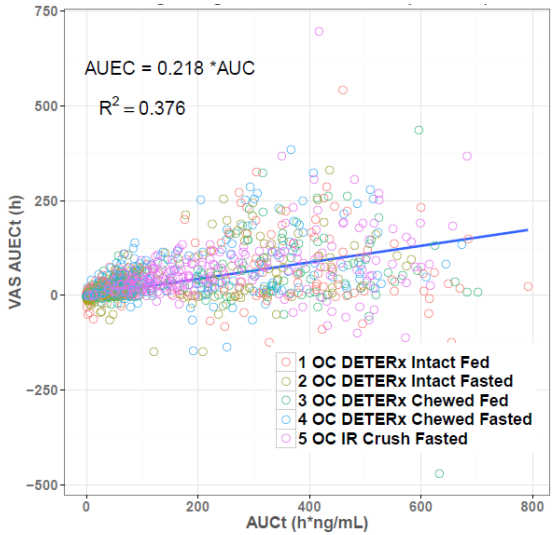
- Cmax and AUC: Upper 95% confidence bound ≤ 125.00%
- pAUC as supportive data: Point estimate ≤ 125.00%

VAS PAUEC$_{0-4}$ and PAUC$_{0-4}$

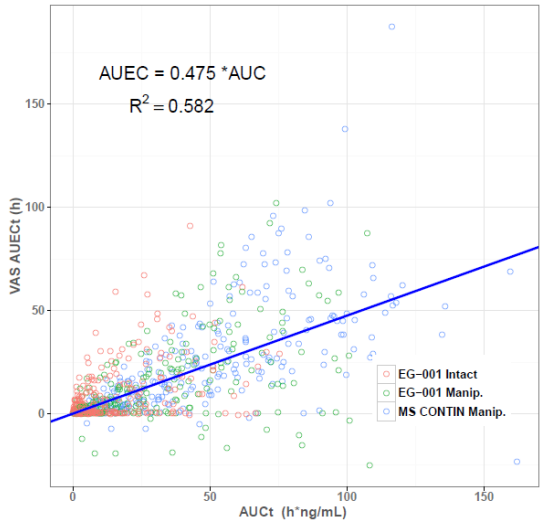
Hydrocodone Oral



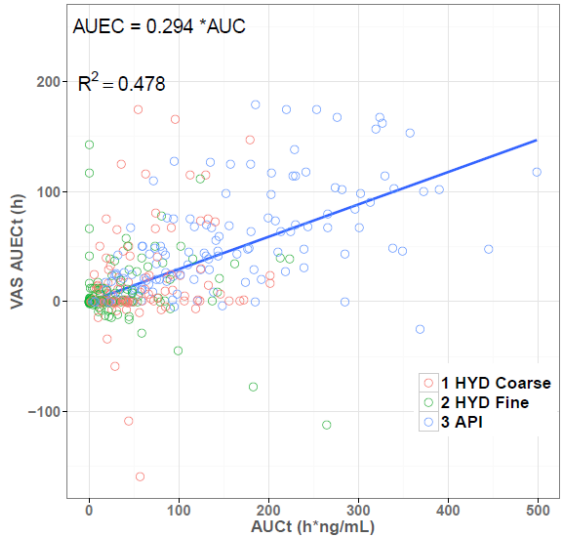
Oxycodone Capsule Oral



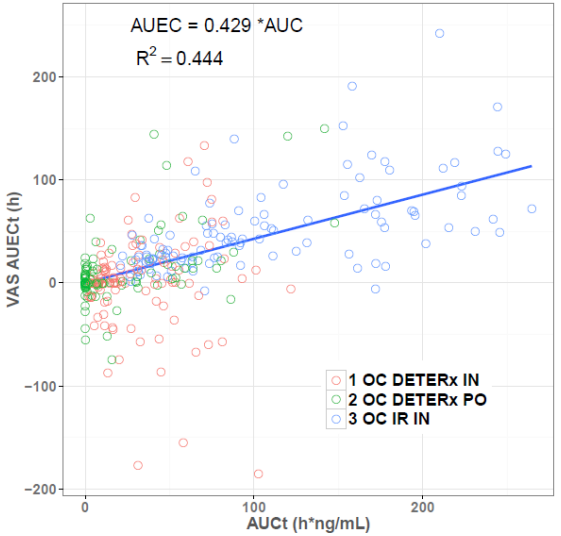
Morphine Oral



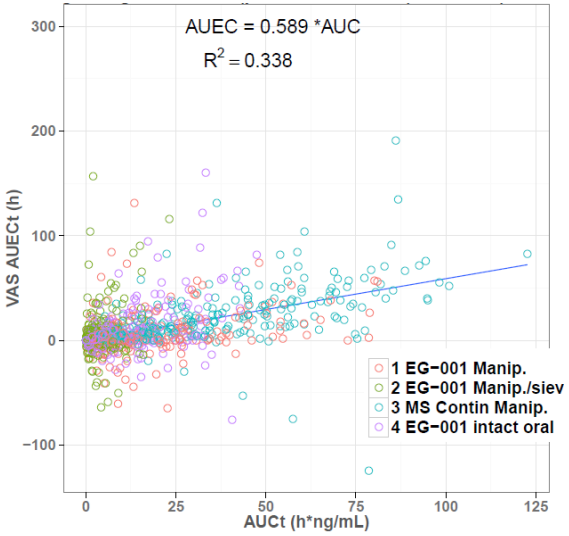
Hydrocodone IN



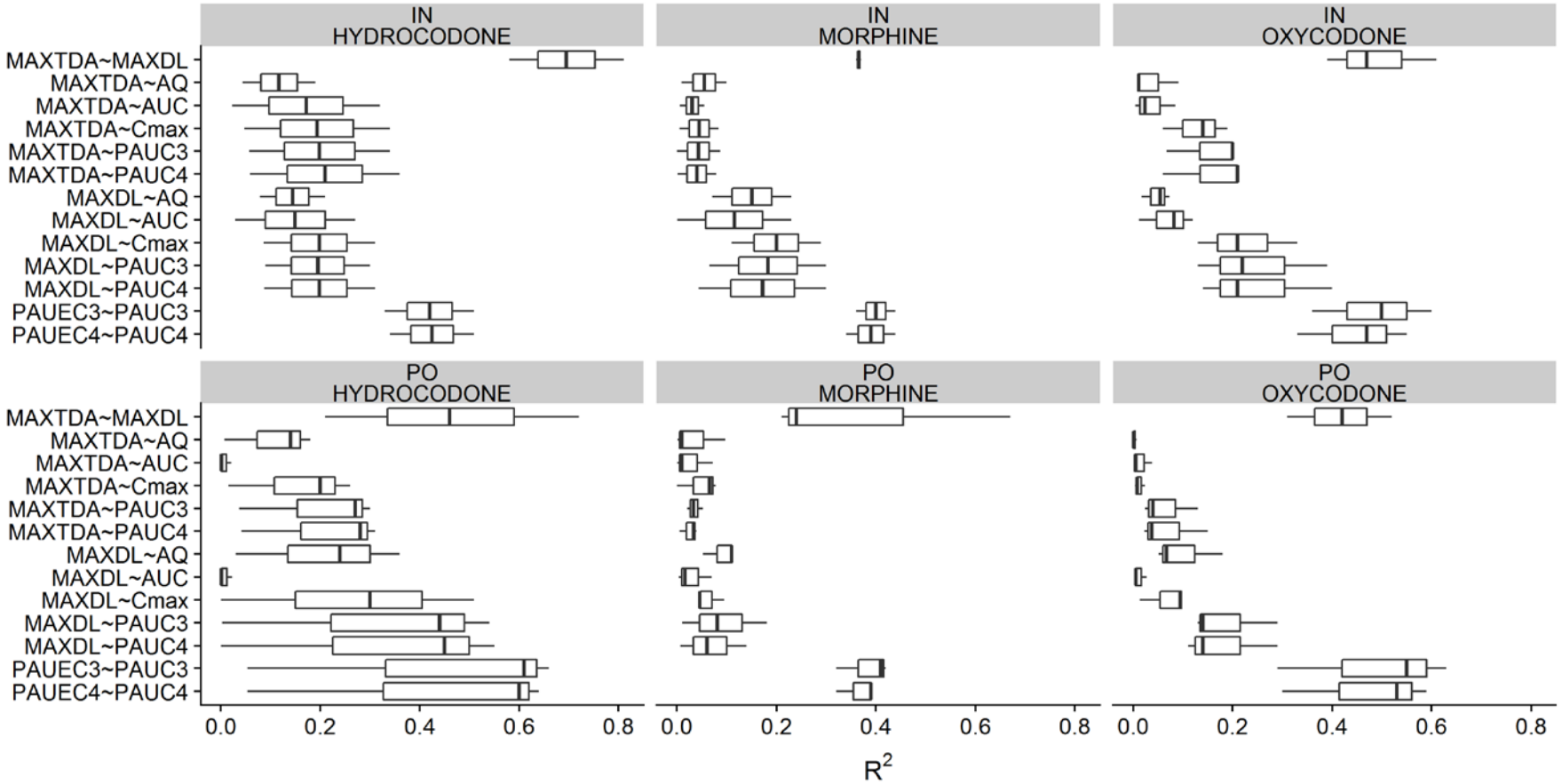
Oxycodone Capsule IN



Morphine IN



Highest Correlation between Early PAUEC and Early PAUC among PK/PD Metrics



- PK metrics: Cmax, AUC, AQ, PAUC3, PAUC4
- PD metrics: MAXDL, MAXTDA, PAUEC3, PAUEC4
- R^2: variation in a PD metric that can be explained by a PK metric using a linear regression model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