Use of Modeling and Simulation to Support New BE Approaches

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Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration

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.***

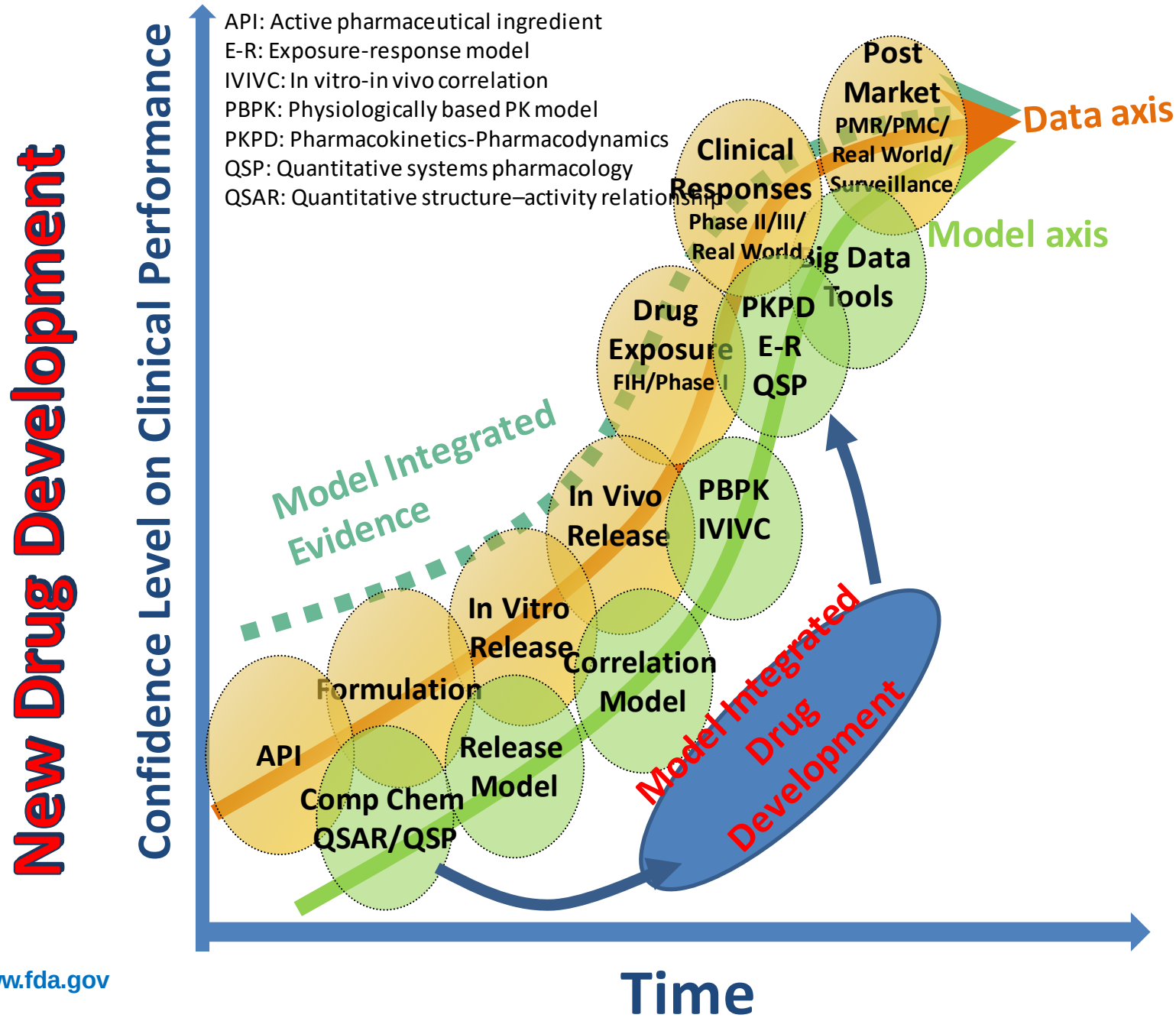
Generating Model Integrated Evidence for Generic Drug Development and Assessment

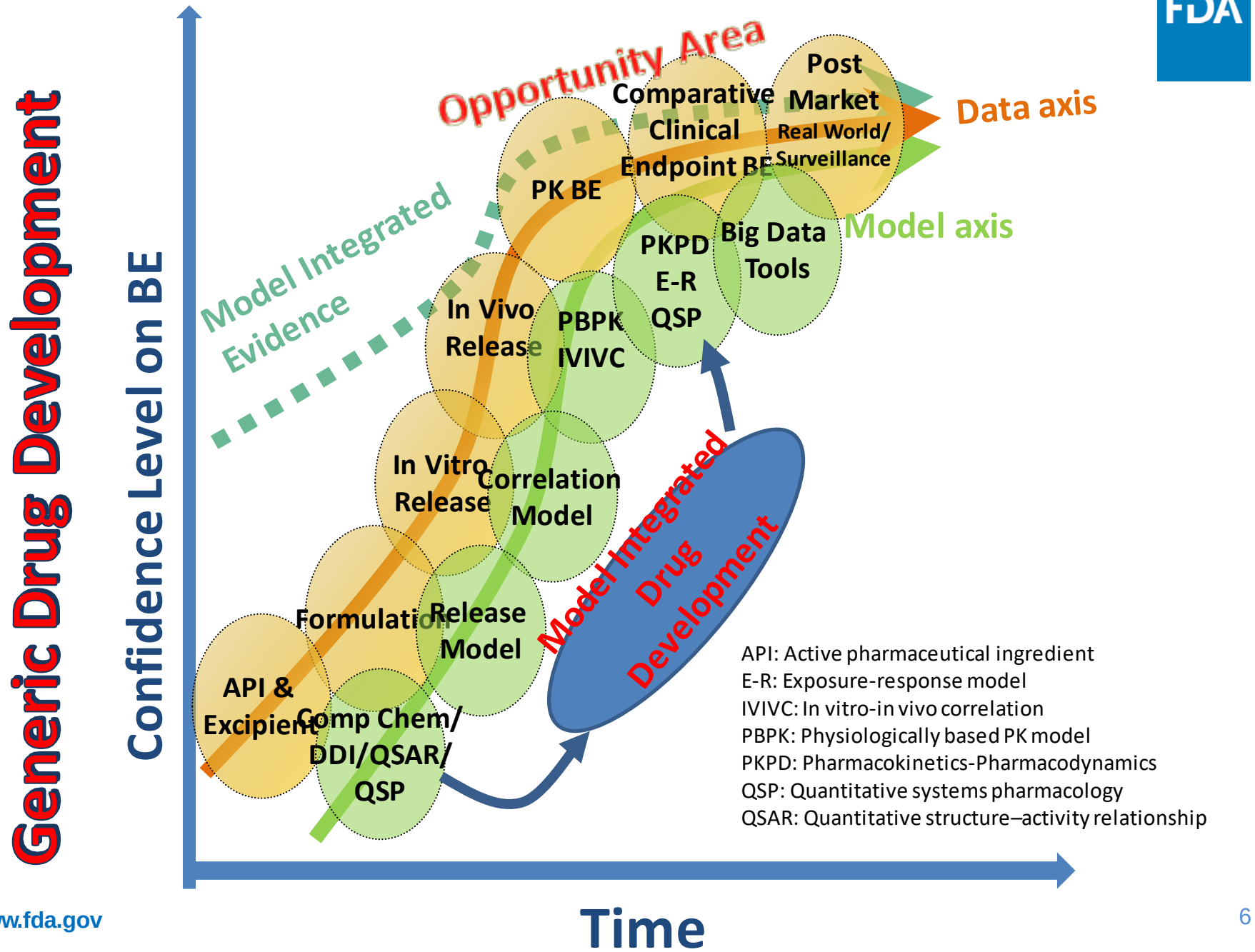
- Quantitative methods and modeling (QMM) has been increasingly applied by the FDA to facilitating generic drug development and review
  - Playing a critical role in the modernization of bioequivalence (BE) assessment

- 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


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
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
Release Model
Comp Chem
QSAR/QSP
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
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Correlation Model
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API & Excipient
Comp Chem/ DDI/QSAR/ QSP
Model Integrated Drug Development
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QSP: Quantitative systems pharmacology
QSAR: Quantitative structure–activity relationship

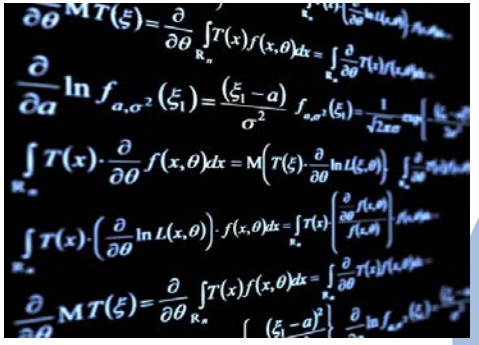
Core Tool Sets to Aid Generic Drug Development and Approval

Our Goal is to facilitate

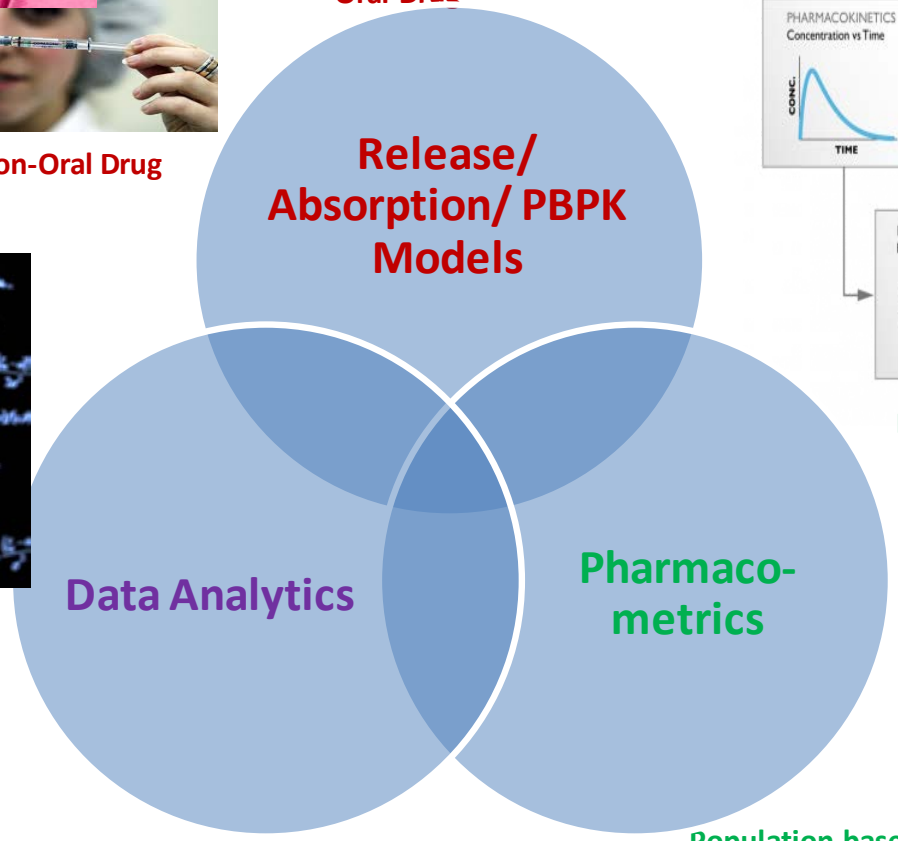
- Generic drug development/review
- Policy development
- Regulatory decisions

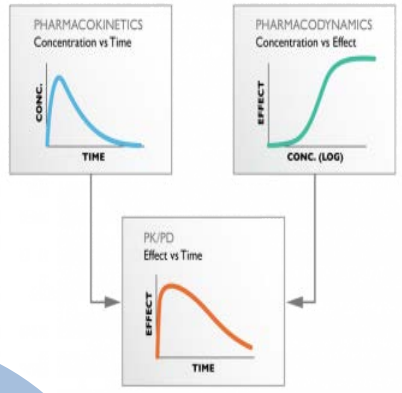
Non-Oral Drug

Oral Drug

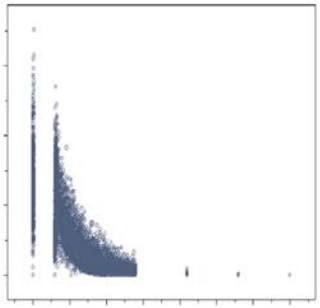


Machine learning toolsets
Analytics for complex mixtures
Systems pharmacology
Risk-based models
Business process models





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

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)

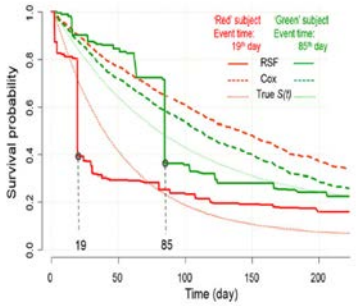
- Bioequivalence (BE) study design and data analysis
  - Pharmacokinetic (PK) endpoints
    - Sparse PK sampling: model-informed optimal BE study design and model-based BE analysis
    - Endogenous baseline correction: appropriate BE metrics and criteria
    - Patient PK study: long-acting injectables
  - 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

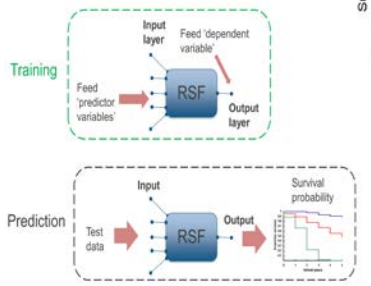
PBPK for Systemically and Locally Acting Products

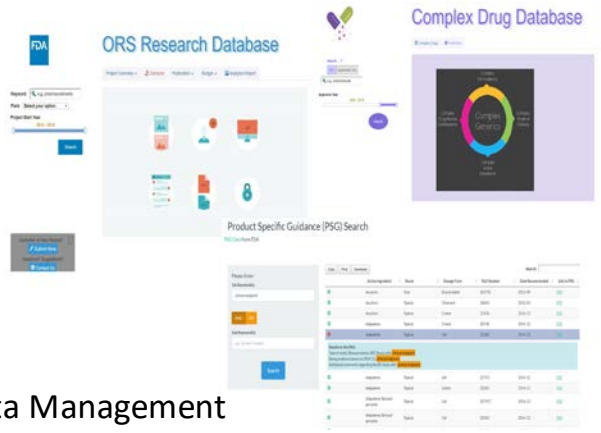
- Use of PBPK modeling to sponsors to support drug product development
  - E.g., Pre-ANDA /ANDA to use PBPK modeling package to support not conducting comparative clinical endpoint (CE) or pharmacodynamic (PD) endpoint studies
  - Review of regulatory submissions containing PBPK and/or CFD modeling – 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





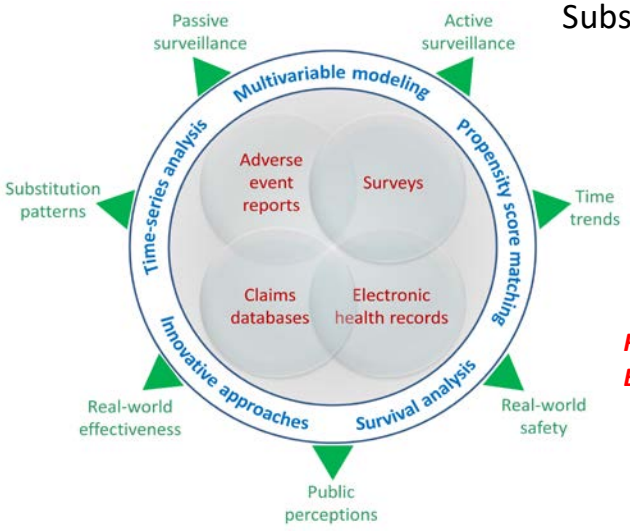


Big Data Analytics

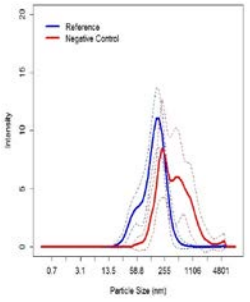
Data Management

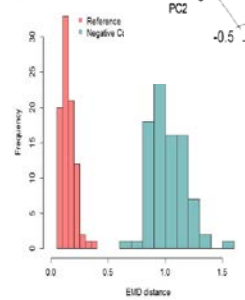
Generic Drug Substitution

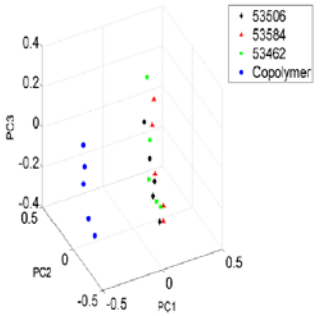
In Vitro Bioequivalence



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

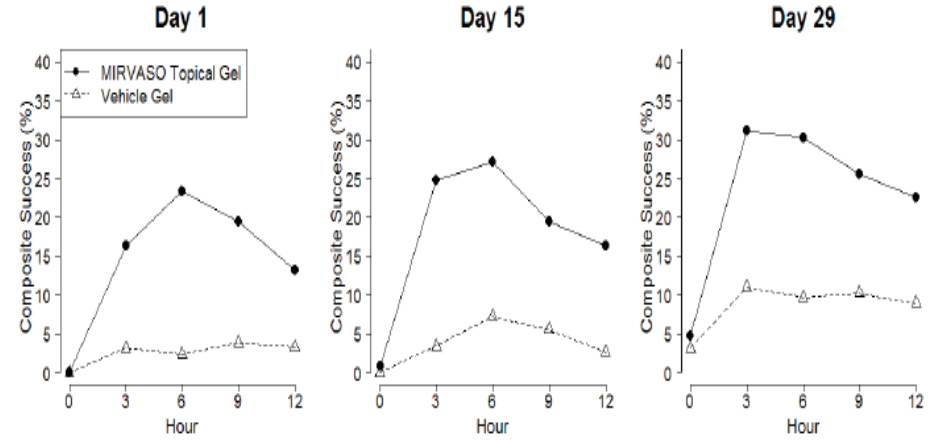
PK/PD Analysis to Bridge Study Design Gap in BE Assessment

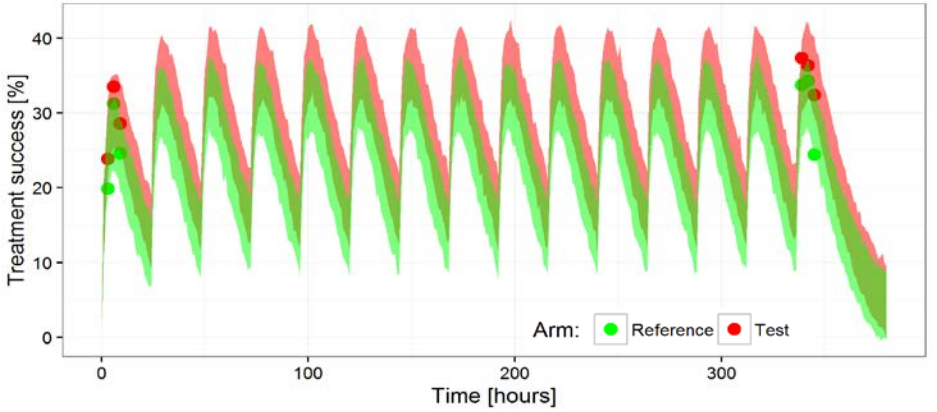
Brimonidine topical gel: for topical treatment of persistent (non-transient) facial erythema of rosacea in adults 18 years of age or older

Background: Clinical endpoint BE study was conducted by the ANDA applicant prior to the issuance of Product Specific Guidance (PSG), sponsor 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.





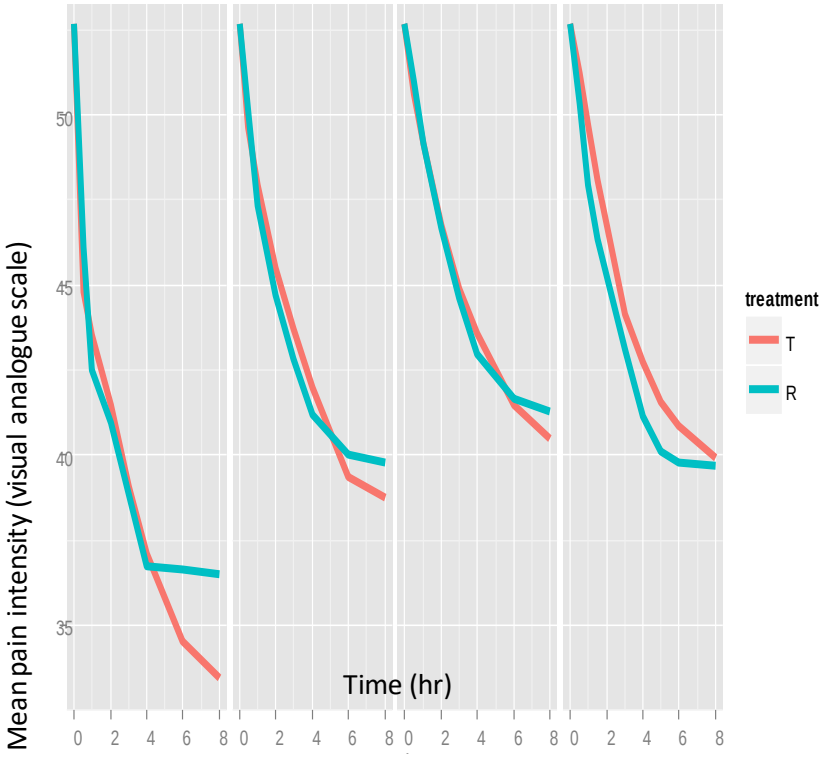
PK/PD Analysis to Evaluate Clinical Impact of PK Differences

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.

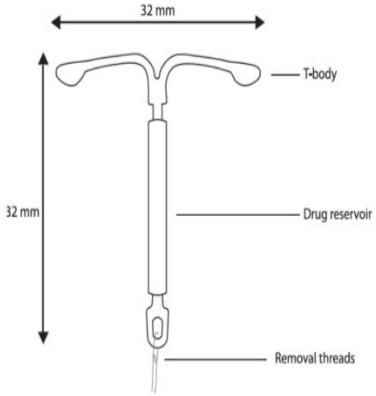
Question: Does Tmax differences observed between generic and RLD have any clinical implications for acute analgesic effect?

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.



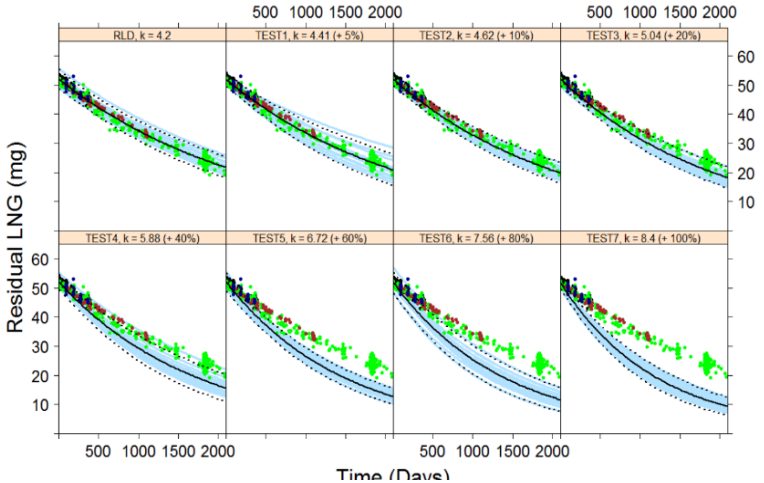
PK/PD Analysis: Alternate Study Design and BE metrics

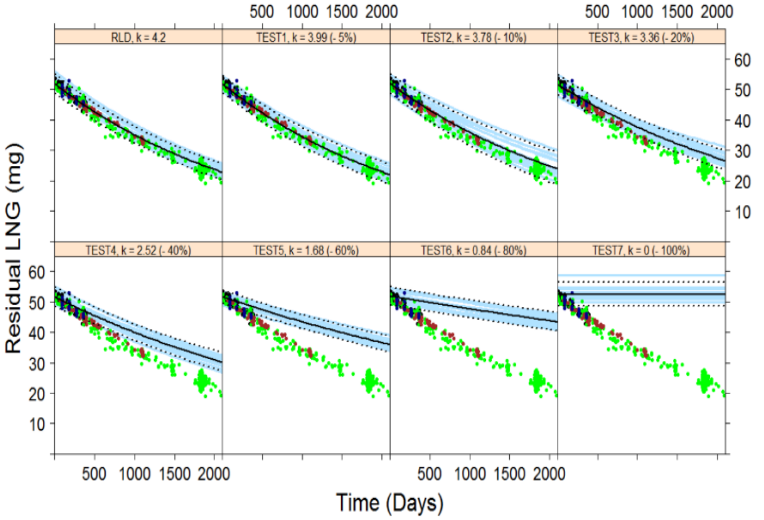
Background: Levonorgestrel (LNG) Intrauterine System is indicated for 5 years for prevention of pregnancy.



Question: Can 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 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: 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 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: 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.

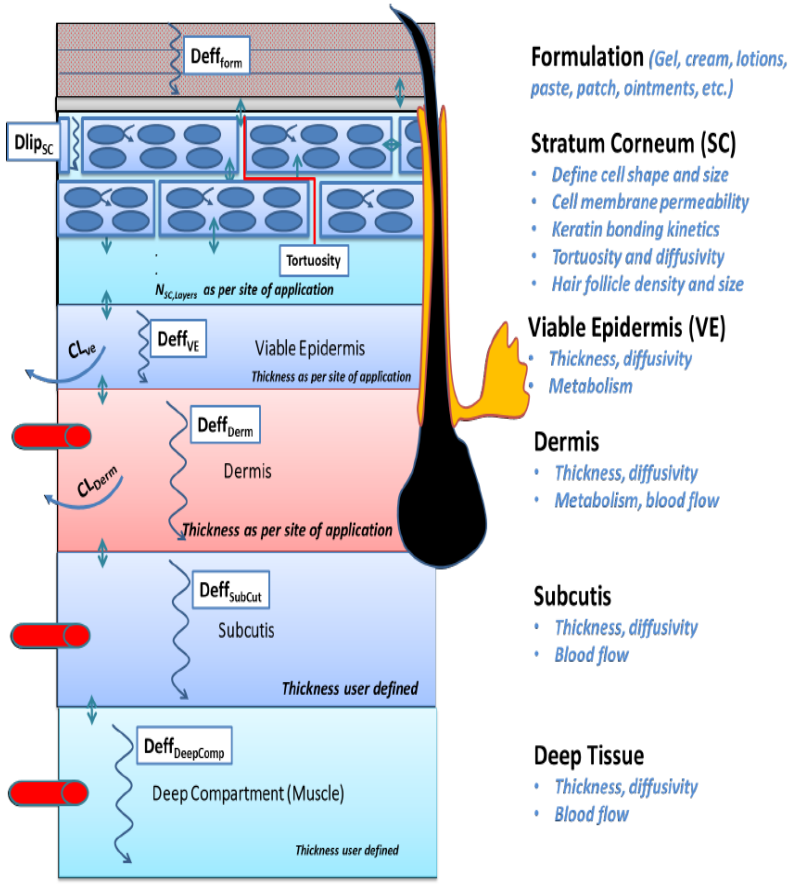
PBPK Modeling Supports Alternative BE Approaches

Product Y, Topical Gel, 1%: a drug indicated for the relief of the pain amenable to topical treatment.

Background: The sponsor 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.



FDA Expectations for Modeling Result Submissions

- 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 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 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

Office of Generic Drugs

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Office of Product Quality

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  - Paul Seo


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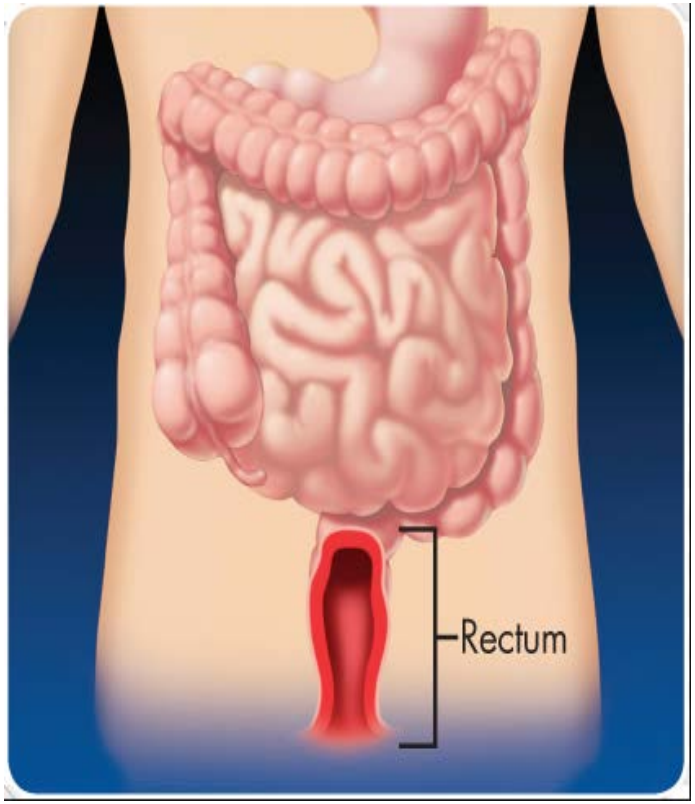
PBPK Analysis Supports Mesalamine Rectal Suppository BE Evaluation

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	$pAUC_{0\text{-}3hr}$, $pAUC_{0\text{-}4hr}$

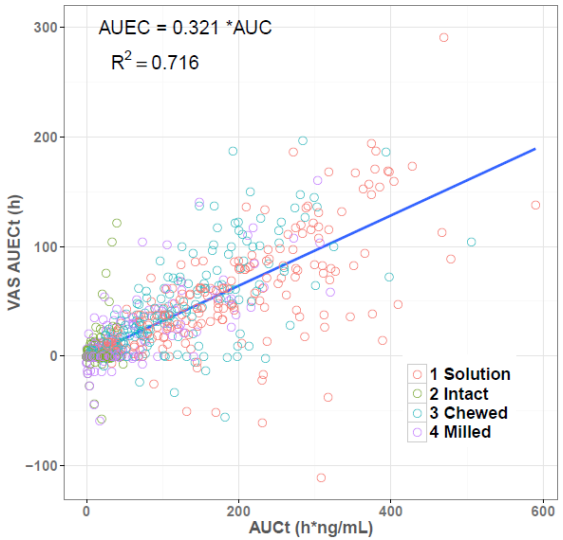
IV: intravenous; IN: intranasal
* The intranasal route is not approved until 2018 due to market exclusivity of MorphaBond

PK metrics of opioids assessing comparative abuse deterrence:

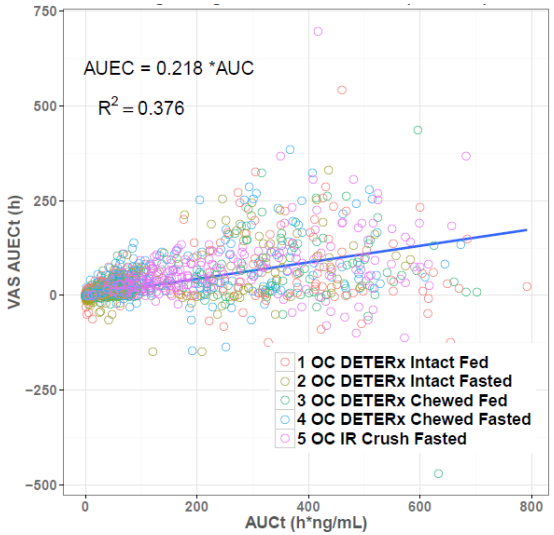
- Cmax and AUC: Upper 95% confidence bound ≤ 125.00%
- pAUC as supportive data: Point estimate ≤ 125.00%

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

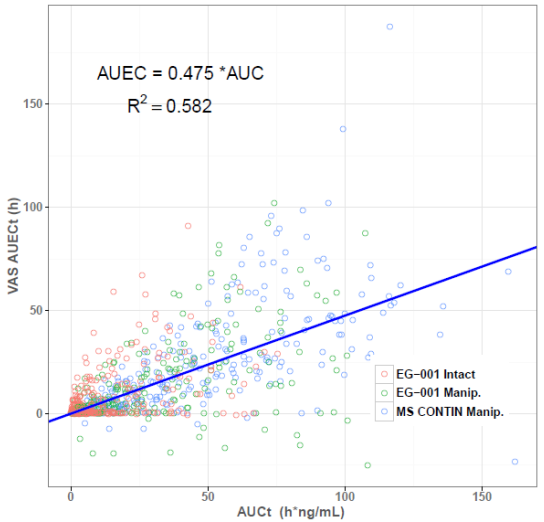
Hydrocodone Oral



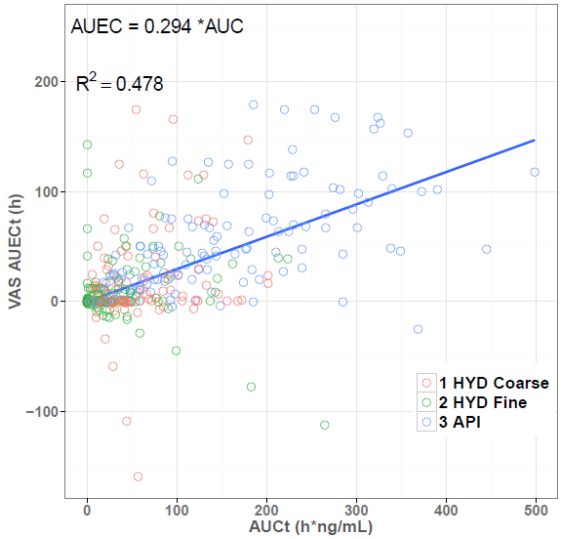
Oxycodone Capsule Oral



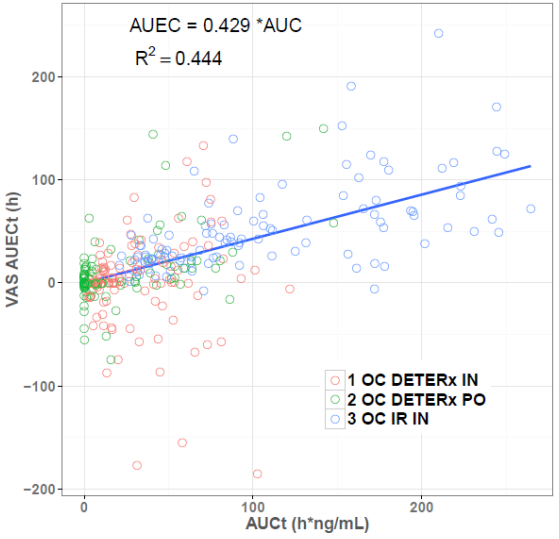
Morphine Oral



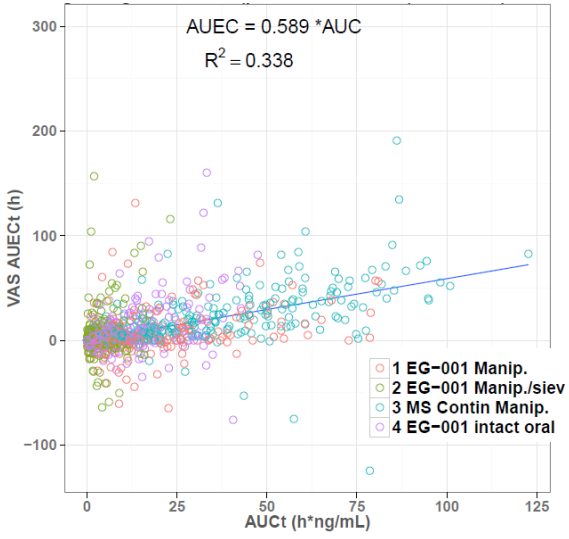
Hydrocodone IN



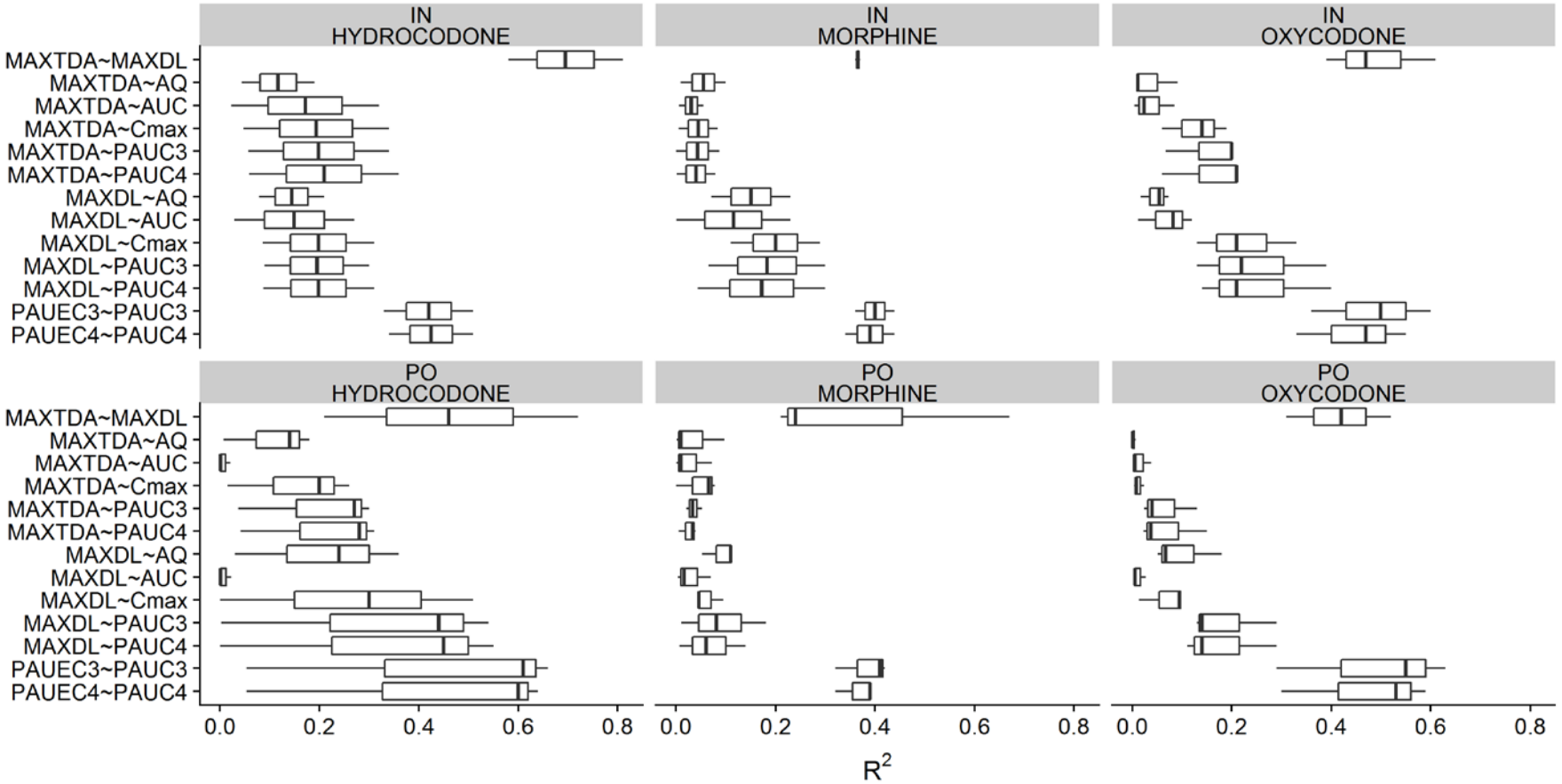
Oxycodone Capsule IN



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

Adapted from the presentation by Zhichuan (Matt) Li in 2018 OGD Science Forum