Impact of Modeling and Simulation on Drug Product Life Cycle Management

Liang Zhao, PhD
Division Director
Division of Quantitative Methods & Modeling
Office of Research and Standards, Office of Generic Drugs, CDER/FDA

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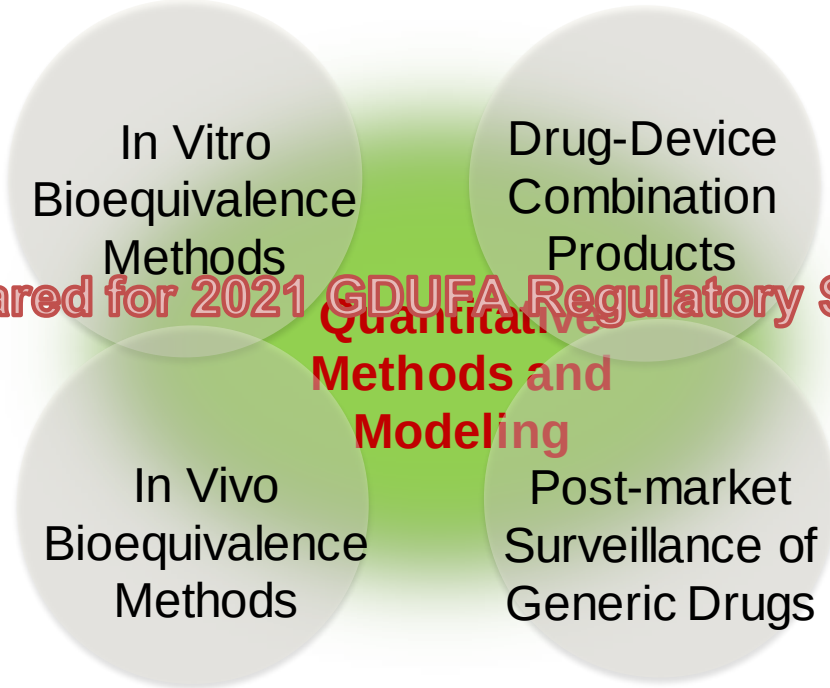
Agenda

- Summary of impacts of modeling and simulation (M&S) on regulatory activities
- Summary of GDUFAII M&S related grants and contracts
- Case Example: Association of partial systemic exposure and abuse potential for opioid analgesics with abuse deterrence labeling claims supporting product specific guidance
  - https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(21)00415-6.pdf

GDUFA: Generic Drug User Fee Act

Quantitative Methods & Modeling (QMM) for Generic Drug Development and Approval



Model integrated evidence (MIE) refers to using model generated information such as the virtual bioequivalence (VBE) study results not just to plan a pivotal study but to serve as pivotal evidence

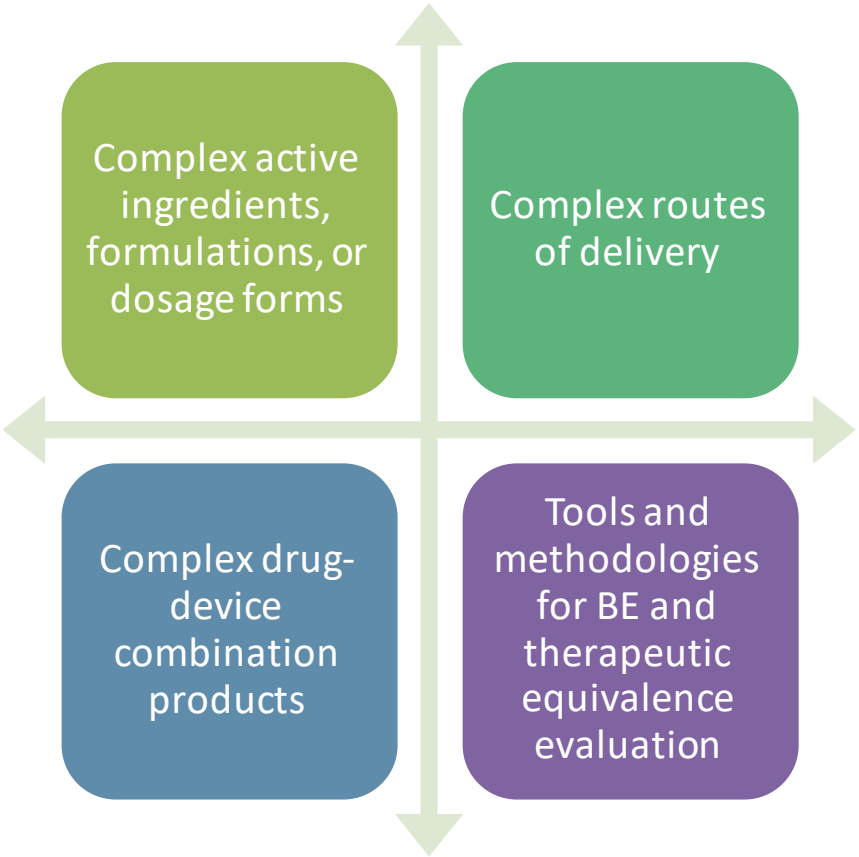
Clin Pharmacol Ther. 2019 Feb;105(2):338-349

QMM/MIE Impact Various Regulatory Activities in the Office of Generic Drugs (CY 2020), Critically Supported by GDUFA Regulatory Science

	Type	No.	Examples
Regulatory	ANDA Review Consults	15	❖ **Particle size distribution space for BE assessment; dose scale analysis with data censoring; model-based CE BE analysis** ❖ Topical dermatological/orally inhaled/long-acting injectable products
	Pre-ANDA Meetings	52	
	Controlled Correspondences	64	❖ Evaluation of alternative BE approaches to the CE study for locally acting products
	BE Guidance	11+	❖ PSGs: New/revised guidance on modified release products; use of pAUC as an additional BE metrics (e.g., methylphenidate)
Research	Internal Regulatory Research Projects	56	❖ Assessment of PD endpoints for BE evaluation ❖ BE evaluation methods (e.g., higher-order crossover design, group/batch effects) ❖ BE study interruption during COVID-19 pandemic
	New Contracts and Grants in GDUFA II since 10/2017	35	❖ Development of model-informed BE for complex generic drugs ❖ Modeling platform development (e.g., long acting injectables, sparse sampling) ❖ Development of PBPK model for locally-acting drug products ❖ Characterizing safety and efficacy of generic drugs, and expanding BCS class 3 waivers

ANDA, abbreviated new drug application; BE, bioequivalence; CE, clinical endpoint; PK, pharmacokinetic; PD, pharmacodynamics; PBPK, physiologically based PK; PSG, product-specific guidance; BCS, Biopharmaceutics Classification System; pAUC, partial area under the curve.

GDUFA II Regulatory Science Priorities



Quick Summary of Research Topics and Outcomes

Based on regulatory research activities reports published by Office of Generic Drugs

Locally-Acting PBPK Modeling

Outcomes

- 45 Journal articles
- 52 Presentations
- 34 Posters
- 2 PSGs

Grant #	Study Title	Institute	Start Date	End Date
1U01FD005201	Development of hybrid CFD-PBPK models for absorption of intranasal corticosteroids	Applied Research Associates, Inc.	9/10/2014	2/28/2018
1U01FD005214	A predictive multiscale computational tool for simulation of lung absorption and pharmacokinetics and optimization of pulmonary drug delivery	CFD Corporation	9/10/2014	3/28/2018
1U01FD005219	An integrated multiscale-multiphysics modeling and simulation of ocular drug delivery with whole-body pharmacokinetic response	CFD Corporation	9/10/2014	3/31/2018
1U01FD005206	Physiologically based pharmacokinetic model for drugs encapsulated into liposomes	University of Buffalo	9/10/2014	5/31/2018
1U01FD005225	Development and validation of dermal PBPK modeling platform toward virtual bioequivalence assessment considering population variability	Simcyp, Ltd.	9/10/2014	8/31/2018
1U01FD005211	PBPK modeling and simulation for ocular dosage forms	Simulations Plus	9/10/2014	8/31/2018
1U01FD005232	Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans	University of South Australia	9/10/2014	2/28/2019
HHSF223201810255P	Simulation Plus Ophthalmic ointment implemenation	Simulations Plus, Inc.	8/21/2018	11/30/2019
1U01FD005838	Enhancing the reliability, efficiency, and usability of Bayesian population PBPK modeling	Colorado State University	9/10/2016	8/31/2020
HHSF223201810144C	Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition In Silico and In Vitro	Virginia Commonwealth University	9/28/2018	7/30/2021
1U01FD006525	Development of Computational Models to Predict Delivery of Inhalation Drug Powders: from Deagglomeration in Devices to Deposition in Airways	University of Sydney	9/1/2018	8/31/2021
1U01FD006526	Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems (U01)	Simulations Plus, Inc.	9/1/2018	8/31/2021

arance Note: Based on regulatory research activities reports published by Office of Generic Dr

Quantitative Clinical Pharmacology

Outcomes

- 27 Journal articles
- 48 Presentations
- 26 Posters
- 38 PSGs
- 1 General guidance

Grant #	Study Title	Institute	Start Date	End Date
1U01FD005192	Pharmacometric modeling and simulation for generic drug substitutability evaluation and post marketing risk assessment	University of Maryland	9/10/2014	2/28/2018
1U01FD005188	Population pharmacokinetic and pharmacodynamic, dose-toxicity modeling and simulation for narrow therapeutic index (NTI) drugs	University of Maryland	9/10/2014	2/28/2018
1U01FD005235	Pharmacokinetic and pharmacodynamic (PK-PD) studies of cardiovascular drugs	University of Florida	9/10/2014	8/31/2018
3U01FD005210-03S1	A model and system based approach to efficacy and safety questions related to generic substitution	University of Florida	9/10/2014	8/31/2018
1U01FD005444	Data-fusion based platform development of population PKPD modeling and statistical analysis for bioequivalence assessment of long-acting injectable products	University of Massachusetts	9/15/2015	8/31/2018
1U01FD005463	Development of PBPK simulation for long-acting injectable microspheres	Simulations Plus	9/15/2015	8/31/2018
1U01FD005875	Generic Drug Substitution in Special Populations	Auburn University	9/5/2016	8/31/2018
HHSF223201610110C	Evaluation of model-based bioequivalence statistical approaches for sparse design PK studies	Inst Nat Sante Et La Recherche Medicale (INSERM)	9/29/2016	3/30/2019
HHSF223201510110C	Computational drug delivery: leveraging predictive models to [illegible]	[illegible]	[illegible]	[illegible]
1U01FD005191	Pharmacometric modeling of immunosuppressants for evaluation of bioequivalence criteria	University of Utah	9/10/2014	2/29/2020

arance Note: Based on regulatory research activities reports published by Office of Generic Dru

Oral Absorption Models and BE

Outcomes

- 36 Journal articles
- 23 Presentations
- 41 Posters
- 17 PSGs
- 4 General guidances

Grant #	Study Title	Institute	Start Date	End Date
HHSF223201310144C	Prediction of In Vivo Performance for Oral Solid Dosage Forms	University of Michigan	9/27/2013	11/15/2017
3U01FD004979-02S3-P2	Effect of Excipient Transporter Interactions on BCS Class Drugs	University of California San Francisco	4/15/2014	3/31/2018
HHSF223201610004I-HHSF22301001T	Evaluation of formulation dependence of drug-drug interaction with proton pump inhibitors (PPIs) for oral extended-release drug products	Biopharma Services USA	9/19/2016	9/18/2018
HHSF223201510157C	In Vivo Predictive Dissolution (IPD) to Advance Oral Product Bioequivalence (BE) Regulation	University of Michigan	9/30/2015	9/30/2018
HHSF223201710137C	Phase behavior and transformation kinetics of a poorly water soluble weakly basic drug upon transit from low to high pH conditions	Purdue University	9/29/2017	3/28/2019
1U01FD005259	Formulation, processing and performance interrelationship for amorphous solid dispersions	Purdue University	9/10/2014	8/31/2019
HHSF223201510146C	Wireless Sampling Pill to Measure in Vivo Drug Dissolution in GI Tract and Computational Model To Distinguish Meaningful Product Quality Differences and Ensure Bioequivalence (BE) in Patients	University of Michigan	9/30/2015	8/31/2020
1U01FD005865	Design, Development, Implementation and Validation of a Mechanistic Physiologically-based Pharmacokinetic (PBPK) Framework for the Prediction of the In Vivo Behaviour of Supersaturating Drug Products	Simcyp (SI)	9/10/2015	8/31/2020

arance Note: Based on regulatory research activities reports published by Office of Generic Dru

Patient Substitution of Generic Drugs

Outcomes

- 30 Journal articles
- 12 Presentations
- 13 Posters

Grant #	Study Title	Institute	Start Date	End Date
1U01FD004899	Bioequivalence and Clinical Implications of Generic Bupropion	Washington University	9/15/2013	2/28/2018
1U01FD005192	Pharmacometic modeling and simulation for generic drug substitutability evaluation and post marketing risk assessment	University of Maryland	9/10/2014	2/28/2018
1U01FD005875	Generic Drug Substitution in Special Populations	Auburn University	9/5/2016	8/31/2018
1U01FD005235	Pharmacokinetic and pharmacodynamic (PK-PD) studies of cardiovascular drugs	University of Florida	9/10/2014	8/31/2018
3U01FD005210-03S1	A model and system based approach to efficacy and safety questions related to generic substitution	University of Florida	9/10/2014	8/31/2018
1U01FD005274	Transplant outcomes using generic and brand name immunosuppressants: studying medications used by people who have received kidney and liver transplants	Arbor Research	9/10/2014	8/31/2018
1U01FD005875	Generic Drug Substitution in Special Populations	Auburn University	9/5/2016	8/31/2018
HHSF223201400188C	Characterization of epilepsy patients at-risk for adverse outcomes related to switching antiepileptic drug products	University of Maryland	9/30/2014	9/29/2018
1U01FD005191	Pharmacometric modeling of immunosuppressant for evaluation of bioequivalence criteria	University of Utah	9/10/2014	2/29/2020

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Data Analytics

Outcomes

- 23 Journal articles
- 15 Presentations
- 7 Posters

Grant #	Study Title	Institute	Start Date	End Date
3U01FD004979-02S3-P1	Molecular Properties of Excipients	University of California San Francisco	4/15/2014	3/31/2018
1U01FD005555	Novel approaches for confounding control in observational studies of generic drugs	Brigham & Women's Hospital	9/15/2015	8/31/2018
HHSF223201510112C	Comparative Surveillance of Generic Drugs by Machine Learning	Marshfield Clinic, Inc.	9/30/2015	9/29/2018
1U01FD005556	Structural nested models for assessing the safety and effectiveness of generic drugs	Johns Hopkins University	9/15/2015	2/28/2019
1U01FD005938-A11	Characterizing safety and efficacy of brand and generic drugs used to treat hypothyroidism among patients who switch therapy formulation	Yale-Mayo CERSI	5/28/2019	9/30/2020
75F40119C10106	Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency	Drexel University	9/30/2019	9/29/2021
75F40120F80605	Software Development Services for Bioequivalence Review Assistance Tool	FUTREND Technology Inc	9/30/2020	9/29/2021
75F40119C10106	Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency	Drexel University	9/30/2019	9/29/2022
1U01FD005938-A10	Use of instrumental variable approaches to assess the safety and efficacy of brand-name and generic drugs used to treat hypothyroidism	Yale-Mayo CERSI	7/20/2018	8/31/2023
1U01FD005938-A2	Characterizing safety and efficacy of brand and generic drugs used to treat hypothyroidism	Yale-Mayo CERSI	5/5/2017	8/31/2023

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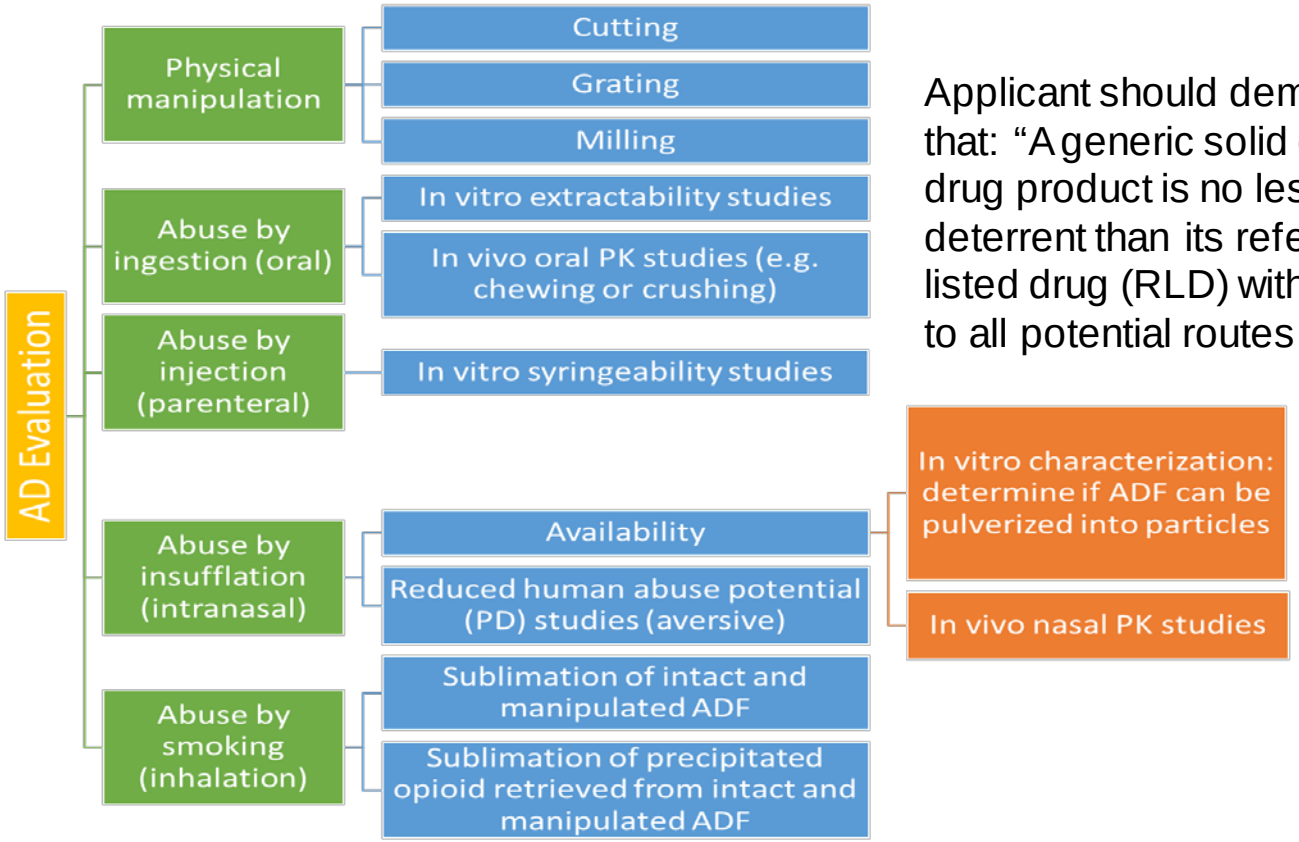
Case Example: Association of Partial Systemic Exposure and Abuse Potential for Opioid Analgesics with Abuse Deterrence Properties

- Background
  - General Principles for Evaluating the Abuse Deterrence (AD) of Generic Solid Oral Opioid Drug Products –2017 FDA Guidance (https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf)
  - Product-specific guidances (PSGs) for Hydrocodone, Oxycodone, and Morphine ER formulation with AD properties (https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm)
  - Consult Office of New Drugs at FDA for new drug applications
- PK-PD analysis to support PK metrics determination for comparative PK studies to evaluate AD
  - PK metrics to evaluate AD potential based on PK-PD relationship

Zhao et al, EclinicalMedicine 41 (2021) 101135.
https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(21)00415-6.pdf
Clearance Note: Slides also cleared in 2019 for ASCPT presentation

Overview of General Guidance for Generic AD Opioids



Applicant should demonstrate that: "A generic solid oral opioid drug product is no less abuse deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse"

Clearance Note: Slides cleared in 2019 for ASCPT presentation

What PK Metrics Should Be Used to Compare Brand vs Generic AD?

Draft Guidance on Hydrocodone Bitartrate

Active Ingredient:	Hydrocodone bitartrate
Dosage Form; Route:	Tablet; extended release; oral
Recommended Studies:	Two bioequivalence studies (1–2) and two in vivo comparative pharmacokinetic (PK) studies for abuse deterrence assessment (3–4)

3. Type of study: Fasting, comparative oral PK study of chewed drug products
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 60 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional Comments: See comments in Study 1. Patient-relevant chewing conditions that can discriminate between test and reference products' ability of deterring chewing should be identified. Determine relevant PK parameters including maximum concentration (C_{max}), area-under-the-curve (AUC_{0-t} and $AUC_{0-\infty}$), and time to maximum concentration (T_{max}). Applicants should submit partial AUCs (e.g., $AUC_{0\text{-}3\ hours}$ and $AUC_{0\text{-}4\ hours}$) as supportive data.

4. Type of study: Fasting, comparative nasal PK study with physically manipulated drug products, consistent with the recommendations in FDA's guidance, "*General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*," for tier 2 evaluation of abuse by insufflation as applicable
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 60 mg
Subjects: Non-dependent recreational opioid users, general population[1]
Additional Comments: See all comments in Study 1. Take scientifically appropriate and ethical steps to protect human subjects. This should include ensuring that each subject is not physically dependent on opioids (e.g., through a naloxone challenge test) and has not been seeking or undergoing treatment for abuse of controlled substances such that participating in the study could make them vulnerable to relapse.[2] Also see comments on PK parameters in Study 3. Pulverize test and reference products to a particle size range that is considered safe and tolerable for human insufflation studies. Characterize the formulation recovery, drug content, and particle size distribution of physically manipulated test and reference drug products used in the nasal PK study using validated analytical procedures.

PK metrics included in 7 PSGs for Morphine, Oxycodone, and Hydrocodone:

"Determine relevant PK parameters including maximum concentration (Cmax), area-under-the-curve (AUC0-t and AUC0-∞), and time to maximum concentration (Tmax). Applicants should submit partial AUCs (e.g., AUC0-3 hours and AUC0-4 hours) as supportive data"

Clearance Note: Slides cleared in 2019 for ASCPT presentation

What PK Metrics Should Be Used to Compare Brand vs Generic AD?

- Comparable C_{max} and AUC may not be sufficient in evaluating abuse deterrence
  - C_{max} and AUC are not significantly correlated with drug abuse potential endpoints (i.e., drug liking and take drug again)
- Additional BE metric can support generics to be no less AD than RLD
  - Literature reports suggest that the rate of rise of drug concentration contributes to differential abuse potential among drugs, formulations, and routes of administration
- Analysis only limited to data from non-combination product using antagonist or product with aversive agent

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The Identification of Appropriate PK Metrics Related to Abuse Potential

PK Metrics

- Cmax: Maximum Drug Concentration
- Tmax: Time to reach to Cmax
- AUC: Area Under Curve
- AQ: Abuse quotient Cmax/Tmax
- PAUCx: Partial AUC for time 0 to x

Drug Abuse Potential

- VAS: Visual analogue scale
- TDA: VAS for take drug again
- DL: VAS for drug liking
- PAUECx: Partial AUC for DL from time 0 to x
- MAXTDA: maximum TDA
- MAXDL: maximum DL

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Research Goal

- Explore potential relationships between PK metrics, especially measures of the ascending part of the PK curve, and opioid abuse potential
- Implement the identified PK metrics in PSGs for AD evaluation

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Summary of randomized, double-blind, placebo-controlled crossover clinical abuse potential trials

Trial	Opioid	Dose, mg*	Route	Last sampling time, hr	No. of PK points	No. of PD points		No. of subjects	
						DL	TDA	PK	PD
01	Oxycodone	30	IN	24	10	8	2	29	30
02	Oxycodone	40	IN, PO	36	14	12	2	36	36
03	Oxycodone	40	PO	36	13	12	2	47	38
04	Oxycodone	30	IN, PO	24	15	13	2	31	29
05	Hydrocodone	60	PO	36	15	15	2	39	35
06	Hydrocodone	60	IN	36	16	15	2	27	25
07	Hydrocodone	45	IN, PO	48	20	19	2	41	34
08	Hydrocodone	45	PO	72	18	17	1	41	42
09	Morphine	60	IN, PO	24	13	11	2	27	25
10	Morphine	60	PO	24	12	11	2	39	38
11	Morphine	60	IN, PO	24	16	13	2	46	46

Zhao et al, EclinicalMedicine 41 (2021) 101135.
https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(21)00415-6.pdf
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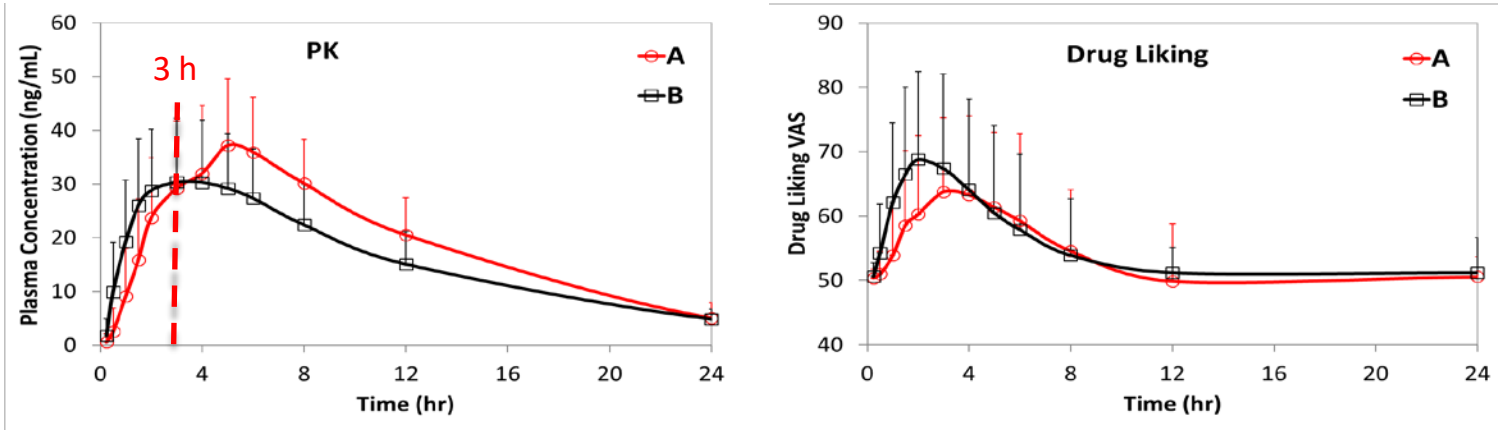
Use of Early pAUC in Addressing Comments from Branded Industry Working Group



- BIWG commented that compared to A, B had lower Cmax, but produced greater MAXDL
- Geometric mean ratio (A/B)
  - pAUC3: 0.66 (90% CI: 56.49-76.48%)
  - pAUC4: 0.76 (90% CI: 66.71-87.50%)

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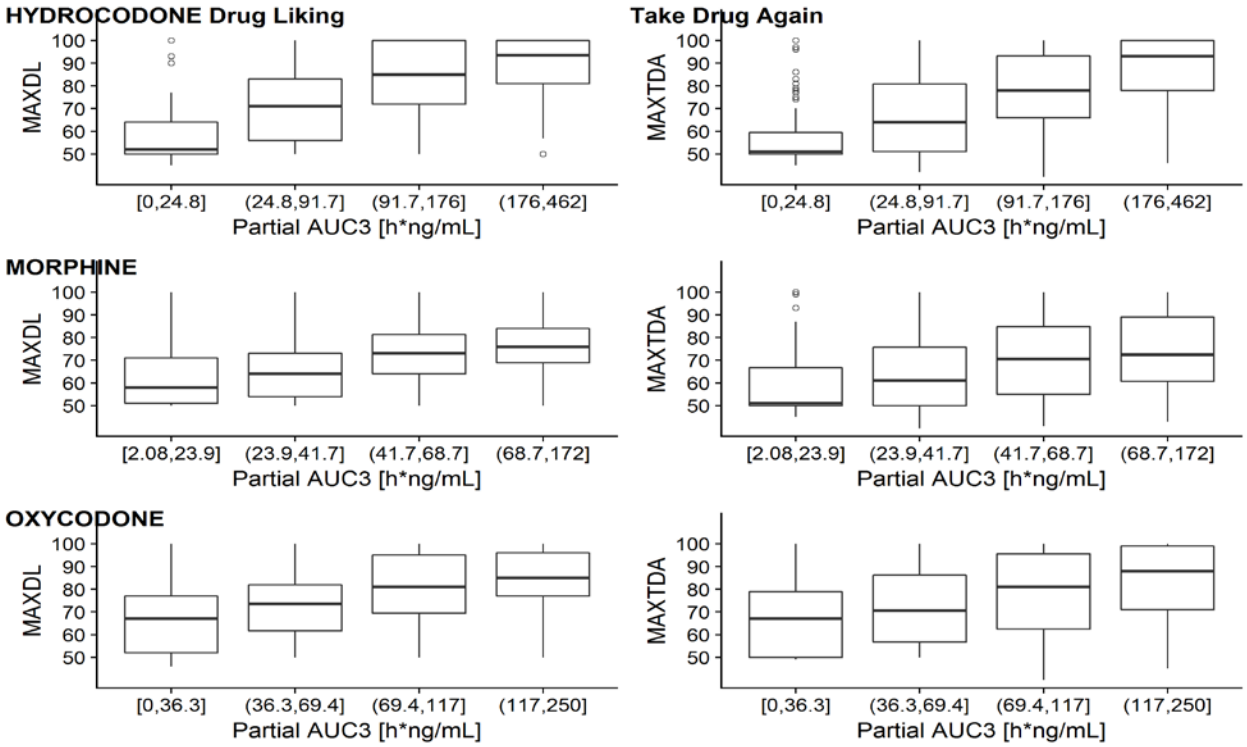
PK/PD Curves Adapted from the presentation by Jeffrey M. Dayno in 2016 FDA Public Meeting on Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products.
(https://www.fda.gov/Drugs/NewsEvents/ucm509853.htm)

Correlation between VAS and Categorized PAUC3 for Each API



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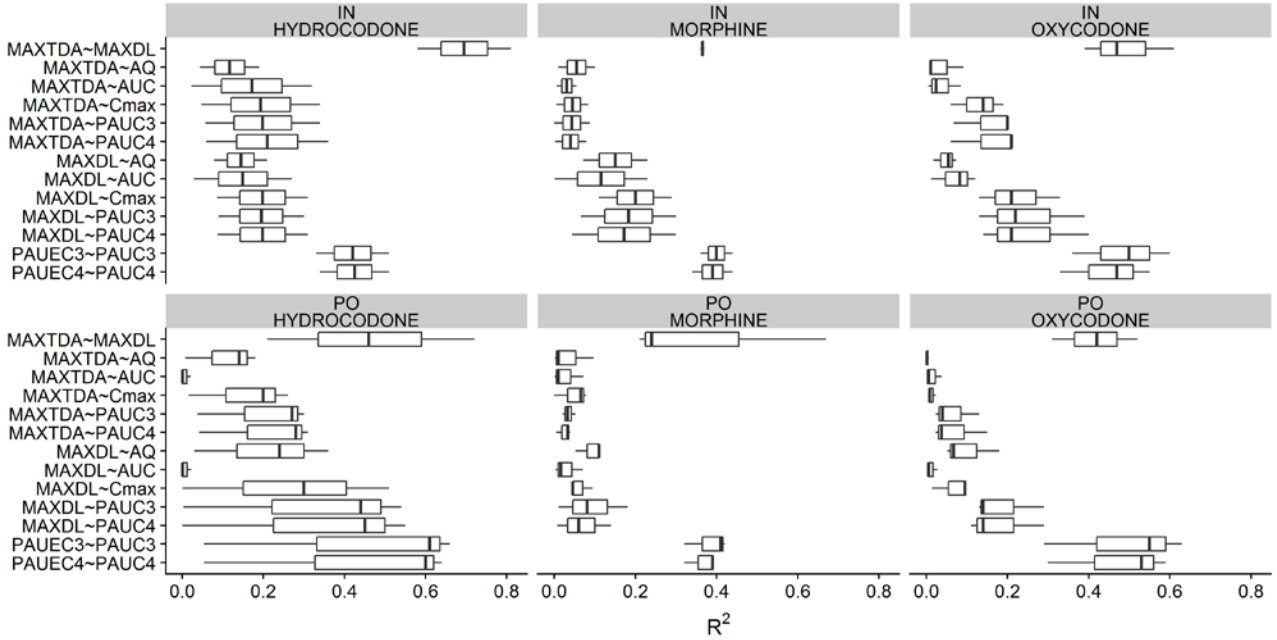
Highest Correlation between Early PAUEC and Early PAUC among PK/PD Metrics



- 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

Zhao et al, EclinicalMedicine 41 (2021) 101135. https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(21)00415-6.pdf

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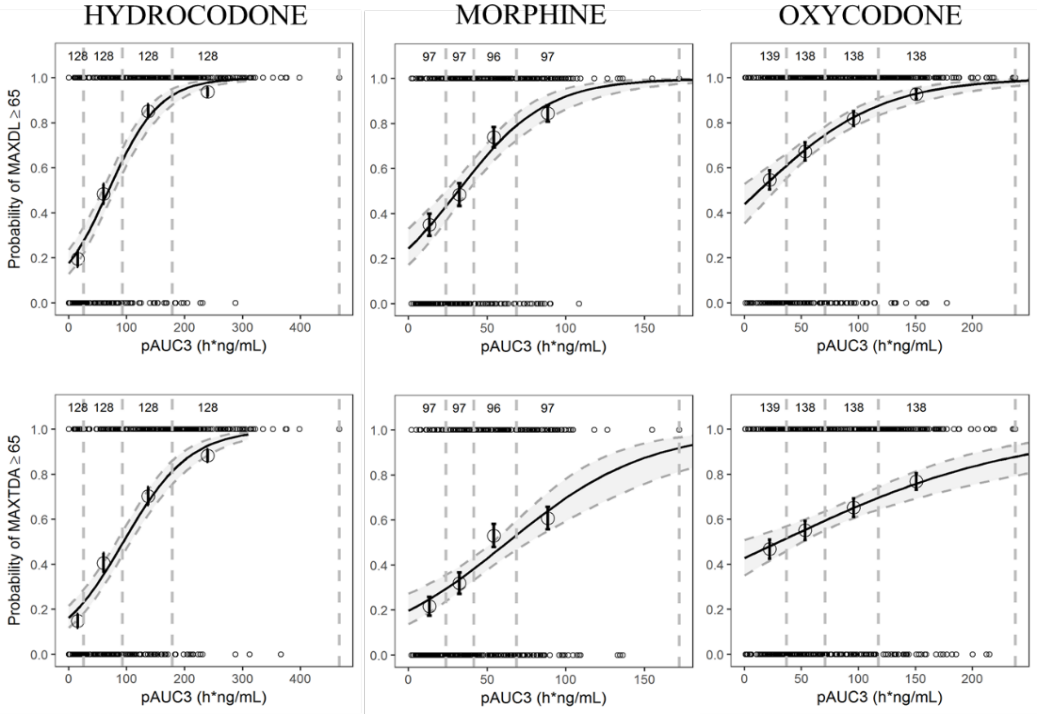
Association of PAUC3 and PD Metrics



Logistic regression analysis based on the pooled data, greater PAUC3 values was associated with greater probability of maximum Drug Liking VAS≥65 and the probability of maximum Taking Drug Again VAS ≥80.

Zhao et al, EclinicalMedicine 41 (2021) 101135. https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(21)00415-6.pdf

Case Conclusions

- In vivo PK studies are part of generic ADF recommendations for bioequivalence assessment

- Based on the identified PK-PD relationship for opioid abuse potential, current PSGs recommend using partial AUCs as supportive measures of AD

- Ongoing internal assessment to further understand the relationships among formulation parameters, PK metrics, and PD endpoints as measures of abuse potential

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Take Home Message

- The GDUFA regulatory science has been advancing and introducing novel quantitative methods and modeling approaches to the community
- Leveraging these new methods ~~advancement~~ in drug development offers new opportunities and values

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