Opportunities and Challenges for Modeling and Simulation in Development of Long-Acting Injectable Drug Products

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The New York Times

PERSONAL HEALTH

The Cost of Not Taking Your Medicine

Paul Rogers

- Increased healthcare utilization (recurrence of symptoms, relapse, hospitalizations, cost)

https://www.nytimes.com/2017/04/17/well/the-cost-of-not-taking-your-medicine.html

Long-Acting Injectable Drug Products

- Long-acting injectable (LAI) drug products are formulated to achieve extended drug release action from days to years when administered via intramuscular (IM) and subcutaneous (SC) routes.

- These products can help improve patient compliance with a better therapeutic option to treat patients who adhere poorly to frequently administered medication.

Examples of FDA Approved Long-Acting Injectable Drug Products and Approved ANDAs

Trade Names	Ingredient	Indication	Dose Frequency	Approved Generic
ABILIFY MAINTENA KIT	ARIPIPRAZOLE	Schizophrenia; bipolar I disorder	Monthly	0
ARISTADA	ARIPIPRAZOLE LAUROXIL	Schizophrenia	Monthly, 6 weeks, 2 months	0
ARISTADA INITIO KIT	ARIPIPRAZOLE LAUROXIL	Schizophrenia	One time	0
SUBLOCADE	BUPRENORPHINE	Opioid use disorder	Monthly	0
PROBUPHINE	BUPRENORPHINE HYDROCHLORIDE	Opioid Dependence	one time (6 months)	0
ATRIDOX	DOXYCYCLINE HYCLATE	Chronic adult periodontitis	1 week	0
BYDUREON BCISE	EXENATIDE	Improve glycemic control in type II diabetes	Weekly	0
BYDUREON...BYDUREON PEN	EXENATIDE SYNTHETIC	Improve glycemic control in type II diabetes	Weekly	0
YUTIQ	FLUOCINOLONE ACETONIDE	Chronic non-infectious uveitis affecting the posterior segment of the eye	36 months (one time)	0
ZOLADEX	GOSERELIN ACETATE	carcinoma of prostate, endometriosis, breast cancer	Monthly (4 weeks)	0
SUSTOL	GRANISETRON	Antiemetics for prevention of acute and delayed nausea and vomiting with chemotherapy	Weekly	0
LUPRON DEPOT...LUPRON DEPOT-PED	LEUPROLIDE ACETATE	Endometriosis, Fibroids, Advanced prostrate cancer; children with central precocious puberty	1,3,4,6 months	0
ELIGARD	LEUPROLIDE ACETATE	Palliative treatment of advanced prostate cancer	1,3,4,6 months	0
LUPANETA PACK	LEUPROLIDE ACETATE; NORETHINDRONE ACETATE	Endometriosis	Monthly	0
DEPO-PROVERA	MEDROXYPROGESTERONE ACETATE	Prevention of Pregnancy	3 months	1
DEPO-SUBQ PROVERA 104	MEDROXYPROGESTERONE ACETATE	Prevention of pregnancy, endometriosis-associated pain	3 months	0
SINUVA	MOMETASONE FUROATE	Nasal polyps who had ethmoid surgery	3 months (one time)	0
VIVITROL	NALTREXONE	Alcohol/Opioid Dependence	Monthly (4 weeks)	0
SANDOSTATIN LAR	OCTREOTIDE ACETATE	Acromegaly, Carcinoid Tumors and Vasoactive Intestinal Peptide secreting tumors	Monthly (4 weeks)	0
ZYPREXA RELPREVV	OLANZAPINE PAMOATE	Schizophrenia	2, 4 weeks	0
INVEGA SUSTENNA	PALIPERIDONE PALMITATE	Schizophrenia, schizoaffective disorder, mood stabilizers or antidepressants	Monthly	0
INVEGA TRINZA	PALIPERIDONE PALMITATE	Schizophrenia	3 months	0
SIGNIFOR LAR KIT	PASIREOTIDE PAMOATE	Acromegaly, Cushing's Disease	4 weeks	0
PERSERIS KIT	RISPERIDONE	Schizophrenia	Monthly	0
RISPERDAL CONSTA	RISPERIDONE	Schizophrenia, Bipolar I Disorder	2 weeks	0
XYOSTED (AUTOINJECTOR)	TESTOSTERONE ENANTHATE	Testosterone replacement therapy	weekly	0
ZILRETTA	TRIAMCINOLONE ACETONIDE	Osteoarthritis pain of the knee	3 months (one time)	0
TRIPTODUR KIT	TRIPTORELIN PAMOATE	precocious puberty	24 weeks	0
TRELSTAR	TRIPTORELIN PAMOATE	Advanced prostrate cancer	4/12/24 weeks	0

Challenges in LAI Product Development and Lifecycle Management

- Long apparent half-life:
  - Longer time to reach steady state
  - Longer wash out time
- Challenging to propose relevant dosing scenarios, e.g.,
  - Impact of early, delayed or missed doses
  - Switching between formulations

Challenges in Life Cycle Management of Long-Acting Injectable Products

- Bioequivalence (BE) Studies are challenging
- High drop out rate
- Steady state BE studies in patients (safety)
- Individual steady state attainment

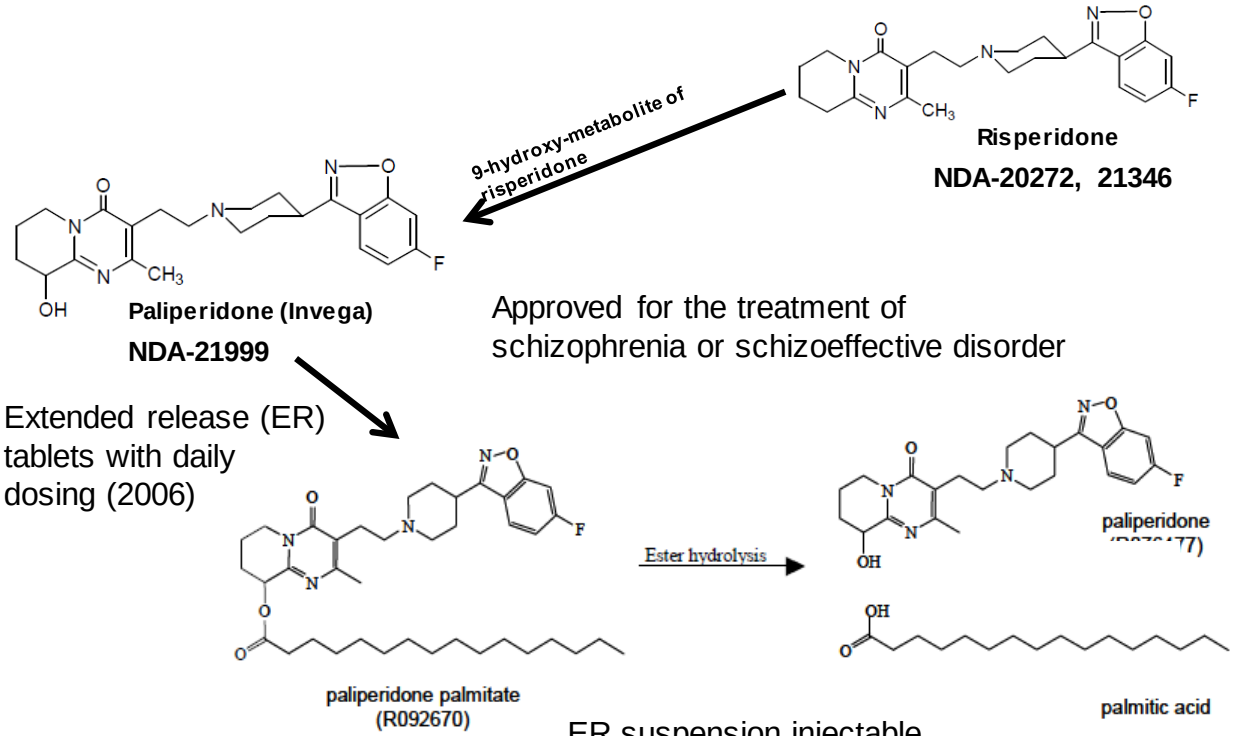
Opportunities for Modeling and Simulation in LAI Product Development

- Dosing regimen
  - Justification for dosing recommendation for missed doses
  - Impact of early, delayed or missed doses
  - Dose adjustment for special population
- Bridging results from previous studies/application
- Reducing cost, time; increasing efficiency

Opportunities for Modeling & Simulation in Life Cycle Management

- Optimize BE study design
- Sample size
- Simulate bio-inequivalent scenarios
- Design/justify a shorter duration BE study

Example: Paliperidone; Paliperidone Palmitate



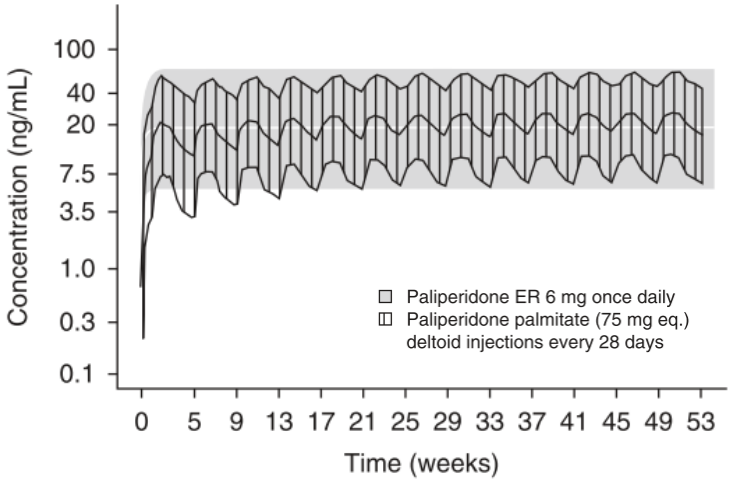
INVEGA SUSTENNA Background

- Invega Sustenna is an atypical antipsychotic administered monthly for:
  - Treatment of schizophrenia in adults
  - Treatment of schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants

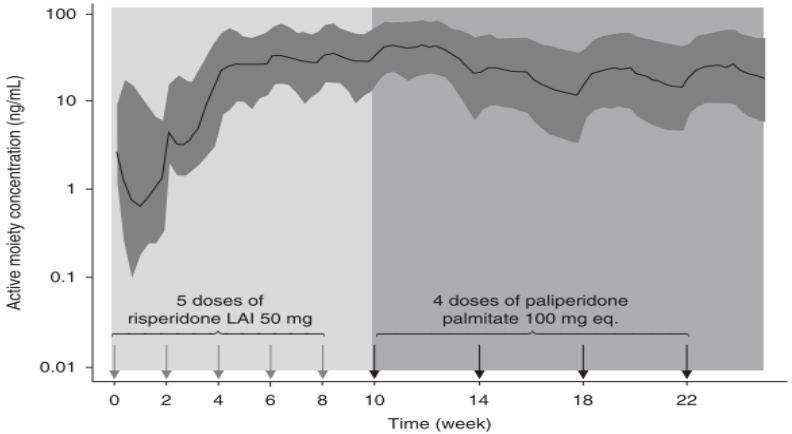
Indication	Initiation Dosing (deltoid)		Monthly Maintenance Dose (deltoid or gluteal)	Maximum Monthly Dose
	Day 1	Day 8		
Schizophrenia	234 mg (150 mg eq.)	156 mg (100 mg eq.)	39 (25 mg eq.) - 234 mg (150 mg eq.)	234 mg (150 mg eq.)
Schizoaffective disorder	234 mg (150 mg eq.)	156 mg (100 mg eq.)	78 mg (50 mg eq.) - 234 mg (150 mg eq.)	234 mg (150 mg eq.)

Application of Quantitative Clinical Pharmacology in New Drug Development

Dosing Regimen Based on Comparable Exposure



Switch Between Risperidone LAI to PP1M



Modeling & Simulation has been effectively used to support development of LAI drug products.

Samtani, et.al , CNS Drugs 2011

Clinical pharmacology review for Invega Sustenna at Drug@FDA

Product-Specific Guidance (PSG)

- FDA publishes PSGs to facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval.

- PSGs describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent (TE = PE + BE) to specific reference listed drugs.

- For two products to be considered bioequivalent, there should be no significant difference in the rate and extent of absorption of the active moiety, which are usually measured by Cmax (the maximum drug concentration) and AUC (the area under the concentration-time curve), respectively.

PE = Pharmaceutically Equivalent
FDA Product Specific Guidance Webpage: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Contains Nonbinding Recommendations

Draft Guidance on Paliperidone Palmitate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Paliperidone palmitate

Dosage Form; Route: Extended-release suspension; intramuscular

Recommended Studies: One study

Type of study: (1) Parallel group, steady-state or (2) two-period, crossover steady-state
Strength: 156 mg/mL
Subjects: Male and nonpregnant female patients with schizophrenia or schizoaffective disorder who are already receiving a stable regimen of paliperidone palmitate extended-release suspension via the intramuscular route. Patients who are already receiving 156 mg of paliperidone injection every month would be eligible to participate in the study if continuing their established maintenance dose.
Additional comments: (1) FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment. (2) Both sites of injection (gluteal and deltoid) should be included in the study design for adequate site representation to support the results of the study. (3) More than three doses may be required to reach steady state. Pharmacokinetic (PK) data should be submitted to demonstrate that steady state has been reached for each individual.

Analytes to measure (in appropriate biological fluid): Paliperidone in plasma

Recommend steady state BE studies.

In patients due to safety concerns.

Individual steady state attainment.

Commonly Asked Questions by ANDA Applicants

- What is the adequate number of doses to attain and confirm steady state?
- Is the proposed sample size sufficient?
- Is PK sampling scheme appropriate?

PK = Pharmacokinetic

Application of Quantitative Clinical Pharmacology for Generic Drug Development

- Models published or publicly available in NDA Clinical Pharmacology reviews.
- Key model parameters that can influence rate and extent of absorption can be identified and simulated to support alternative BE proposal.
- Virtual BE trial simulation taking formulation factors into account.

NDA = New Drug Application

Example: Paliperidone Palmitate 1 month Injection

ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2009; 48 (9): 585-600

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Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizop

A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsyc

Mahesh N. Samtani,[1] *An Vermeulen*[2] and *Kim Stuyckens*[2]

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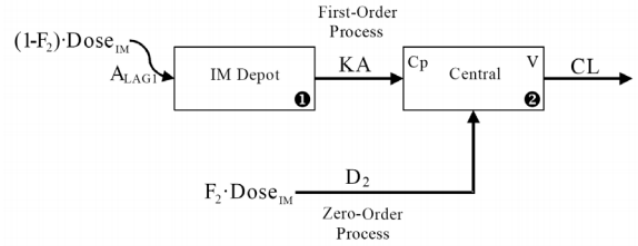

Note: Alag = Lag time for the first order absorption process; CL =clearance; Cp=plasma concentration; D2=duration of zero order input; F2=faction of dose entering via zero order input; IM=intramuscular; KA=first order absorption rate constant; V=volume of distribution

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Invega Su Company Applicati Approval

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elease Injectable Suspension

Dataset used	Index + Validation		Index + Validation	
IOV Status	IOV Included		IOV Turned Off	
Number of outliers excluded	54		54	
Theta # Parameter*	Estimate	Precision	Estimate	Precision
1 CL (L/hr)	4.95	1%	5.1	2%
2 CL - CRCL Power	0.376	3%	0.369	60%
3 V: Shift factor for Females	0.726	8%	0.778	14%
4 V (L)	391	3%	385	6%
5 V - BMI Power	0.889	1%	0.807	56%
6 KA: Shift factor for Females	0.765	7%	0.777	7%
7 KA: Shift factor for Deltoid Injection	1.23	3%	1.18	5%
8 KA x 10^3 (hr^{-1})	0.488	2%	0.558	9%
9 KA: Age Power	0.311	14%	0.349	25%
10 KA: Injection Volume Exponent	0.359	3%	0.308	24%
11 ALAG1 or D2 (hr)	319	1%	316	1%
12 F2: Shift factor for Females	0.781	4%	0.8	4%
13 F2: Shift factor for Deltoid Injection	1.37	3%	1.37	4%
14 F2: Shift factor Deltoid 1.5 inch needle	1.54	6%	1.46	7%
15 F2	0.168	2%	0.171	4%
16 F2: BMI Power	0.642	1%	0.717	8%
17 F2: Injection Volume Exponent	0.288	1%	0.274	18%
IIV CL (CV%)	40%	2%	45%	11%
IIV V (CV%)	69%	4%	79%	13%
IIV KA (CV%)	59%	3%	70%	14%
IIV F2 (SD)†	0.064	2%	0.098	8%
IOV CL (CV%)	26%	2%	0 FIX	N/A
IOV V (CV%)	14%	2%	0 FIX	N/A
IOV F2 (SD)†	0.07	2%	0 FIX	N/A
Sigma (SD)	0.22	3%	0.27	3%
OFV	-20238		-17934	

* For parameter equations refer to the footer in Table 11

† IOV and IIV for F2 is computed for 100 mg eq. gluteal injection for a male subject with BMI of 26.8 kg/m^2

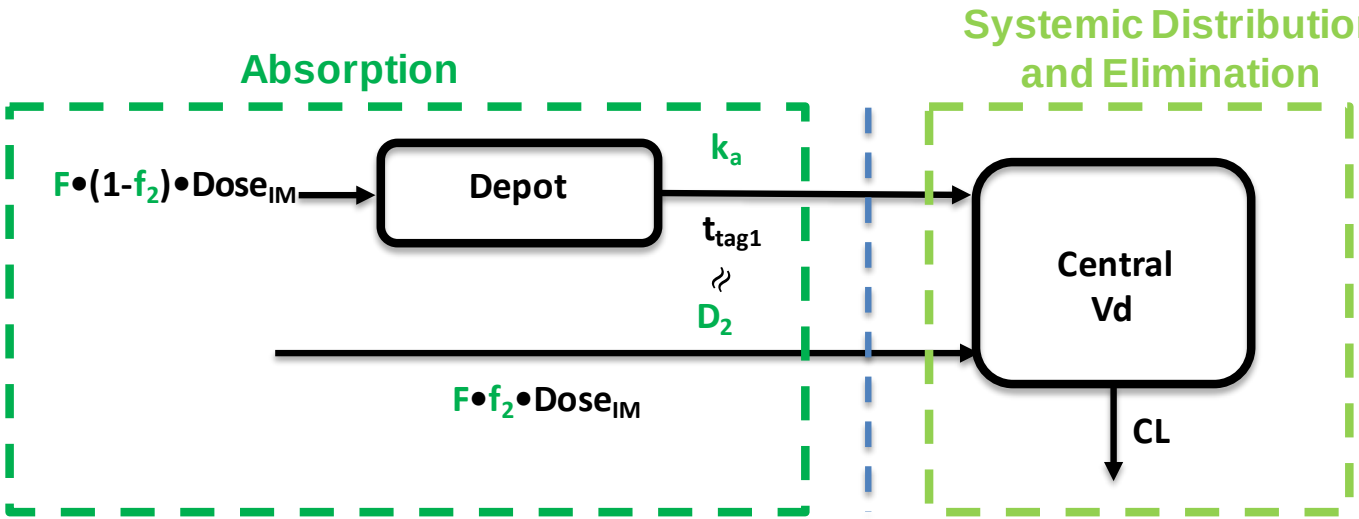
N/A: Not applicable

Samtani, et.al , Clin Pharmacokinet 2009

Clinical pharmacology review for Invega Sustenna at Drug@FDA

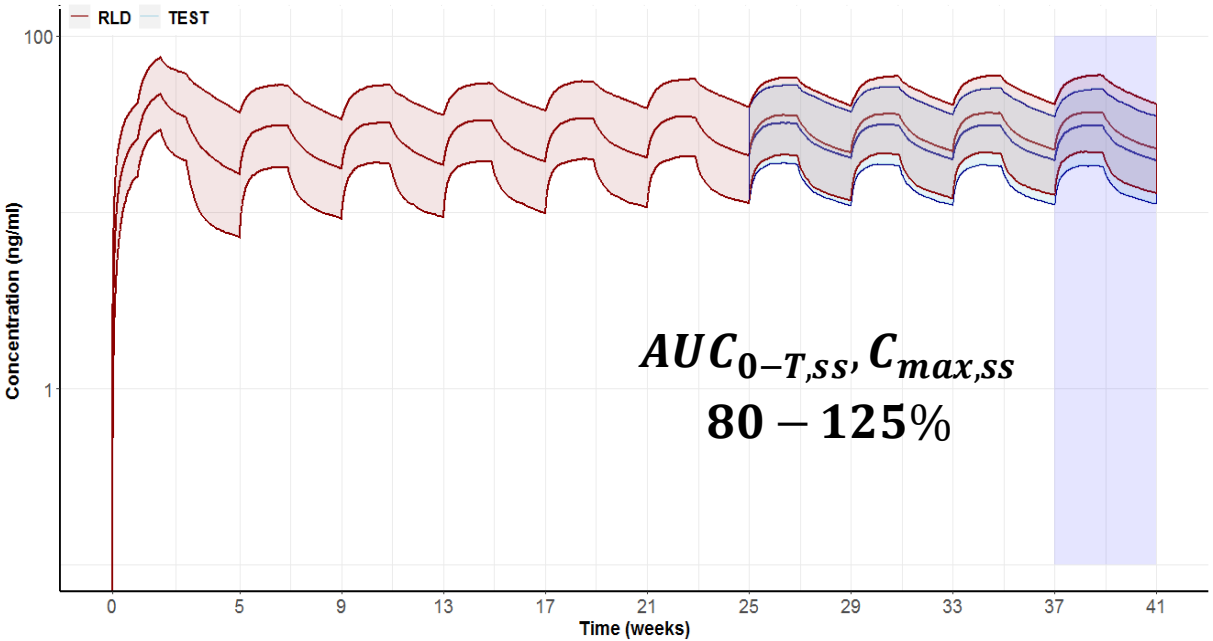
www.fda.gov

Example: Paliperidone Palmitate 1 month Injection



- Formulation dependent
- For BE assessment, key model parameters that can influence rate and extent of absorption can be modified to test alternative BE scenarios
- These parameters are generally drug dependent

Bioequivalence Trial Simulation



- The red solid lines and shaded areas represent the median paliperidone concentrations and 90% prediction intervals.
- Blue solid lines and shaded areas represent the median paliperidone concentrations and 90% prediction intervals for hypothetical generic TEST formulation with lower bioavailability.

- Can improve efficiency of BE study:
  - Number of subjects achieving steady state
  - Sample size determination
  - How many doses will lead to attainment of steady state?
  - PK sampling time points
  - Test alternate BE scenarios
  - Probability of BE success

Other Opportunities for Modeling and Simulation

- Propose alternate study designs for handling washout periods in the study design; reduce trial duration
- Incorporate critical quality attributes → in vitro/dissolution → in vivo dissolution/release using PBPK modeling and simulation approach

PBPK = Physiologically Based Pharmacokinetic

List of M&S Grants/Contracts for LAI Products

Project title	Study duration	Grantee/Contractor	Grant/Contract No.
Development of model-informed bioequivalence evaluation strategies for long-acting injectable products	2019-2021	Uppsala University	75F40119C10018
Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection*	2015-2019	University of Utah	U01FD005442
Development of PBPK simulation for long-acting injectable microspheres	2015-2018	Simulations Plus Inc.	U01FD005463

Welcome to propose and submit proposals to advance regulatory science.

GDUFA Regulatory Science: https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-regulatory-science

Summary

- Modeling & Simulation provides an important tool to support new and generic drug development:
  - Alternative BE approaches
  - Sample size determination
  - Effects of dose initiation; early, delayed, missed doses; switching products
  - Efficiency of BE studies, attainment of steady state; test alternative BE scenarios

Thank You!

- Model-Informed Drug Development Pilot Program (New Drug Development) https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program
- For information about Model-Informed Drug Development Pilot Program (New Drug Development) please contact MIDD@fda.hhs.gov
- Alternative approaches to demonstrate bioequivalence: Applicants can submit their proposal through FDA's Pre-ANDA program.
- Pre-ANDA Program Information: https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm578012.htm
- For questions about submitting Pre-ANDA meeting requests for complex generic drug products online please contact PreANDAHelp@fda.hhs.gov

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Challenge Question

Q) What are the challenges in lifecycle management of long acting injectable products?

1) Long durations of bioequivalence studies

2) Highly variable gastric emptying time

3) Both 1 and 2

4) None of the above