U.S. FOOD & DRUG ADMINISTRATION

Overview of the GDUFA Research Portfolio

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2024 Generic Drug Science and Research Initiatives Public Workshop

A Portfolio View

- Higher level than project view used to organize reporting
- FDA's FY2024 GUDFA research priorities
  - Available at https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects
- FY 2023 GDUFA Science and Research Report that will be available soon
  - Link will be added

GDUFA Research Portfolio

- Impurities
- Complex Active Ingredients
- BE for Complex Routes of Delivery
- BE for Complex Dosage Forms and Formulations
- BE for Oral and Parenteral Generics
- Drug-Device Combination Products
- Quantitative Medicine
- Artificial Intelligence (AI) and Machine Learning (ML)

BE - bioequivalence

Today

- The portfolio is large and stable
- Each year we want to have a focused review of some subsections of the portfolio
- Today and tomorrow we have sessions on
  - Impurities
  - Predictive Tools (Quantitative Medicine)
  - Drug-Device Combination Products

Today

- This year we have added more public comment periods in the focus session but also in a general session tomorrow
  - Here we are listening for project-level input
  - What specific projects would create value for generic competition across the research portfolio

Today

- We are also listening for input on which product-specific guidances (PSGs) are the highest industry priorities
  - We have a forecast list for PSGs expected in the next year
    - https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development
  - We are most interested in input on PSGs that are not on the forecast list

Today

- I will give an overview of the entire portfolio
- I hope this will stimulate discussion

Impurities

- Goal
  - Tools to efficiently evaluate and mitigate the risk of potential harmful impurities
- Areas of Focus
  - Nitrosamine-related compounds
- Key Accomplishment
  - Anti-oxidants can reduce certain impurities
  - Scientific foundation for minimizing BE studies for reformulations that add anti-oxidants to reduce potentially genotoxic impurities

Impurities: Projects

Continuing Grant(s) and Contract(s)

- Grant (3U01FD005978) *Effects of Antioxidants in Drugs Products on Intestinal Drug Transporters* with Dr. Sook Wah Yee at UCSF

Completed Grant(s) and Contract(s)

- Contract (75F40119D10024-75F40122F19003) *Quality and Bioequivalence Considerations for Generic Drug Reformulation to Mitigate Nitrosamine Risks* with Dr. Chris Bode at Pharmaron

Active FDA Research

- *Assessing the Prevalence of NDSRI Contamination in Pharmaceutical Products and Gaining Insights into the Contributing Factors for the Contamination by Screening NDSRIs in Various Drug Products*
- *Evaluating the Mutagenicity of Nitrosamines and NDSRIs Using Different In Vitro Assay Methods*
- *Excipient-Mediated Nitrosamine Formation in Pharmaceuticals: Approaches to Risk Assessment and Mitigation*
- *Investigation of N-Nitroso Compounds Formation in Pharmaceuticals: Risk Assessment, Approaches and Analytical Methods*
- *In Vitro and In Silico Modeling Approaches for Supporting Biowaiver for Non Q1/Q2 BCS Class 3 Drug Products*
- *Mitigation Studies of Nitrosamine Formation in Metformin and Bumetanide Drug Products*
- *Roles of Excipients in the Formation of NDMA in Metformin Drug Products*

Complex Active Ingredients

- Goal
  - Methods to characterize complex active ingredients and their immunogenicity risk
- Areas of Focus
  - Peptides
    - ~10% of products have generic competition
    - Surge in ANDA submissions
  - Oligonucleotides
    - No generics
- Key Accomplishment
  - FY23: 15 new PSGs for peptides and oligonucleotides

Complex Active Ingredients: Projects

FDA

New Grants and Contracts

- Contract (75F40123C00118) *Investigating the Impact of API Purity, Lipid Source and Manufacturing Process on Performance and Quality of Complex siRNA Lipid Nanoparticles* with Xiuling Lu at University of Connecticut

Continuing Grant(s) and Contract(s)

- Grant (1U01FD007651) *Multidimensional Analytical and Computational Approach to Determine Diastereomer Compositions in Oligonucleotide Drug Products* with Jace Jones at University of Maryland Baltimore

Active FDA Research

- *Analytical Characterization of Recombinant and Synthetic Peptide Product Impurities*
- *API Characterization and Impurity Profiling of Synthetic Oligonucleotides Using MS-based Multi-Attribute Method for Oligonucleotides (MAMO) Platform*
- *Assessment of Higher Order Structure Equivalence between Reference Peptide/Protein/Nucleic Acid Drug and its Follow-on/Generic/Biosimilar products using NMR Spectroscopy*
- *Characterization of Active Pharmaceutical Ingredients in Premarin (Conjugated Estrogen Creams)*
- *Developing High-resolution NMR Methods for Characterizing Multi-attributes of Complex API Mixtures*
- *Development and Optimization of Bioassays to Assess Immunogenicity Risk of Product and Process Related Impurities*
- *Development of Quantitative Approaches to Facilitate API Sameness Assessment*
- *In Vitro Innate Immune Response Assessment*
- *Process-Related Impurity Profile Characterization in Peptide Drug Products*

Complex Dosage Forms and Formulations

- Goal
  - Efficient characterization-based (in vitro) BE approaches for **systemically acting** complex dosage forms
- Areas of Focus
  - Long-acting injectables and implants
    - Only 4 of 39 active reference listed drug products have generic competition
  - Liposomes and iron colloids
- Key Accomplishment
  - July 2023: ANDA 213195 Naltrexone
    - First Generic for PLGA based LAI

Complex Dosage Forms and Formulations: Projects

New Grants and Contracts

- Contract (75F40123C00142) *Impact of API CQAs on In Situ Forming Implants and Understanding In Vitro and In Vivo Performance Differences* with Diane J. Burgess at University of Connecticut
- Contract (75F40123C00196) *In Vitro and In Vivo Assessment of Buprenorphine Extended Release Injection for Generic Product Equivalence* with Qingguo Xu at Virginia Commonwealth University
- Contract (75F40123C00192) *New PLGA Analytical Methods for Mini-Size Complex Long-Acting Injectable Formulations* with Kinam Park at Akina

Continuing Grants and Contracts

- Grant (1U01FD005443) *Development of Real-Time and Accelerated Dissolution Methods for a Long-Acting Levonorgestrel Intrauterine System* with Diane J Burgess at University of Connecticut
- Contract (75F40120C00136) *Assessing Long-Acting Injectable Formulations Using In Vivo Imaging* with Xiuling Lu at University of Connecticut
- Contract (75F40120C00127) *Characterization of Exparel, Understanding of Critical Manufacturing Process Parameters and Characterization of Drug Release Mechanisms In Vitro and In Vivo* with Anna Schwendeman at Regents of the University of Michigan
- Contract (75F40122C00019) *Correlation Between Material Properties Manufacturing Process Structural Properties and Quality Attributes of Long-acting Biodurable Implants Study* with Feng Zhang at University of Texas at Austin
- Contract (75F40122C00163) *Correlative 3D Imaging and AI Analysis to Establish Critical Performance Attributes of Polymeric Microsphere Products in Support of Performance Evaluation* with Shawn Zhang at DigiM Solution LLC
- Contract (75F40120C00198) *Effect of Repeat Unit Ordering on the Properties of Melt-Extruded, Poly(lactide-co-glycolide)-Based, Long-Acting Implants* with Feng Zhang at University of Texas at Austin
- Contract (75F40121C00133) *Enhancement and Validation of In Vitro - In Vivo Correlation Method for Long Acting Injectable Drug Products to Accelerate their Generic Development* with Diane J Burgess at University of Connecticut
- Contract (HHSF223201810187C) *Influence of Raw Materials, Manufacturing Variables, and Storage Conditions on In Vitro and In Vivo Performance of Exenatide in PLGA Microspheres* with Steven Schwendeman at Regents of the University of Michigan, College of Pharmacy

Active FDA Research

- *AI-Assisted Regulatory Tool to Improve the Quality and Assessment of PLGA Formulations*
- *Characterization and Manufacturing Process Evaluation of Multivesicular Liposomes*
- *Characterization of Bupivacaine HCL Implant, Understanding Impact of Variations in Raw Materials and Critical Manufacturing Process Parameters on Formulation Performance*
- *Characterization of Dexamethasone Ophthalmic Insert, Understanding of Raw Materials and Critical Manufacturing Process Parameters and Determination of Drug Release Mechanisms*
- *Comparing the Performance of Neural ODE and Population PK Models in Modeling Long-acting Injectable Products*
- *Evaluation and Development of Model-Integrated Bioequivalence Analysis Strategies*
- *Model Integrated Evidence Based Bioequivalence Using In-Silico Dosing to Steady State for Long Acting Injectable*
- *Product and Process Understanding of Long-acting Intrauterine System and Development of Accelerated In Vitro Release Testing Methods*

Complex Routes of Delivery

- Goal
  - Efficient characterization-based (in vitro) BE approaches for **locally acting** complex dosage forms
- Areas of Focus
  - Inhalation
    - Few MDI and DPI ANDAs => Support alternatives to FEV1 clinical study
    - Transition to environmentally friendly propellants
  - Topical
    - non-Q1Q2 formulation BE methods
    - Implementation of IVPT/IVRT
  - Ophthalmic and Otic
    - Studies to support Q2 changes and Q1Q2 waiver requests
    - Long-acting ophthalmic implants (no generics)
  - Nasal
  - GI-acting
- Key Accomplishment
  - PSG for 9 nasal sprays added in vitro option to remove PK study
  - FY23, 20 topical product ANDAs approved via Q3 methods

Complex Routes of Delivery: Nasal and Inhalation Projects

New Grants and Contracts

- Grant (1U01FD007987) *A Prospective Study to Support Validation of Lung Deposition Models with Nuclear Medicine Imaging Methods* with Benjamin Lavon at Fluidda, Inc.
- Grant (1U01FD007936) *Feasibility of Predicting Regional Lung Exposure from Systemic Pharmacokinetic Data of Generic OIDPs via Population Pharmacokinetic Modeling and Non-Compartmental Approaches* with Jurgen Bulitta at University of Florida
- Contract (75F40123C00201) *Development of a Laser-based Testing Platform for Generic Dry Powder Inhaler (DPI) Evaluation and In-silico Model Validation* with Agisilaos Kourmatzis at University of Sydney
- Contract (75F40123C00186) *Research Challenges Related to Environmentally Friendly Propellants In Metered Dose Inhalers* with Jagdeep Shur at Nanopharm

Continuing Grants and Contracts

- Grant (1U01FD007338) *A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia* with Charles Richard Esther at University of North Carolina at Chapel Hill
- Grant (1U01FD007353) *Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers* with Worth Longest at Virginia Commonwealth University
- Grant (1U01FD007657) *Integration of Drug Release and Permeability with Systems Data Relevant to PBPK Model of Nose-to-Brain Axis and Verification Using Clinical Data* with Kayode Ogungbenro at University of Manchester
- Contract (75F40122C00182) *Advancing In Vitro and (Patho)physiology-Based Pharmacokinetics Models to Understand and Predict Pulmonary Absorption and Tissue Retention of Inhaled Drugs* with Rodrigo Cristofoletti at University of Florida
- Contract (75F40122C00197) *DissolvIt® – An In Vitro Test Model Built to Resemble Relevant Lung Physiology for Evaluating the Dissolution- and Absorption of Drugs Administered via the Inhalation Route* with Maria Malmlof at Inhalation Sciences Sweden AB (ISAB)
- Contract (75F40120C00172) *Evaluation of Current Approaches Used to Establish Bioequivalence of Nasal Sprays for Local Action in Children* with Laleh Golshahi at Virginia Commonwealth University
- Contract (75F40122C00202) *Identification of Drug Distribution in Aerosols: A Nanospectroscopy and Nanothermal Analysis* with Hak Kim Chan at the University of Sydney
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London

Active FDA Research

- *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways*
- *Alternative BE Approach Assessment for Orally Inhaled Drug Products*
- *CFD Models of Soft Mist Inhalers*
- *Characterizing ADASUVE (loxapine, 10 mg) Staccato Inhalation Powder Particle Size Distribution*
- *Characterizing XERESE Cream (5% Acyclovir and 1% Hydrocortisone) Using MDRS*
- *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery*
- *Development of a Nasal PBPK Modeling Platform*
- *Dissolution for Inhalation Products*
- *Evaluating Process-Relevant Quality Attributes of Inhalation Powders*
- *Evaluation of the Staccato Drug Delivery Platform*
- *Explore the Use of Lung-On-A-Chip to Obtain Physiologically Relevant Parameters for Orally Inhaled Drug Products*
- *In Vitro Performance Testing of Soft Mist Inhalers*
- *Measurement of Delivered Dose Performance of Spiriva Handihaler*
- *Morphological and Performance Evaluation of Spray-dried Phospholipid Porous Particles*
- *Optimization of an In Vitro Method for Regional Deposition Prediction of Nasal Powders*
- *Predicting APSD Parameters of Orally Inhaled Drug Products using Artificial Intelligence and Machine Learning Algorithms*
- *Scientific Investigation of the Low Target Delivery Dose for Unit Dose Dry Powder Inhalers*

Complex Routes of Delivery: Topical Projects

New Grants and Contracts

- Grant (1U01FD007957) *Development and Validation of a Multi-Functional, Multi-Purpose Quantitative Tool for Dermal PBPK Modeling* with M. Begona Delgado-Charro at University of Bath
- Grant (1U01FD007954) *Formulation Toolbox for Topically Applied Drugs to Account for Physical Parameters, Dynamic Metamorphosis and Influence of Excipients* with James Clarke at Certara UK, LTD
- Contract (75F40123C00204) *In Vitro Tests to Support Bioequivalence Determination When Generic Dermatological Formulation has Differences from the Brand Product Formulation* with Ajay Banga at The Corporation of Mercer University
- Contract (75F40123C00213) *Role of Excipients and Excipient Substitution in Topical Semi-Solid Formulations and Their Effect on Product Performance and Quality* with Bozena Michniak-Kohn at Rutgers University

Continuing Grants and Contracts

- Grant (1U01FD006700) *Bioequivalence of Topical Products: Elucidating the Sensorial and Functional Characteristics of Compositionally Different Topical Formulations* with Yousuf Hussain Mohammed at University of Queensland
- Grant (1U01FD006507) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Sathyanarayana N Murthy at Topical Product Testing LLC
- Grant (1U01FD006533) *Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products using Non-Invasive Techniques (U01)* with Richard H. Guy at the University of Bath
- Grant (1U01FD006521) *Characterization of Key System Parameters of Mechanistic Dermal PBPK Models in Various Skin Diseases and Performance Verification of the Model Using Observed Local and Systemic Concentrations* with Sebastian Polak at Certara UK, LTD
- Grant (1U01FD007320) *Dermal Drug Product Quality and Bioequivalence Assessment through Advanced Mechanistic Absorption Modeling and Physiologically-Based Pharmacokinetic Simulation* with Jessica Rose Spires at Simulations Plus, Inc
- Grant (1U01FD006930) *Elucidating Fundamental Principles of Dermal Pharmacokinetics via Microdialysis* with David Taft at Long Island University, Brooklyn Campus
- Grant (1U01FD006496) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Michael Roberts at University of South Australia
- Grant (1U01FD007656) *In Vitro Based Approaches to Evaluate the Bioequivalence of Locally-Acting Rectal and Vaginal Semi-Solid Drug Products* with Jie Shen at Northeastern University
- Grant (1U01FD007669) *Optimized Clinical Dermal Open Flow Microperfusion Study Design to Demonstrate Bioequivalence Based on Cutaneous Pharmacokinetics* with Frank Sinner at Joanneum Research
- Grant (1U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School
- Grant (1U01FD007323) *Progressing Integration of In Vitro Topical Formulation Characterisation, Release and Permeation Data to the Next Level - PBPK Based Extrapolation to Bioequivalence Assessment in Virtual Populations* with Sebastian Polak at Certara UK Limited

Active FDA Research

- *CFD Analysis of Spreadability of Topical Formulations*
- *Characterization of Topical Gel, Cream, Foam Formulations to Elucidate the Impact of Drug Product Microstructure on Product Performance/Bioavailability to Facilitate the Development of Product Specific Guidances.*

Complex Routes of Delivery: Ophthalmic and Otic Projects

New Grant(s) and Contract(s)

- Contract (75F40123C00072) *A CFD-PBPK Framework for Supporting Bioequivalence Evaluation of Ophthalmic Drugs* with Carrie German at CFD Research Corporation
- Contract (75F40123C00192) *New PLGA Analytical Methods for Mini-Size Complex Long-Acting Injectable Formulations* with Kinam Park at Akina Inc.

Continuing Grant(s) and Contract(s)

- Grant (1U01FD006927) *Development and Validation of a PBPK/PD Modeling Strategy for Ophthalmic Drug Products to Support Translation from Preclinical Species to Human* with Jessica Spires at Simulations Plus, Inc.
- Contract (75F40120C00198) *Effect of Repeat Unit Ordering on the Properties of Melt-Extruded, Poly(lactide-co-glycolide)-Based, Long-Acting Implants* with Zhang Feng at University of Texas at Austin
- Contract (75F40119C10096) *New Analytical Methods for Complex Sameness of Injectable, Long-Acting PLGA Formulations* with Haesun Park at Akina, Inc.
- Contract (75F40119D10024-75F40120F19002) *PK/PD of Topically Administered Ophthalmic IOP Drug Formulations in Rabbits* with Vatsala Naageshwaran at Absorption Systems

Active FDA Research

- *Development of an Ophthalmic PBPK Modeling Platform*
- *Evaluation of Dexamethasone Intracanalicular Insert to Support Determination of Bioequivalence*
- *Ophthalmic Antimicrobial Kill Rate Study*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*

Complex Routes of Delivery: GI Acting Projects

Continuing Grant(s) and Contract(s)

- Grant (1U01FD007662) *Development and Verification of In Vitro Integrated Mechanistic Population-Based PBPK Model Framework Towards Virtual Bioequivalence Assessment of Locally Acting Drug Products in the GI Tract* with Rodrigo Cristofoletti at University of Florida
- Grant (1U01FD007660) *Development of PBBM Framework to Support an Assessment of Bioequivalence for Locally Acting Drugs in the Gastrointestinal Tract in Healthy Subjects and Patients* with Nikoletta Fotaki at University of Bath
- Contract (75F40120C00150) *Robust In Vitro/In Silico Model to Accelerate Generic Drug Product Development for the Oral Cavity Route of Administration* with Giovanni M. Pauletti at University of Health Sciences and Pharmacy in St. Louis

Active FDA Research

- *Best Practice for Using PBPK Modeling for Orally Absorbed Generic Drug Products*
- *GDUFA III Product-Specific Guidance Improvement for Oral Products*

Drug-Device Combination Products

- Goal
  - Methods to evaluate the impact of differences in the device constituent part compared to the reference listed drug
- Areas of Focus
  - Role of Human Factors studies in ANDA evaluation
    - Alternatives to evaluate user interface differences
  - Transdermal Systems
- Key Accomplishment
  - Addition of Device Advice to PSG

Drug-Device Combination Products: Projects

New Grants and Contracts

- Contract (75F40123D00028-75F40123F19001) *Comparative Use Human Factors Studies to Assess the Impact of Differences Between the User Interfaces of a Generic Drug-Device Combination Product and its Reference Listed Drug* with Jennifer Soosaar at Core Human Factors, Inc

Continuing Grants and Contracts

- Grant (1U01FD007360) *Development of a Combination Product Taxonomy and Comparative Human Factors Testing Method for Drug-Device Combination Products Submitted in an ANDA* with Megan O'Meara Conrad at University of Detroit Mercy
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London

Active FDA Research

- *Developing Clinically Meaningful Disintegration and Dissolution Methods for Teriparatide Loaded Microneedles*
- *Development of a Biopredictive In Vitro Permeation Test to Evaluate Absorption from Naloxone Nasal Spray*
- *Development of New BE methods for Transdermal Irritation and Sensitization*
- *Evaluation and Comparison of Electronic Components of Three Approved New Drug/ Device Combination Inhaler Products Indicated for Treatment of Bronchospasm or Asthma and Implications for Development of Future Generic Versions of Combination Drug/Device Products*
- *Evaluation of Critical Parameters Affecting the Performance of Staccato Drug Delivery System in Support of Development of Guidance for ADASUVE (Staccato Loxapine)*

BE for Oral and Parenteral Generics

- Goal
  - More efficient BE evaluations via waiver expansions and global harmonization
- Areas of Focus
  - M13 Implementation
  - Strength “waivers” for modified-release (MR) products
- Key Accomplishment
  - M13 finalization and Implementation in 2024

BE for Oral and Parenteral Generics: Projects

New Grants and Contracts

- Grant (1U01FD007959) *Evaluation of Oral Modified-Release Tablets to Support the Approval of Additional Strengths* with Jie Shen at Northeastern University

Continuing Grants and Contracts

- Grant (3U01FD005978) *The Effect of Sodium Lauryl Sulfate on the Oral Absorption of Fexofenadine in Humans* with Katherine Yang at University of California, San Francisco
- Contract (75F40121C00132) *Applying a Robotic Soft Esophagus (Rose) to Assess the Swallowability of Opioid Drugs* with Peter Xu at The University of Auckland
- Grant (1U01FD007352) *Development and Validation of a Best Practices Framework for PBPK Analysis for Biopharmaceutic Applications in Support of Model-Informed Biowaivers of Fed State BE Studies for BCS Class II Drugs* with Rodrigo Cristofoletti at University of Florida
- Contract (75F40121C00020) *Disintegration and Dissolution of Solid Dosage Forms and Influence of Food Induced Viscosity on Its Kinetics, Tools and Methodologies for Bioequivalence and Substitutability Evaluation* with Peter Langguth at Johannes Gutenberg University
- Contract (75F40120C00200) *Setting Patient-Centric Quality Standards (PCQS) for Modified Release (MR) Oral Drug Products with Biopredictive in Vitro Dissolution-Models* with Duxin Sun, Amit Pai Manjunath at University of Michigan, College of Pharmacy

Active FDA Research

- *Analysis of the Predictability of Bioequivalence in the Fed State*
- *Baseline Correction in Bioequivalence Studies for Drug Products Containing an Endogenous Compound*
- *Development of New Approaches to BE Evaluations of Multi-Strength MR Products*
- *Evaluation of BCS Class 3 Waiver Expansion*
- *Evaluation of Formulation Dependence of Drug-Drug Interaction with Proton Pump Inhibitors (PPIs) for Oral Extended-Release Drug Products*
- *Evaluation of the Need for Sprinkle BE Studies*
- *Exploration for Exclusion of Males and Females of Reproductive Potential as a Bioequivalence Study Population in Product-Specific Guidances for Generic Drug Development*
- *Exploration of Food Conditions and Study Populations in Bioequivalence Studies with Pharmacokinetic Endpoints for Antineoplastic Drugs in Generic Drug Development*
- *GDUFA III Product-Specific Guidance Improvement for Oral Products*
- *Identification of Critical Factors for Oral Solution Bioequivalence*
- *Improvement of Drug Dissolution Method for Application to Nanocrystal Drugs*
- *Improve BE Analysis for Narrow Therapeutic Index Drugs*
- *Investigation of Bayesian Estimation Based Procedure for Bioequivalence Assessment*
- *Modeling and Simulation to Support the Regulatory Harmonization on Bioequivalence Studies for Modified-Release Products*
- *Prioritization and Optimization of Modified Release BE Guidances*
- *Safety Considerations in Study Subject Selection in Bioequivalence Studies for Generic Drug Development*
- *Swallowability Factors Related to Size, Shape and Material of Generic Tablets*
- *U.S. FDA Efforts to Support Harmonization of Generic Drug Approval Standards*

Quantitative Medicine

- Goal
  - Predictive models to support more efficient BE evaluations across product categories
- Areas of Focus
  - PBPK for local routes of delivery
  - Model-integrated evidence (MIE) for long-acting injectables
  - Oral Absorption models for waiver evaluations
- Key Accomplishment
  - MIE meeting pilot program initiated

Quantitative Medicine: Projects

New Grants and Contracts

5 New Cross-cutting projects in other sections

- Grant (1U01FD007906) *Development and Validation of a Workflow to Conduct Virtual Bioequivalence Studies using PBBM-PBPK Models* with Frederico Martins at Simulations Plus, Inc.
- Grant (1U01FD007904) *A State-of-the-Art Virtual Bioequivalence Platform and Case Studies on Complex Formulations, Systemic and Local Concentration-based Bioequivalence* with Frederic Bois at Certara UK, LTD

Continuing Grants and Contracts

21 Continuing Cross-cutting projects in other sections

- Contract (75F40122C00139) *Model-Integrated Strategies for Bioequivalence Evaluation of Drugs with High Variability and/or Long Half-Life* with Mats O. Karlsson at Uppsala University

Active FDA Research

11 Continuing Cross-cutting projects in other sections

- *Clinical Trial Simulation for Clinical Endpoint Bioequivalence Studies*
- *Evaluation and Application of Repeated Crossover Study Design for Bioequivalence Assessment*
- *Evaluation and Development of Model-Integrated Bioequivalence Analysis Strategies*
- *Investigation of Bayesian Estimation Based Procedure for Bioequivalence Assessment*

AI/ML

- Goal
  - Develop AI/ML methods which FDA can use to improve the efficiency and consistency of scientific assessments and advice
- Areas of Focus
  - Natural language processing to understand drug labels and other FDA data
  - AI driven model development and validation
- Key Accomplishment
  - Generic Drug Structured Assessment (GDSA) in review use

AI/ML: Projects

New Grants and Contracts

- Grant (2U01FD005978) *Large Language Models to Support BE Evaluation* with Russ Altman, Percy Liang, and Kathleen Giacomini at CERSI - University of California, San Francisco (UCSF) – Stanford University

Continuing Grant(s) and Contract(s)

- Contract (75F40122C00163) *Correlative 3D Imaging and AI Analysis to Establish Critical Performance Attributes of Polymeric Microsphere Products in Support of Performance Evaluation* with Shawn Zhang at DigiM Solution LLC
- Contract (75F40122C00121) *Machine-Learning-Based Heterogeneous Treatment Effect Models for Informing Product-Specific Guidance Development* with Hualou Liang at Drexel University

Active FDA Research

- *AI-Assisted Tool to Improve the Quality and Assessment of PLGA Formulations*
- *Developing Tools Based on Text Analysis and Machine Learning to Enhance PSG Review Efficiency*
- *Development and Analysis of a Complex Product Database*
- *Development of PK Data Warehouse for BE Analysis*
- *Development of Quantitative Approaches to Facilitate API Sameness Assessment*
- *Machine Learning for Generic Drug Analysis*
- *Postmarketing Surveillance of Generic Drugs Using Sentinel*

Summary

- We look forward to your input as we refine and focus our research portfolio to accelerate access to safe and effective generic products!


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