Characterization of Complex Excipients and Formulations

Public Workshop
December 7-8, 2023

Agenda

Characterization of complex excipients and/or formulations is essential for developing complex generic products with respect to facilitating reverse-engineering, supporting Qualitatively (Q1) and Quantitatively (Q2) sameness (when applicable), developing methods for quality control (QC), supporting bioequivalence (BE), exploring alternative in vitro BE approaches, etc. However, development of "fit for purpose" characterization methods may not be straightforward depending on the complexity of excipient and/or formulation.

The purpose of this two-day workshop is to discuss the scientific principles and practical considerations that inform current FDA thinking for characterization of complex excipient and formulations to support generic product development. The workshop will provide an update on the progress of research activities funded by the Generic Drug User Fee Amendments (GDUFA) program, explore challenging issues that would benefit from broader discussion, identify areas that need further research, and discuss opportunities for coordination and collaboration between the FDA, generic drug industry, academic institutions, excipient vendors, contract research organizations, consultants, and other stakeholders.

FDA and the Center for Research on Complex Generics, which is a collaboration between the University of Maryland School of Pharmacy and the University of Michigan College of Pharmacy, are dedicated to advancing programs that stimulate scientific dialogue, disseminate current insights about complex generics, and generate new knowledge in support of FDA's mission to promote and protect the public health by increasing access to safe and effective generic medicines.

GENERAL TOPICS THAT WILL BE THE FOCUS OF THE WORKSHOP:

- Discussing characterization of complex excipients (e.g., polymers and lipids) for supporting regulatory and scientific needs during product development and approval
- Exploring potential alternative in vitro and/or in vivo studies for supporting product development and BE of complex dosage forms including injectable/insertable and ophthalmic products
- Sharing regulatory experiences on assessing complex dosage forms and highlighting internal research efforts for supporting development of product specific guidance and abbreviated new drug application (ANDA) assessment/approval
- Discussing opportunities for utilizing new technologies to support development and approval of complex dosage forms

Day 1 December 7, 2023

8:30 AM – 8:45 AM	**Welcome and Opening Remarks**	
	James Polli, PhD	Co-Director, CRCG
	Darby Kozak, PhD	Deputy Division Director, DTP I, ORS, OGD, FDA
Session 1:	**Characterization of Complex Excipients That are Commonly Used in Complex Injectable, Insertable, and Ophthalmic Products** FDA, academic, and industry presenters will share current thinking in the characterization and assessment of complex polymeric excipients used in long-acting products during product development and regulatory assessment.	
8:45 AM – 9:05 AM	***Understanding and Characterizing the Sequence Blockiness of Poly(lactide-co-glycolide)***	
	Nathaniel A. Lynd, PhD	Associate Professor, Cockrell School of Engineering, UT at Austin
9:05 AM – 9:25 AM	***Analysis of PLGAs in Complex Long-Acting Injectable Formulations***	
	Kinam Park, PhD	President, Akina, Inc.; Showalter Distinguished Professor, Biomedical Engineering, Purdue Univ.
9:25 AM – 9:45 AM	***Common Deficiencies or Expectations on Characterization of PLGA Polymer and PLGA-Based Products***	
	Young Kuk Jhon, PhD	Senior Chemist, DLBP I, OLDP, OPQ, FDA
9:45 AM – 10:05 AM	***Characterization of Ethylene Vinyl Acetate Copolymers for Drug Delivery Implants***	
	Jeffrey Haley, PhD	Manager, EVA and Long-Acting Drug Delivery Global Technology, Celanese
10:05 AM – 10:20 AM	***Coffee Break***	
10:20 AM – 10:40 AM	***Characterization of Silicone Excipients***	
	Matthew Kihara, MS, MBA	Senior Application Technologies Engineer, NuSil Technology-an Avantor Comp.
10:40 AM – 11:10 AM	***Q&A Session with Panel***	
Moderator:	**Yan Wang, PhD**	Lead Pharmacologist, DTP I, ORS, OGD, FDA
Panelists:	**Jeffrey Haley, PhD**	Manager, EVA and Long-Acting Drug Delivery Global Technology, Celanese
	Mohamed Jafri, PhD	Scientist, Orally Inhaled and Nasal Product Development, Vectura Fertin Pharma Ltd.
	Young Kuk Jhon, PhD	Senior Chemist, DLBP I, OLDP, OPQ, FDA
	Lindsay Johnson, PhD, PMP	Global Technical Marketing Manager, BASF Pharma Solutions
	Matthew Kihara, MS, MBA	Senior Application Technologies Engineer, NuSil Technology- an Avantor Comp.
	Nathaniel A. Lynd, PhD	Associate Professor, Cockrell School of Engineering, UT at Austin
	Kinam Park, PhD	President, Akina, Inc.; Showalter Distinguished Professor, Biomedical Engineering, Purdue Univ.
Session 2:	**Characterization of Complex Injectable, Insertable, and Ophthalmic Products** This session will highlight GDUFA research efforts on complex dosage forms including injectable and insertable drug products and ophthalmic products. The research outcomes are aimed to facilitate development of potential alternative in vitro or in vitro/in vivo BE approaches and provide more guidance on product assessment. In addition, presenters from industry will also share their experiences on exploring potential alternative approaches during product development.	
11:10 AM – 11:30 AM	***Understanding In Situ Forming Implants and Development of Appropriate In Vitro Testing Methods***	
	Diane J. Burgess, PhD	Distinguished Professor, Pfizer Distinguished Chair in Pharmaceutical Technology, Univ. of Connecticut
11:30 AM – 11:50 AM	***Role of PLGA Variability in Controlled Drug Release from Dexamethasone Intravitreal Implants***	
	Feng Zhang, PhD	Associate Professor, College of Pharmacy, UT at Austin
11:50 AM – 12:10 PM	***Exenatide PLGA Microspheres***	
	Steven Schwendeman, PhD	Ara G. Paul Professor and Chair of Pharmaceutical Sciences; Professor of Biomedical Engineering, Univ. of Michigan Biointerfaces Institute
12:10 PM – 1:00 PM	***Lunch Break***	
1:00 PM – 1:20 PM	***Insight Into In Vitro Drug Release Method Development for Ophthalmic Products: Key Considerations and Challenges***	

	Harshil Shah, BPharm, MS	Senior Manager, Bioequivalence, Cosette Pharmaceuticals Inc.
1:20 PM – 1:40 PM	***Development of Sensitive and Reproducible IVRT Method for Ophthalmic Gel Based on Polycarbophil***	
	Ana Krese, PhD	Senior Scientist R&D, Sandoz Global Development
1:40 PM – 2:10 PM	***Q&A Session with Panel***	
Moderator:	**Bin Qin, PhD**	Senior Staff Fellow, DTP I, ORS, OGD, FDA
Panelists:	**Diane Burgess, PhD**	Distinguished Professor, Pfizer Distinguished Chair in Pharmaceutical Technology, Univ. of Connecticut
	Greg Huang, PhD	Senior Chemist, DLBP II, OLDP, OPQ, FDA
	Ana Krese, PhD	Senior Scientist R&D, Sandoz Global Development
	Amrit Paudel, PhD	Associate Professor, Graz Univ. of Technology; Deputy Director, RCPE
	Dama Venugopal Rao, PhD	Lead-Structural Characterization, Dr. Reddy's Laboratories, Ltd.
	Steven Schwendeman, PhD	Ara G. Paul Professor and Chair of Pharmaceutical Sciences; Professor of Biomedical Engineering, Univ. of Michigan Biointerfaces Institute
	Harshil Shah, BPharm, MS	Senior Manager, Bioequivalence, Cosette Pharmaceuticals Inc
	Feng Zhang, PhD	Associate Professor, College of Pharmacy, UT at Austin
2:10 PM – 2:15 PM	***Closing remarks for the virtual session*** (End of virtual session for Day 1)	
	Bin Qin, PhD	Senior Staff Fellow, DTP I, ORS, OGD, FDA
2:15 PM – 2:30 PM	***Coffee Break***	
Session 3:	**Small Group Discussion**	
2:30 PM –3:30 PM	***Small Group Discussions (In person only)*** ***Discussion Topic: Remaining challenges for establishing formulation Q1 sameness*** • ***Technical challenges to establish Q1 sameness*** • ***Design space providing more flexibility for starting polymers***	
3:30 PM – 4:30 PM	***Small Group Discussions (In person only)*** ***Discussion Topic: Remaining challenges for developing complex generics*** • ***General expectations for formulation development: raw materials and development strategies for products with multiple strengths differing only in fill volume*** • ***Potential needs for having more than one supplier (i.e., polymer/lipid)*** • ***Industry's feedback on major challenges: e.g., in vitro drug release testing for long-acting products***	
4:30 PM – 4:40 PM	***Break***	
4:40 PM – 5:40 PM	***Small Group Discussions (In person only)*** ***Discussion Topic: Remaining challenges for the recommended in vitro BE study(ies) for long-acting products made of non-biodegradable polymers*** • ***Excipient and formulation characterization*** • ***Real time in vitro drug release testing*** • ***General expectations when exploring accelerated in vitro drug release testing***	

Day 2 December 8, 2023

8:30 AM – 8:40 AM	**Recap of Day 1**	
	Yan Wang, PhD	Lead Pharmacologist, DTP I, ORS, OGD, FDA
Session 4:	**Scientific and Regulatory Considerations When Developing Product Specific Guidance and Assessing ANDAs** This session will focus on various complex products. One talk will discuss common deficiencies and/or expectations when assessing intravaginal ring products. In addition, this session will present case studies to highlight FDA's efforts to support assessment and approval of complex products and develop scientifically sound BE approaches. The industry presenter and panelists will share their regulatory experiences during development of these complex products.	
8:40 AM – 9:00 AM	***Common Deficiencies or Expectations on PDMS/EVA Based Vaginal Rings/Implants***	
	Cedar Boakye, PhD	Senior Staff Fellow, DIMRP III, OLDP, OPQ, FDA
9:00 AM – 9:20 AM	***Industry Perspective: Challenges in Developing a Generic PLGA Based Long-Acting Injectables***	
	Ameya Kohojkar, MS	Director of Regulatory Affairs-US, Pharmathen
9:20 AM – 9:40 AM	***Assessing Qualitative Sameness of Polyoxyl Castor Oil in Phytonadione Injectables***	
	William C. Smith, PhD	Research Scientist, DPQR, OTR, OPQ, FDA
9:40 AM – 10:00 AM	***Understanding Drug Release Mechanism in Long-acting Intrauterine Systems***	
	Rokon Zaman, PhD	Staff Fellow, DPQR, OTR, OPQ, FDA
10:00 AM – 10:15 AM	***Coffee Break***	
10:15 AM – 10:45 AM	***Q&A Session with Panel***	
Moderator:	**Yogeeta Narkar, PhD**	Sr. Pharmaceutical Quality Assessor, DIMRP II, OLDP, OPQ, FDA
Panelists:	**Cedar Boakye, PhD**	Senior Staff Fellow, DIMRP III, OLDP, OPQ, FDA
	Meenal Chavan, PhD	Senior Pharmaceutical Quality Assessor, DIMRP III, OLDP, OPQ, FDA
	Sridhar Desikan, PhD	Vice President, R&D and Regulatory Affairs, Nexus Pharmaceuticals, USA
	Ameya Kohojkar, MS	Director of Regulatory Affairs-US, Pharmathen
	William C. Smith, PhD	Research Scientist, DPQR, OTR, OPQ, FDA
	Siva Vaithiyalingam, PhD	Sr. Vice President, Regulatory Affairs, Cipla Ltd.
	Xiaoming Xu, PhD	Division Director, DPQR, OTR, OPQ, FDA
	Rokon Zaman, PhD	Staff Fellow, DPQR, OTR, OPQ, FDA
	Nirav Khatri, PhD	Delivery Manager, Formulation Development Complex Injectables, Dr. Reddy's Laboratories Ltd.
Session 5:	**Advanced Technologies for Characterization of Complex Drug Products** This session will focus on the use of advanced technologies to obtain improved mechanistic understanding of complex dosage forms, such as in situ forming implant, polymeric microspheres, intrauterine systems, and nano materials. Industry panelists will share their experiences on using new technologies during product development.	
10:45 AM – 11:05 AM	***Imaging In Situ Forming Implants for Advanced Characterization***	
	Xiuling Lu, PhD	Professor, School of Pharmacy, Univ. of Connecticut; Associate Director, Center for Pharmaceutical Processing Research
11:05 AM – 11:25 AM	***Image-Based Porosity, Density, and In Silico Modeling for Product Equivalence Assessment***	
	Shawn Zhang, PhD	Founder & Managing Director, DigiM
11:25 AM – 11:45 AM	***High Resolution Chemical Imaging for Characterization of Intrauterine Systems and Nanomaterial Containing Drug Products***	
	Huzeyfe Yilmaz, PhD	Research Scientist, DCDA, OTR, OPQ, FDA
11:45 AM – 12:05 PM	***PBPK Models of Complex Injectable and Ophthalmic Drug Products: Case Studies***	
	Maxime Le Merdy, PharmD, PhD	Associate Director, Research and Collaboration, Simulations Plus
12:05 PM – 12:35 PM	***Q&A Session with Panel***	
Moderator:	**William C. Smith, PhD**	Research Scientist, DPQR, OTR, OPQ, FDA
Panelists:	**Khondoker Alam, PhD**	Senior Staff Fellow, DQMM, ORS, OGD, FDA

	Maxime Le Merdy, PharmD, PhD	Associate Director, Research and Collaboration, Simulations Plus
	Xiuling Lu, PhD	Professor, School of Pharmacy, Univ. of Connecticut; Associate Director, Center for Pharmaceutical Processing Research
	Brenda Pillari, PhD	Head of Regulatory Affairs, North America, Viatris
	Huzeyfe Yilmaz, PhD	Research Scientist, DCDA, OTR, OPQ, FDA
	Shawn Zhang, PhD	Founder & Managing Director, DigiM
12:35 PM – 12:45 PM	***Closing remarks for the virtual session*** (End of virtual session)	
	James Polli, PhD	Co-Director, CRCG
12:45 PM – 1:35 PM	***Lunch Break***	
Session 6:	**Small Group Discussion**	
1:35 PM – 2:35 PM	***Small Group Discussions (In person only)***	
	Discussion Topic: Exploring in vitro bioequivalence studies for long-acting implants	
	• ***In situ forming depots***	
	• ***Ophthalmic implants***	
2:35 PM – 3:35 PM	***Small Group Discussions (In person only)***	
	Discussion Topic: Implementation of advanced technologies for characterizing complex products during product development and ANDA assessment	
	• ***Applying advanced technologies during product development***	
	• ***Developing acceptance criteria for assessing data generated using advanced technologies***	
3:35 PM – 3:45 PM	***Closing Remarks***	
	Robert Lionberger, PhD	Director, ORS, OGD, FDA

Appendix of Abbreviations

AAPS	American Association of Pharmaceutical Scientists
AIMBE	American Institute for Medical and Biological Engineering
ANDA	Abbreviated New Drug Application
APGI	Association de Pharmacie Galènique Industrielle
API	Active Pharmaceutical Ingredients
APSTJ	Academy of Pharmaceutical Science and Technology, Japan
ASQ	American Society for Quality
ATL	Application Technical Lead
BE	Bioequivalence
BITS	Birla Institute of Technology & Science
BPharm	Bachelor's in Pharmaceutical Sciences
BS(c)	Bachelor's in Science
CMC	Chemistry, Manufacturing, and Controls
CMO	Contract Manufacturing Organization
Comp	Company
CRCG	Center for Research on Complex Generics
CRO	Contract Research Organization
CRS	Controlled Release Society
DCDA	Division of Complex Drug Analysis
d.d.	delniška družba (Joint Stock Option)
DIMRP III	Division of Immediate and Modified Release Products III
DLBP I	Division of Liquid-Based Products I
DLBP II	Division of Liquid-Based Products II
DMF	Drug Master File
DPQR	Division of Product Quality Research
DQMM	Division of Quantitative Methods and Modeling
DTP I	Division of Therapeutic Performance I
EU	European Union
EVA	Ethylene-vinyl Acetate
FDA	Food and Drug Administration
GDUFA	Generic Drug User Fee Amendments
Inc	Incorporated
IQA	Integrated Quality Assessment
IPEC	International Pharmaceutical Excipients Council
IUDs	Intrauterine Device
IVIVC	In Vitro In Vivo Correlation
IVRT	In Vitro Release Test
LAI	Long Acting Injectable
LLC	Limited Liability Company
Ltd	Limited
MBA	Master of Business Administration
MS	Master of Science

NIH	National Institutes of Health
NMIMS	Narsee Monjee Institute of Management Studies
NRC	National Research Council
NSF	National Science Foundation
OGD	Office of Generic Drugs
OPQ	Office of Pharmaceutical Quality
OLDP	Office of Lifecycle Drug Products
ORS	Office of Research and Standards
OTR	Office of Testing and Research
OTS	Office of Translational Sciences
PBPK	Physiologically Based Pharmacokinetic Modeling
PDMS	Polydimethylsiloxane
PharmD	Doctor of Pharmacy
PLGA	Poly(lactic-co-glycolic acid)
PhD	Doctor of Philosophy
PMP	Project Management in the Pharmaceutical Industry
PQRI	Product Quality Research Institute
PSG	Product-Specific Guidances
QC	Quality Control
Q1	Qualitatively
Q2	Quantitatively
RA	Regulatory Affairs
R&D	Research & Development
RTP	Research Triangle Park
Univ	University
USAID	United States Agency for International Development
USP	United States Pharmacopeia
UT	University of Texas