FDA-CRCG Workshop on In Vitro Release Testing and In Vitro In Vivo Correlation of Complex Ophthalmic, Injectable, Implantable, and Inserted Products

Virtual Public Workshop
June 29th, 2022

In vitro release testing (IVRT) is an important tool to support a demonstration of bioequivalence and/or product quality for various generic drug products. An In vitro-in vivo correlation (IVIVC) is a prediction of the in vivo drug product performance based on the drug product's IVRT profiles, which can be useful for an IVRT-based bioequivalence approach and/or to support post approval changes.

The purpose of this workshop is to discuss the scientific principles and practical considerations that inform current FDA thinking for IVRT and IVIVC studies to support generic product development and the approval of complex ophthalmic, injectable, implantable, and inserted drug products. 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, dissolution equipment manufacturers, contract research organizations, consultants, and other stakeholders.

FDA and the Center for Research on Complex Generics (CRCG), 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.

WORKSHOP TOPICS:

- IVRT study design considerations for supporting bioequivalence and product quality, when applicable, for complex ophthalmic products including emulsions, suspensions, ointments, and implants.
- IVRT study designs for supporting a demonstration of bioequivalence and as part of quality control for complex injectable and implantable products including suspensions, polymeric microspheres, in situ forming gels/implants, as well as solid implants like intrauterine systems and intravaginal systems.
- Novel IVRT methods for supporting product development and/or bioequivalence.
- Theoretical principles and practical challenges of IVRT and IVIVC method development, validation.
- Submission of IVRT information in Abbreviated New Drug Applications (ANDAs), including format of data/results, organization of information, and common deficiencies.

WORKSHOP OUTLINE:

8:30-8:40 AM	**Welcome and Opening Remarks**	
	James Polli, PhD	Co-Director, CRCG
8:40-9:00 AM	**Keynote Address**	
	A Scientific and Regulatory Overview of IVRT: Current Considerations and Challenges	
	Darby Kozak, PhD	Deputy Director, DTP I, ORS, OGD, FDA

SESSION 1: Scientific and Regulatory Uses of IVRT Studies

This session will share information on how IVRT studies have been used to support 1) generic drug product development, and 2) scientific and regulatory assessment on complex generic parenteral and ophthalmic products.

9:00-9:20 AM	***Regulatory Uses of IVRT Studies on Complex Generic Ophthalmic, Injectable, Implantable, and Inserted Products***	
	Bin Qin, PhD	DTP I, ORS, OGD, FDA
9:20-9:40 AM	***Role of IVRT in Supporting Generic Drug Development***	
	Mark Halus, PhD	Teva Pharmaceuticals
9:40-10:00 AM	***Bioequivalence Considerations for IVRT Methods for Ophthalmic Products***	
	Eunjung Park, PhD	DB II, OB, OGD, FDA
10:00-10:10 AM	*Coffee Break*	

SESSION 2: IVRT Method Development and Validation

This session will address 1) general scientific and regulatory expectations for IVRT method development and validation, 2) common deficiencies observed during regulatory assessment; and 3) challenges faced during IVRT method development and validation.

10:10-10:30 AM	***Expectations and Common Deficiencies with IVRT Studies Submitted in ANDAs for Ophthalmic Emulsion Products***	
	Alaa AbuZnait, PhD	DB I, OB, OGD, FDA
10:30-10:50 AM	***Common Deficiencies and Considerations on Setting Appropriate Specifications for Intravaginal Rings***	
	Kalpana Paudel, PhD	DB, ONDP, OPQ, FDA
10:50-11:10 AM	***IVRT Method Development for API Suspension Products and Validation with In Vivo Models***	
	Diane Burgess, PhD	University of Connecticut
11:10 AM-12:10 PM	Audience Q&A with panelists	
Moderator:	**Bin Qin, PhD**	DTP I, ORS, OGD, FDA
Panelists:	**Ripen Misri, PhD**	Apotex Inc.
	Alaa AbuZnait, PhD	DB I, OB, OGD, FDA
	Eunjung Park, PhD	DB II, OB, OGD, FDA
	Kalpana Paudel, PhD	DB, ONDP, OPQ, FDA
	Bryan DeBarr, BS	Viatris Inc.
	Mark Halus, PhD	Teva Pharmaceuticals
	Diane Burgess, PhD	University of Connecticut
12:10-1:00 PM	*Lunch Break*	

SESSION 3: IVIVC for Complex Parenteral and Ophthalmic Products

This session will address current research exploring IVIVCs for complex parenteral and ophthalmic products.

1:00-1:20 PM	***Challenges and Opportunities in the Development of IVRT and IVIVC of Complex Injectable Formulations***	
	Xavier Pepin, PharmD, PhD	Simulations Plus, Inc.

1:20-1:40 PM	***Relevant Challenges with IVRT with Iron-Carbohydrate Complexes: Application to IVIVC Models***	
	Amy Barton, PharmD, MHI	Vifor Pharma
1:40-2:00 PM	***Melt-extruded Dexamethasone Ophthalmic Implants – Process, Structure, and In Vitro Drug Release***	
	Feng Zhang, PhD	University of Texas Austin
2:00-2:45 PM	Audience Q&A with panelists	
Moderator:	**Yan Wang, PhD**	DTP I, ORS, OGD, FDA
Panelists:	**Xavier Pepin, PharmD, PhD**	Simulations Plus, Inc.
	Amy Barton, PharmD, MHI	Vifor Pharma
	Feng Zhang, PhD	University of Texas Austin
	Harshil Parikh, MS	Teva Pharmaceuticals
	Mingliang Tan, PhD	DQMM, ORS, OGD, FDA
2:45-2:55 PM	*Coffee Break*	

SESSION 4: Novel IVRT Methods

This session will address novel IVRT methods that may be used to support generic drug product development and a demonstration of bioequivalence for complex generic parenteral and ophthalmic products.

2:55-3:15 PM	***Thinking Outside the Box: Adaptive Perfusion Method to Study Drug Release from Emulsions***	
	Xiaoming Xu, PhD	DPQR, OTR, OPQ, FDA
3:15-3:35 PM	***Developing Discriminatory IVRT Methods for Injectable Suspensions: Start with Why***	
	William Smith, PhD	DPQR, OTR, OPQ, FDA
3:35-3:55 PM	***Advanced Imaging Technologies and AI-based Image Analysis for Mechanistic Characterization and Prediction of Complex Drug Release***	
	Shawn Zhang, PhD	DigiM Solution LLC
3:55-4:40 PM	Audience Q&A with panelists	
Moderator:	**Xiaoming Xu, PhD**	DPQR, OTR, OPQ, FDA
Panelists:	**Jie Shen, PhD**	University of Rhode Island
	Shawn Zhang, PhD	DigiM Solution LLC
	Parnali Chatterjee, PhD, RPh	DB, ONDP, OPQ, FDA
	Yoriko Harigaya, PharmD	DB II, OB, OGD, FDA
	William Smith, PhD	DPQR, OTR, OPQ, FDA
4:40-4:50 PM	**Workshop Summary**	
	Yan Wang, PhD	DTP I, ORS, OGD, FDA
4:50-5:00 PM	**Closing Remarks**	
	Anna Schwendeman, PhD	Co-Director, CRCG

Appendix of Abbreviations

AI	Artificial Intelligence
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BS	Bachelor of Science
CRCG	Center for Research on Complex Generics
DB	Division of Biopharmaceutics
DB I	Division of Bioequivalence I
DB II	Division of Bioequivalence II
DPQR	Division of Product Quality Research
DTP I	Division of Therapeutic Performance I
DQMM	Division of Quantitative Methods and Modeling
FDA	United States Food and Drug Administration
IVRT	In Vitro Release Testing
LLC	Limited Liability Corporation
Ltd.	Limited
MS	Master of Science
MHI	Master of Healthcare Innovation
OB	Office of Bioequivalence
OGD	Office of Generic Drugs
ONDP	Office of New Drug Products
OPQ	Office of Pharmaceutical Quality
ORS	Office of Research and Standards
OTR	Office of Testing and Research
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
RPh	Registered Pharmacist