dx.doi.org/10.14227/DT280421P450

Summary Report on Workshop on In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods

BEST PRACTICES AND SCIENTIFIC CONSIDERATIONS FOR ANDA SUBMISSIONS

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Virtual Public Workshop Hosted by Center for Complex Generics (CRCG) and US DFA

August 18–20, 2021

The Center for Complex Generics (CRCG) was formed thru a grant from the United States Food and Drug Administration (FDA) to University of Maryland and University of Michigan.

The mission of the CRCG is to

- Support FDA Office of Generic Drug's efforts to enhance research collaborations with the generic industry and further its mission to increase access to safe and effective generic drugs.
- Promote generic industry training and engaging the public in complex generics research.
- Conduct collaborative research and technique development that facilitate complex generics.

Recently, the CRCG in collaboration with the FDA, hosted a free virtual public workshop on **August 18–20, 2021**, titled "In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions."

The purpose of this workshop was to discuss the scientific principles and practical considerations that inform current FDA thinking and United States Pharmacopeia (USP) recommendations for in vitro release and permeation studies (IVRT and IVPT, respectively), explore challenging issues that would benefit from broader discussion, identify areas that would benefit from further research, and discuss opportunities for coordination and collaboration between the FDA, USP, academic institutions, product manufacturers, diffusion cell equipment manufacturers, contract research organizations, consultants, and other stakeholders.

Along these lines, the general topics that were the focus of the workshop were:

- IVRT study designs in different contexts including supporting a demonstration of bioequivalence for topical generics, scale up and post approval changes and different dosage forms
- IVPT study designs in different contexts including supporting demonstration of bioequivalence for topical generics, heat effects of topical and transdermal systems, and bioavailability of sunscreen products
- Challenges with aberrant data, outliers, inclusion/exclusion criteria, and statistical analysis of IVPT data
- Theoretical principles and practical challenges with IVRT and IVPT methods development, validation, and transfer
- Operational principles and practical challenges of IVRT and IVPT diffusion cell apparatus
- Submission of IVRT and IVPT information for Abbreviated New Drug Application (ANDA) including reportable information, format of data/report, organization of information and common deficiencies

- Quality management systems, retention samples, laboratory qualification and inspection of IVRT and IVPT submitted in ANDAs.

The first day of the workshop focusing on IVPT started with a Keynote Address by Dr. Howard Maibach, followed by Foundation Lecture by Dr. Sam Raney. The second day of the workshop focused on IVRT, beginning with Keynote Address by Dr. Vinod Shah and a second Foundation Lecture by Dr. Sam Raney. On the third and final day presentations included different apparatus in use, quality management systems, and IVRT and IVPT related information required for ANDAs.

Slides and notes can be found at http://www.complexgenerics.org/IVRTIVPT/

Day 1 - August 18, 2021	
Keynote Address	
The In Vitro Permeation Test (IVPT): Historical Perspective, Current Context, and Future Directions	*Howard Maibach, MD*
Foundation Lecture	
IVPT Fundamentals: Scientific and Practical Considerations	*Sam Raney, PhD*
Scientific and Regulatory Uses of IVPT Studies	
IVPT Studies with Sunscreen Products: Experimental Parameters	*Yang Yang, PhD*
IVPT Studies with Sunscreen Products: Potential Regulatory Utility	*E. Dennis Bashaw, PharmD*
IVPT Studies with Topical and Transdermal Products	*Audra Stinchcomb, PhD*
Panel Discussion	*Moderator: Bozena Michniak-Kohn, PhD*
IVPT Method Development, Validation, and Transfer	
IVPT Studies During Topical Product Development	*Leandro Santos, PhD*
Panel Discussion	*Moderator: Hiren Patel, PhD*
IVPT Data Challenges and Statistical Analysis	
IVPT Data Challenges in the Real World	*Paul Lehman, MS*
IVPT Data Analysis and Statistics	*Elena Rantou, PhD*
Panel Discussion	*Moderator: Priyanka Ghosh, PhD*
Day 2 - August 19, 2021	
Keynote Address	
The In Vitro Release Test (IVRT): Historical Perspective, Current Context, and Future Directions	*Vinod Shah, PhD*
Foundation Lecture	
IVRT Fundamentals: Scientific and Practical Considerations	*Sam Raney, PhD*
U.S. Pharmacopeia (USP) General Chapters <1724> and <1002>	
USP General Chapter Revision Process	*Margareth Marques, PhD; Leandro Santos, PhD*
Panel Discussion	*Moderator: Kailas Thakker, PhD*
IVRT Method Development, Validation, and Transfer	
Key Aspects in Developing Appropriate IVRT Methods for Topical Generic Products: Advances and Challenges	*Theo Kapanadze, PhD*
IVRT Studies During Topical Product Development: Lifecycle Management for SUPAC-SS and Generics	*Cristina Yen, BS*
IVRT Studies During Topical Product Development: Challenges in Method Development and Transfer	*Kailas Thakker, PhD*
Panel Discussion	*Moderator: Tannaz Ramezanli, PharmD, PhD*

Day 3 - August 20, 2021	
Diffusion Cell Apparatus	
Diffusion Cell Apparatus: Scientific Principles and Practical Challenges I	*Ahmed Zidan, PhD*
Diffusion Cell Apparatus: Scientific Principles and Practical Challenges II	*Jon Lenn, PhD*
Diffusion Cell Apparatus: Considerations for Design and Use I	*Ashvin Patel, PhD*
Diffusion Cell Apparatus: Considerations for Design and Use II	*Luke Lee, PhD*
Panel Discussion	*Moderator: Rong Wang, PhD*
Submission of Information in Abbreviated New Drug Applications (ANDAs)	
Considerations for IVRT Data and Information Submitted in ANDAs	*Tian Ma, PhD*
Considerations for IVPT Data and Information Submitted in ANDAs	*Archana Manerikar, MS, PharmD*
Panel Discussion	*Moderator: Usha Katragadda, PhD*
Quality Management Systems (QMS)	
QMS: Study Integrity Considerations	*Sam Haidar, PhD*
QMS: Industry Perspectives	*Kendall Powell, PhD*
Panel Discussion	*Moderator: Sam Haidar, PhD*
Workshop Summation	*Sam Raney, PhD*