FDA-CRCG Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Topical Product Development

Virtual Public Workshop
November 3rd
2022

Agenda

The limited number of certain generic topical products may have resulted from the difficulty in demonstrating bioequivalence (BE) efficiently. To address this public health issue, FDA invested in research and developed new in vitro (laboratory), in silico (computational modeling) and in vivo (clinical) approaches, which could be used to establish the BE of topical products in a more efficient manner. Efficient characterization-based approaches to demonstrate BE are now established for prospective generic drug products, but their utility is limited to instances when the formulation composition of prospective generic products is well matched to that of the reference standard. In other instances, comparative clinical endpoint BE studies continue to be utilized.

The purpose of this workshop is to discuss efficient, science-based BE approaches in development that may be useful for certain prospective generic products that are compositionally different compared to the reference standard. These approaches may utilize sophisticated techniques that have been developed to characterize the physical, structural, sensorial, and thermodynamic properties of topical drug products applied on the skin, as well as in vivo cutaneous pharmacokinetics (PK) studies. The workshop will provide an update on the progress of research activities funded by the Generic Drug User Fee Amendments, explore challenging issues that would benefit from broader discussion, identify areas that should be targeted with further research, and discuss opportunities for coordination and collaboration between FDA, the generic drug industry, academic institutions, contract research organizations, consultants and others involved in generic drug development.

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.

GENERAL TOPICS THAT WILL BE THE FOCUS OF THE WORKSHOP:

- Understanding the influence of inactive ingredients and other aspects of topical formulations on their performance
- Establishing the theoretical framework and scientific principles for well-controlled in vivo cutaneous PK studies that are sensitive and discriminating
- Elucidating practical challenges associated with method development and validation of in vivo cutaneous PK methodologies

WORKSHOP OUTLINE:

9:30 AM – 9:40 AM	**Welcome and Opening Remarks**	
	James Polli, PhD	Co-Director, CRCG
	Anna Schwendeman, PhD	Co-Director, CRCG
9:40 AM – 9:50 AM	***Clinical Relevance of Understanding the Impact of Formulation on Product Performance***	
	Markham Luke, MD, PhD, FAAD	Director, DTP-I, ORS, OGD, FDA
9:50 AM – 10:00 AM	***Overview of GDUFA Research Efforts to Develop Efficient Approaches by which to Demonstrate BE for Drug Products Applied to the Skin***	
	Sam Raney, PhD	Associate Director for Science, ORS, OGD, FDA
10:00 AM – 10:10 AM	***Coffee Break***	

SESSION 1: Understanding the Influence of Formulation Differences on Product Performance

This session will focus on understanding the current challenges with demonstrating BE efficiently for prospective generic topical drug products that may have formulation differences compared to the reference standard. The session will also discuss new techniques that have been developed to characterize the quality and performance attributes of topical drug products applied on the skin, including sensorial and thermodynamics considerations, to understand the influence of formulation differences on the physicochemical and structural (Q3) characteristics of the product, and on the bioavailability and therapeutic equivalence.

10:10 AM – 10:15 AM	***Introduction to Session 1***	
	Priyanka Ghosh, PhD	Senior Pharmacologist, DTP-I, ORS, OGD, FDA
10:15 AM – 10:30 AM	***Effect of Formulation Differences on Critical Quality Attributes and Performance of the Complex Topical Products***	
	Sameer Sachdeva, PhD	Associate Director/Sr. Research Scientist, Amneal Pharmaceuticals
10:30 AM – 10:45 AM	***Development Strategies for Generic Topical Products with Formulation Differences to Reference Product***	
	Vaibhav Dubey, MPharm, PhD	Deputy GM, Specialty Formulations, Alembic Pharmaceuticals Ltd.
10:45 AM – 11:00 AM	***Establishing Bioequivalence Using Characterization Based Approaches For Topical Products–Challenges & Solutions***	
	Romit Jani, MS-Pharm	Director, Formulation R&D, Solaris Pharma Corporation
11:00 AM – 11:20 AM	***Influence of Progressive Change in the Degree of Saturation of API on the Performance of Topical Products***	
	Narasimha Murthy, PhD	CSO, Topical Product Testing, LLC
11:20 AM – 11:40 AM	***Development of Methods for Evaluation of Formulation Differences and their Impact on Therapeutic Equivalence: Broadening the Therapeutic Scope***	
	Yousuf Mohammed, PhD	Sr. Research Fellow/Leader, Univ. of Queensland, Diamantina Institute
11:40 AM – 12:15 PM	***Q&A Session with Panel***	
Moderator:	**Priyanka Ghosh, PhD**	Senior Pharmacologist, DTP-I, ORS, OGD, FDA
Panelists:	**Vaibhav Dubey, PhD**	Deputy GM, Specialty Formulations, Alembic Pharmaceuticals Ltd.
	Romit Jani, MS	Director, Formulation R&D, Solaris Pharma Corporation
	Likan Liang, PhD	Branch 5 Chief, DLBP-II, OLDP, OPQ, FDA
	Markham Luke, MD, PhD, FAAD	Director, DTP-I, ORS, OGD, FDA
	Yousuf Mohammed, PhD	Sr. Research Fellow/Leader, University of Queensland, Diamantina Institute
	Narasimha Murthy, PhD	CSO, Topical Product Testing, LLC
	Sam Raney, PhD	Associate Director for Science, ORS, OGD, FDA
	Sameer Sachdeva, PhD	Associate Director/Sr. Research Scientist, Amneal Pharmaceuticals
12:15 PM – 1:30 PM	***Lunch Break***	

SESSION 2: Development of Cutaneous PK Based Approaches

This session will discuss advances in the systematic development of in vivo methodologies, study designs, controls, validation procedures, and equipment to measure and compare the in vivo cutaneous PK of drugs applied topically on the skin. The session will focus on assessing the body of evidence currently available using dermal open flow microperfusion (dOFM) and dermal microdialysis (dMD) methodologies with multiple drugs and multiple dosage forms, and discuss the general utility of these cutaneous PK methodologies to support a demonstration of BE. A key goal of the session is to solicit generic industry perspectives about any practical challenges that may discourage the adoption of in vivo cutaneous PK BE approaches, and to discuss strategies to address those challenges, for example, by improving the efficiency of study designs and data analysis, or by clarifying the context in which these methodologies might support a demonstration of BE.

1:30 PM – 1:35 PM	***Introduction to Session 2***	
	Sam Raney, PhD	Associate Director for Science, ORS, OGD, FDA
1:35 PM – 2:00 PM	***A Microdialysis Approach to Assess Cutaneous Pharmacokinetics of Topical Dermatological Drug Products***	
	Benjamin Kuzma, PhD	Research Scientist, Global DMPK, Vertex Pharmaceuticals Inc.
2:00 PM – 2:25 PM	***Continuous Skin Sampling Methods for the Assessment of Cutaneous PK-Based Bioequivalence***	
	Frank Sinner, PhD	VP Regulatory & Strategic Affairs, IBHS, Joanneum Research, GmbH
2:25 PM – 2:45 PM	***Cutaneous PK-based Techniques: Translating Scientific Advances to Regulatory Methods***	
	Tannaz Ramezanli, PharmD, PhD	Senior Pharmacologist, DTP-I, ORS, OGD, FDA
2:45 PM – 3:20 PM	***Q&A Session with Panel***	
Moderator:	**Sam Raney, PhD**	Associate Director for Science, ORS, OGD, FDA
Panelists:	**Charlie DiLiberti, MS**	President, Montclair Bioequivalence Services, LLC
	Candis Edwards, MS	Senior Vice President, Regulatory Affairs, Amneal Pharmaceuticals
	Benjamin Kuzma , PhD	Research Scientist, Global DMPK, Vertex Pharmaceuticals Inc.
	Hiren Patel, PhD	Staff Fellow, DB-II, OB, OGD, FDA
	Tannaz Ramezanli, PharmD, PhD	Senior Pharmacologist, DTP-I, ORS, OGD, FDA
	Chinmay Shukla, PhD	Clinical Pharmacology Team Leader, DIIP, OCP, OTS, FDA
	Frank Sinner, PhD	VP Regulatory & Strategic Affairs, IBHS, Joanneum Research, GmbH
	Nageshwar Thudi, PhD	VP Global Generics and Biosimilar Clinical Dev/Ops, Teva Pharmaceuticals
3:20 PM – 3:30 PM	***Coffee Break***	

SESSION 3: Method Development and Validation of Cutaneous PK Based Approaches

This session will discuss potential technical challenges associated with method development and method validation, as well as anticipated non-technical challenges with the implementation of in vivo cutaneous PK based methodologies to support a demonstration of BE. The format of the session will be an open question and answer (Q&A) session that encourages dialogue to elucidate any efforts that can optimize the utility, improve the feasibility, and encourage the adoption of in vivo cutaneous PK based methodologies to support the development of complex topical products.

3:30 PM – 3:35 PM	***Introduction to Session 3***	
	Tannaz Ramezanli, PharmD, PhD	Senior Pharmacologist, DTP-I, ORS, OGD, FDA
3:35 PM – 4:10 PM	***Q&A Session with Panel***	
Topics:		

- Method development and validation strategies
- Data analysis
- Anticipated non-technical challenges

Moderator:	**Tannaz Ramezanli, PharmD, PhD**	Senior Pharmacologist, DTP-I, ORS, OGD, FDA
Panelists:	**Manfred Bodenlenz, PhD**	Senior Scientist, Joanneum Research, GmbH
	Robert Lionberger, PhD	Director, ORS, OGD, FDA
	Hiren Patel, PhD	Staff Fellow, DB-II, OB, OGD, FDA
	Sam Raney, PhD	Associate Director for Science, ORS, OGD, FDA
	Elena Rantou, PhD	Lead Mathematical Statistician, Office of Biostatistics, OTS, FDA
	Nilufer Tampal, PhD	Associate Director, OB, OGD, FDA
	Eleftheria Tsakalozou, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA
	Miyoung Yoon, PhD	Team Lead, DQMM, ORS, OGD, FDA
	Jinhui Zhang, PhD	Chemist, DPQR, OTR, OPQ, FDA
4:10 PM – 4:30 PM	**Workshop Summation and Closing Remarks**	
	Priyanka Ghosh, PhD	Senior Pharmacologist, DTP-I, ORS, OGD, FDA

Appendix of Abbreviations

API	Active Pharmaceutical Ingredient
BE	Bioequivalence
CRCG	Center for Research on Complex Generics
CSO	Chief Scientific Officer
DB-II	Division of Bioequivalence II
Dev/Ops	Development and Operations
DIIP	Division of Inflammation and Immune Pharmacology
DLBP-II	Division of Liquid-Based Products II
DPQR	Division of Product Quality Research, Office of Testing and Research
DQMM	Division of Quantitative Methods and Modeling
DTP-I	Division of Therapeutic Performance I
FAAD	Fellow of the American Academy of Dermatology
FDA	United States Food and Drug Administration
GM	General Manager
GmbH	Gesellschaft mit beschränkter Haftung (limited liability corporation; LLC)
IBHS	Institute for Biomedicine and Health Sciences
Inc.	Incorporated
LLC	Limited Liability Corporation
Ltd.	Limited
MD	Doctor of Medicine
MS	Master of Science
OB	Office of Bioequivalence
OCP	Office of Clinical Pharmacology
OGD	Office of Generic Drugs
OLDP	Office of Lifecycle Drug Products
OPQ	Office of Pharmaceutical Quality
ORS	Office of Research and Standards
OTR	Office of Testing and Research
OTS	Office of Translational Sciences
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
PK	Pharmacokinetics
R&D	Research and Development
Sr.	Senior
Univ.	University
VP	Vice President