FDA-CRCG Webinar on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned

Virtual Public Webinar
December 6, 2022

Agenda

Establishing bioequivalence for drug products often involves having inactive ingredient sameness in a proposed generic's formulation with its reference listed drug (RLD). In general, to determine whether a proposed formulation will meet FDA's standards for sameness, the Agency provides formulation assessments through the controlled correspondence pathway. However, the challenges associated with meeting formulation sameness can differ between dosage forms and include differences in regulatory requirements for formulation sameness, analytical challenges associated with complex inactive ingredients, as well as safety considerations for exposure levels of inactive ingredients. To aid in the development of generic drug products, FDA publishes product-specific and general guidances that provide recommendations for establishing bioequivalence along with other considerations related to inactive ingredients and formulation sameness. However, even with the availability of FDA guidances and other informative tools like the inactive ingredient database, establishing formulation sameness can pose a significant challenge for generic drug applicants.

The goal of this webinar is to provide an overview of the regulatory framework, scientific concepts, product-specific challenges, and best practices related to development of complex generic drug products that are either required or recommended to have the same formulation as their respective RLDs. This information will provide a better understanding for the considerations that go into developing appropriate formulations, as well as best practices to present and support a formulation assessment that can reduce the time to potential product approval. The one-day webinar will include five sessions composed of presentations from FDA and the pharmaceutical industry followed by panel discussions to answer attendee questions.

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 WEBINAR:

- Providing an overview of the regulatory framework for formulation sameness assessment
- Understanding the concepts related to (1) qualitative (Q1) and quantitative (Q2) formulation sameness, and (2) "no significant difference" assessments
- Understanding the considerations for inactive ingredient levels in a formulation and the use of inactive ingredient database
- Identifying considerations and potential challenges during formulation development
- Providing best practices for submitting formulation assessment requests and supporting formulation sameness in ANDA submissions with an emphasis on complex generic drug products

WEBINAR OUTLINE:

8:00 AM – 8:10 AM	**Welcome and Opening Remarks**	
	James Polli, PhD	Co-Director, CRCG
	Anna Schwendeman, PhD	Co-Director, CRCG
8:10 AM – 8:25 AM	***Webinar Overview- Importance of Formulation in Generic Drug Development***	
	Darby Kozak, PhD	Deputy Director, DTP-I, ORS, OGD, FDA

SESSION 1: Regulatory Concepts for Formulation Sameness and Assessment

This session will provide an overview of the regulatory framework surrounding inactive ingredients as well as present the requirements and recommendations for formulation sameness across different types of drug products. Presenters will also provide some insight into FDA's responses that generic developers may receive following a formulation assessment request, as well as a discussion on the regulatory concepts generic developers may consider when selecting an appropriate RLD or reference standard during formulation development.

8:25 AM – 8:30 AM	***Introduction to Session 1***	
	Colleen Lee, JD	Acting Deputy Division Director, DLRS, OGDP, OGD, FDA
8:30 AM – 8:50 AM	***Requirements and Recommendations Related to Inactive Ingredients***	
	Melissa Mannion, PharmD, JD	Regulatory Counsel, DPD, OGDP, OGD, FDA
8:50 AM – 9:10 AM	***FDA Responses to Questions on QQ Sameness***	
	Melissa Mannion, PharmD, JD	Regulatory Counsel, DPD, OGDP, OGD, FDA
9:10 AM – 9:30 AM	***Formulation Considerations for Selecting an Appropriate RLD or RS***	
	Timothy H. Kim, PharmD	Acting Director, DOBPRA, OGDP, OGD, FDA
9:30 AM – 9:50 AM	***Q&A Session with Panel***	
Moderator:	**Colleen Lee, JD**	Acting Deputy Division Director, DLRS, OGDP, OGD, FDA
Panelists:	**Melissa Mannion, PharmD, JD**	Regulatory Counsel, DPD, OGDP, OGD, FDA
	Timothy H. Kim, PharmD	Acting Director, DOBPRA, OGDP, OGD, FDA
	Priyanka Ghosh, PhD	Senior Pharmacologist, DTP-I, ORS, OGD, FDA
	Truong-Vinh (Vinh) Phung, PharmD	Supervisory Pharmacist, DFR, ORO, OGD, FDA
9:50 AM – 10:00 AM	***Break***	

SESSION 2: Qualitative and Quantitative Considerations for Formulation Assessments

This session will provide an overview of the concepts and factors involved with determining whether the inactive ingredients in a proposed generic formulation are qualitatively and quantitatively (Q1/Q2) the same as the RLD product. Presenters will discuss different types of inactive ingredients across various dosage forms, characterization methods that can support qualitative sameness, and the general principles for performing a quantitative sameness comparison. This approach to formulation assessment will also be compared with the "no significant difference" formulation assessment approach.

10:00 AM – 10:05 AM	***Introduction to Session 2***	
	Bryan Newman, PhD	Lead Pharmacologist, DTP-I, ORS, OGD, FDA
10:05 AM – 10:25 AM	***Considerations for the Qualitative Sameness Evaluation of a Proposed Generic Formulation***	
	Yan Wang, PhD	Team Lead, DTP-I, ORS, OGD, FDA
10:25 AM – 10:45 AM	***General Considerations for the Quantitative Sameness Evaluation of a Proposed Generic Formulation***	
	Anubhav Kaviratna, PhD	Staff Fellow, DTP-I, ORS, OGD, FDA
10:45 AM – 11:05 AM	***General Considerations for the "No Significant Difference" Evaluation of a Proposed Generic Formulation***	
	Megan Kelchen, PhD	Pharmacologist, DTP-I, ORS, OGD, FDA
11:05 AM – 11:25 AM	***Q&A Session with Panel***	
Moderator:	**Bryan Newman, PhD**	Lead Pharmacologist, DTP-I, ORS, OGD, FDA
Panelists:	**Yan Wang, PhD**	Team Lead, DTP-I, ORS, OGD, FDA
	Anubhav Kaviratna, PhD	Staff Fellow, DTP-I, ORS, OGD, FDA
	Megan Kelchen, PhD	Pharmacologist, DTP-I, ORS, OGD, FDA
	Colleen Lee, JD	Acting Deputy Division Director, DLRS, OGDP, OGD, FDA
	Hiren Patel, PhD	Staff Fellow, DB-II, OB, OGD, FDA
11:25 AM – 12:25 PM	***Lunch Break***	

SESSION 3: Inactive Ingredient Database and Excipient Considerations

This session will provide information on the inactive ingredient database and related considerations to support the safe use and levels for an inactive ingredient in a proposed generic formulation. Presenters will give an overview of the inactive ingredient database and how its information can be used. Next, a discussion on the safety considerations for an inactive ingredient in a proposed generic formulation will be presented, which will include highlighting challenges when the proposed product is indicated for a pediatric population.

12:25 PM – 12:30 PM	***Introduction to Session 3***	
	Michelle Lin, MD	Senior Physician, DCR, OSCE, OGD, FDA
12:30 PM – 12:50 PM	***Inactive Ingredient Database Overview***	
	Susan Zuk, MS	Branch Chief, DRGS, OPPQ, OPQ, FDA
12:50 PM – 1:10 PM	***General Approach to Safety Assessment of Excipients in Generic Formulations***	
	Stuti Agarwal, PhD	Staff Fellow, DPTR, OSCE, OGD, FDA
1:10 PM – 1:30 PM	***General Approach to the Safety Review of Pediatric Excipients***	
	Amrita Ghosh, MD, PhD	Lead Physician, DCR, OSCE, OGD, FDA
1:30 PM – 1:50 PM	***Q&A Session with Panel***	
Moderator:	**Michelle Lin, MD**	Senior Physician, DCR, OSCE, OGD, FDA
Panelists:	**Susan Zuk, MS**	Branch Chief, DRGS, OPPQ, OPQ, FDA
	Stuti Agarwal, PhD	Staff Fellow, DPTR, OSCE, OGD, FDA
	Lisa Faulcon, PhD	Division Director, DCR, OSCE, OGD, FDA
	Bryan Newman, PhD	Lead Pharmacologist, DTP-I, ORS, OGD, FDA
	Yi Zhang, PhD	Lead Pharmacologist, DB-III, OB, OGD, FDA
1:50 PM – 2:00 PM	***Break***	

SESSION 4: Scientific Challenges and Considerations During Formulation Development

This session will provide an opportunity for industry speakers to share their experience with the scientific challenges encountered during formulation development and ensuring sameness with the RLD, whether using the qualitative and quantitative (Q1/Q2) sameness approach or the no significant difference approach. An FDA presenter will also provide an overview of the Agency's recently published Guidance for Industry: *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use.*

2:00 PM – 2:05 PM	***Introduction to Session 4***	
	Pamela Garner Dorsey, PhD	Senior Pharmacologist, DB-III, OB, OGD, FDA
2:05 PM – 2:25 PM	***Scientific Challenges Related to Establishing Q1/Q2 Sameness – An Industry Perspective***	
	Nitin Bhattad, MPharm	Global Head of Regulatory Science, Viatris, Inc.
2:25 PM – 2:45 PM	***Specificity & Discriminatory Challenges Limiting Accurate, Complete Identification and Quantification of Excipients in RLD Deformulation***	
	Babita Mallick, PhD	Team Lead, Analytical Development, Sandoz Inc.
2:45 PM – 3:05 PM	***Overview of the Guidance for Industry: Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use***	
	Xinran Li, PhD	Pharmacologist, DB-II, OB, OGD, FDA
3:05 PM – 3:25 PM	***Q&A Session with Panel***	
Moderator:	**Pamela Garner Dorsey, PhD**	Senior Pharmacologist, DB-III, OB, OGD, FDA
Panelists:	**Nitin Bhattad, MPharm**	Global Head of Regulatory Science, Viatris, Inc.
	Babita Mallick, PhD	Team Lead, Analytical Development, Sandoz Inc.
	Melissa Mannion, PharmD, JD	Regulatory Counsel, DPD, OGDP, OGD, FDA
	Hiren Patel, PhD	Staff Fellow, DB-II, OB, OGD, FDA
	Yan Wang, PhD	Team Lead, DTP-I, ORS, OGD, FDA
3:25 PM – 3:35 PM	***Break***	

SESSION 5: Best Practices for Submitting Formulation Assessment Requests and Avoiding Information Requests

This session will provide FDA's thoughts and recommendations for submitting an appropriate formulation assessment request. Presenters will provide details on the proposed generic formulation information that should be provided to FDA in a formulation assessment request to facilitate FDA's assessment and avoid potential requests for additional information. Next, presenters will give an overview of the additional ways generic applicants can request information from FDA if more feedback is needed, and when these communication methods may be more suitable than a controlled correspondence formulation assessment request.

3:35 PM – 3:40 PM	***Introduction to Session 5***	
	Truong-Vinh (Vinh) Phung, PharmD	Supervisory Pharmacist, DFR, ORO, OGD, FDA
3:40 PM – 4:00 PM	***Tips for Submitting a Proposed Formulation Table***	
	Elizabeth Kim, MSN	Controlled Correspondence Coordinator, DFR, ORO, OGD, FDA
4:00 PM – 4:20 PM	***Pathways for Receiving FDA's Feedback on Formulations***	
	Truong-Vinh (Vinh) Phung, PharmD	Supervisory Pharmacist, DFR, ORO, OGD, FDA
4:20 PM – 4:40 PM	***Q&A Session with Panel***	
Moderator:	**Truong-Vinh (Vinh) Phung, PharmD**	Supervisory Pharmacist, DFR, ORO, OGD, FDA
Panelists:	**Elizabeth Kim, MSN**	Controlled Correspondence Coordinator, DFR, ORO, OGD, FDA
	Julia Lee, PharmD	Deputy Division Director, DFR, ORO, OGD, FDA
	Melissa Mannion, PharmD, JD	Regulatory Counsel, DPD, OGDP, OGD, FDA
	Bryan Newman, PhD	Lead Pharmacologist, DTP-I, ORS, OGD, FDA
4:40 PM – 4:50 PM	**Closing Remarks**	
	Bryan Newman, PhD	Lead Pharmacologist, DTP-I, ORS, OGD, FDA

Appendix of Abbreviations

ANDA	Abbreviated New Drug Application
CDER	Center for Drug Evaluation and Research
CRCG	Center for Research on Complex Generics
CTP	Center for Tobacco Products
DARS	Division of Applied Regulatory Science
DB-II	Division of Bioequivalence II
DB-III	Division of Bioequivalence III
DCR	Division of Clinical Review
DFR	Division of Filing Review
DLRS	Division of Legal and Regulatory Support
DOBPRA	Division of Orange Book Publication and Regulatory Assessment
DPTR	Division of Pharmacology and Toxicology
DTP-I	Division of Therapeutic Performance I
FDA	Food and Drug Administration
GDUFA	Generic Drug User Fee Amendments
IID	Inactive Ingredient Database
JD	Juris Doctor
MD	Doctor of Medicine
MS	Master of Science
MSN	Master of Science in Nursing
OB	Office of Bioequivalence
OBP	Office of Biological Products
OGD	Office of Generic Drugs
OGDP	Office of Generic Drug Policy
OPQ	Office of Pharmaceutical Quality
ORO	Office of Regulatory Operations
ORS	Office of Research and Standards
OSCE	Office of Safety and Clinical Evaluation
OTS	Office of Translational Sciences
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
PK	Pharmacokinetics
R&D	Research and Development
RLD	Reference Listed Drug
RS	Reference Standard
USP	US Pharmacopeia
USPHS	United States Public Health Service Commissioned Corps