Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products

Public Workshop

October 7-8, 2024

Agenda

Day 1 October 7, 2024

8:30 AM – 8:35 AM	**Welcome and Opening Remarks**	
	Anna Schwendeman, PhD	Co-Director, CRCG
8:35 AM – 8:45 AM	**FDA Opening Remarks**	
	Iilun Murphy, MD	Director, OGD/CDER/FDA

Introduction

8:45 AM – 9:05 AM	***Introduction: Immunogenicity of Generic Products – History and Present***	
	Eric Pang, PhD	Team Lead (acting), DTP I/ORS/OGD/CDER/FDA

Session 1: Adaptive Immunogenicity Risk Mitigation - Product-Related Impurities (Chair: Dr. Daniela Verthelyi)

In this session, presenters from industry and FDA will provide an introduction to the major histocompatibility complex (MHC). The in silico analysis and in vitro MHC binding tools available will be discussed. Strategies for standardization of in vitro assay protocols will be considered including selection of cell lines, reference standard sourcing and qualification, and establishing appropriate test compound assay concentration.

9:05 AM – 9:10 AM	***Speaker Introductions***	
	Daniela Verthelyi, MD, PhD	Chief, Lab of Immunology, DPQR IV/OPQR/OPQ/CDER/FDA
9:10 AM – 9:30 AM	***Adaptive Immunogenicity Risk Mitigation of Generic Peptide Drug Products – A Perspective from a Company***	
	Narasimha Rao SP, MSc	Lead Immunogenicity, Global Clinical Mgmt. IPDO, Dr. Reddy's Labs Ltd.
9:30 AM – 9:50 AM	***Considering Tolerance When Evaluating Immunogenicity Risk: In Silico and In Vitro***	
	Anne (Annie) De Groot, MD	CSO and Chairman of the Board, EpiVax, Inc.
9:50 AM – 10:10 AM	***Tiered, Data-driven Approach for Assessing the Safety of Peptide-Related Impurities in Support of Commercial Control Strategy Development***	
	Robert (Rob) Siegel, PhD	Associate Vice President, Lab for Experimental Medicine, Eli Lilly & Company
10:10 AM – 10:40 AM	***Coffee Break***	
10:40 AM – 11:00 AM	***In Vitro Assays to Screen T-Cell Responses***	
	Sophie Tourdot, PhD	Immunogenicity Sciences Lead, Pfizer
11:00 AM – 11:20 AM	***In Vitro Tools and Assays: Review, Challenges, Suitability Standards***	
	Mohanraj Manangeeswaran, PhD	Senior Research Scientist, DPQR IV/OPQR/OPQ/CDER/FDA
11:20 AM- 11:50 AM	***Q&A Session with Panel***	
Moderator:	**Daniela Verthelyi, MD, PhD**	Chief, Lab of Immunology, DPQR IV/OPQR/OPQ/CDER/FDA
Panelists:	**Anne (Annie) De Groot, MD**	CSO and Chairman of the Board, EpiVax, Inc.
	Mohanraj Manangeeswaran, PhD	Senior Research Scientist, DPQR IV/OPQR/OPQ/CDER/FDA
	Narasimha Rao SP, MSc	Lead Immunogenicity, Global Clinical Mgmt. IPDO, Dr. Reddy's Labs Ltd.
	Robert (Rob) Siegel, PhD	Associate Vice President, Lab for Experimental Medicine, Eli Lilly & Company
	Sophie Tourdot, PhD	Immunogenicity Sciences Lead, Pfizer
11:50 AM – 12:50 PM	***Lunch Break***	

Session 2: Innate Immunogenicity Risk Mitigation - Process-Related Impurities (Chair: Dr. Eric Pang)

This session will discuss the innate immune response modulating impurity (IIRMI) assay in the context of protocols, appropriate controls and reference standards, assay validation, and selection of cell lines such as for PBMC (peripheral blood mononuclear cells).

12:50 PM – 12:55 PM	***Speaker Introductions***	
	Eric Pang, PhD	Team Lead (acting), DTP I/ORS/OGD/CDER/FDA
12:55 PM – 1:15 PM	***Comparative Assessment of Innate Immunogenicity for Generic Peptides: An Overview of Methods and Controls***	
	Andrew Graves, MS, SCYM	Director, Immunogenicity Assessment, Teva Pharmaceuticals
1:15 PM – 1:35 PM	***Validating the ProStorm IIRMI Assay: Insights and Experiences with Whole Blood***	
	Jeremy Fry, DPhil	Director of Sales, ProImmune
1:35 PM – 1:55 PM	***IIRMI Assay Validation and Experience***	
	Sofie Denies, PhD	Biostatistician, ImmunXperts
1:55 PM – 2:15 PM	***IIRMI Assay Validation and Experience - PBMC***	
	Noel Smith, PhD	Director, Head of Immunology, Early Development Services, Lonza Biologics
2:15 PM – 2:35 PM	***Fit for Purpose Assays to Assess Innate Immune Response Modulating Impurities***	
	Seth G. Thacker, PhD	Research Scientist, DPQR IV/OPQR/OPQ/CDER/FDA
2:35 PM – 2:55 PM	***Additional Considerations for IIRMI Assays***	
	Daniela Verthelyi, MD, PhD	Chief of Lab of Immunology, DPQR IV/OPQR/OPQ/CDER/FDA
2:55 PM – 3:25 PM	***Coffee Break***	
3:30 PM – 4:00 PM	***Q&A Session with Panel***	
Moderator:	**Eric Pang, PhD**	Team Lead (acting), DTP I/ORS/OGD/CDER/FDA
Panelists:	**Sofie Denies, PhD**	Biostatistician, ImmunXperts
	Jeremy Fry, DPhil	Director of Sales, ProImmune
	Andrew Graves, MS, SCYM	Director, Immunogenicity Assessment, Teva Pharmaceuticals
	Noel Smith, PhD	Director, Head of Immunology, Early Development Services, Lonza Biologics
	Seth G. Thacker, PhD	Research Scientist, DPQR IV/OPQR/OPQ/CDER/FDA
	Daniela Verthelyi, MD, PhD	Chief, Lab of Immunology, DPQR IV/OPQR/OPQ/CDER/FDA
4:00 PM – 4:05 PM	***Closing Remarks for Virtual Attendees (End of Hybrid Sessions for Day 1)***	
	Cameron Smith, PhD	Supervisory Chemist, DPQA IV/OPQA I/OPQ/CDER/FDA

Session 3: Small Group Working Sessions (In-Person Attendees Only)

Small group working sessions will involve structured activities with in-person attendees, focusing on the areas discussed during Day 1 of the workshop. Discussions will consider the challenges with conducting both adaptive and innate immunogenicity assays and understanding the regulatory expectations for conducting such assays.

4:05 PM –4:50 PM	***Small Group Working Session 1*** ***Discussion Topic: Adaptive Immunogenicity Risk Mitigation - Product-Related Impurities***
4:50 PM – 5:35 PM	***Small Group Working Session 2*** ***Discussion Topic: Innate Immune Response Modulating Impurities***

Day 2 October 8, 2024

8:30 AM – 8:40 AM	**Day 1 Summary**	
	Cameron Smith, PhD	Supervisory Chemist, DPQA IV/OPQA I/OPQ/CDER/FDA
8:40 AM – 8:50 AM	**Introduction to Day 2**	
	Steve Kozlowski, MD	Director, OPQA III/OPQ/CDER/FDA

Session 4: Host Cell Proteins and Alternative Models (Chair: Dr. Montserrat Puig)

This session will discuss regulatory pathways for recombinantly manufactured peptide products and strategies for immunogenicity risk mitigation using an in vitro approach. More specifically, immunogenicity risk assessment of host cell proteins as potential contaminants in peptide drug products. Also discussed in this session will be alternative models for immunogenicity risk assessment.

8:50 AM – 8:55 AM	***Speaker Introductions***	
	Montserrat Puig, PhD	Lead Biologist, DPQR IV/OPQR/OPQ/CDER/FDA
8:55 AM – 9:15 AM	***Recombinant Peptides: Role of In Vitro Data in Immunogenicity Risk Mitigation***	
	Sophie Shubow, PhD	Senior Biologist, OCP/OTS/CDER/FDA
9:15 AM – 9:35 AM	***Risk Assessment of Host Cell Proteins Related to Therapeutic Proteins and Cell/Gene Therapies***	
	Vibha Jawa, PhD, FAAPS	Executive Director, Bristol Myers Squibb
9:35 AM – 9:55 AM	***Introduction to MHC-associated Peptide Proteomics (MAPPs) Assay for Characterization of Presented Peptide Epitopes***	
	Emilee Knowlton, PhD	Senior Immunology Sales Specialist, ProImmune
9:55 AM – 10:25 AM	***Coffee Break***	
10:25 AM – 10:45 AM	***Alternative Models: From Humanized Mice to Microphysiological Systems and Beyond***	
	Kristina Howard, DVM, PhD	Research Veterinary Medical Officer, DARS/OCP/OTS/CDER/FDA
10:45 AM – 11:05 AM	***A New In Vitro Framework for Assessing Immunogenicity Using Comprehensive Profiling of Injectable Human Skin Modules***	
	Nicolas (Nico) Gaudenzio, MSc, PhD	Research Director, Inserm; Chief Scientific Officer, Genoskin, Inc.
11:05 AM – 11:35 AM	***Q&A Session with Panel***	
Moderator:	**Montserrat Puig, PhD**	Lead Biologist, DPQR IV/OPQR/OPQ/CDER/FDA
Panelists:	**Nicolas (Nico) Gaudenzio, MSc, PhD**	Research Director, Inserm; Chief Scientific Officer, Genoskin, Inc.
	Kristina Howard, DVM, PhD	Research Veterinary Medical Officer, DARS/OCP/OTS/CDER/FDA
	Vibha Jawa, PhD, FAAPS	Executive Director, Bristol Myers Squibb
	Emilee Knowlton, PhD	Senior Immunology Sales Specialist, ProImmune
	Sophie Shubow, PhD	Senior Biologist, OCP/OTS/CDER/FDA
11:35 AM – 12:35 PM	***Lunch Break***	

Session 5: Synthetic Oligonucleotide Therapeutics (Chair: Dr. Deyi Zhang)

This session will discuss the challenges of characterization of sequence-related impurities for oligonucleotide drug products and considerations of structure of such impurities and immunogenicity risk. Also discussed will be the role of innate immune response modulating impurities (IIRMIs) in the overall risk assessment.

12:35 PM – 12:40 PM	***Speaker Introductions***	
	Deyi Zhang, PhD	Senior Chemist, DTP I/ORS/OGD/CDER/FDA
12:40 PM – 12:50 PM	***Introduction***	
	Markham C. Luke, MD, PhD	Director, DTP I/ORS/OGD/CDER/FDA
12:50 PM – 1:10 PM	***Comprehensive Impurity Characterization and Profiling in Synthetic Oligonucleotides through Precision Analytics***	
	Kui Yang, PhD	Senior Research Scientist, DPQR II/OPQR/OPQ/CDER/FDA
1:10 PM – 1:30 PM	***Regulatory Oversight of the Immunogenicity Risks of Oligonucleotide Therapeutics***	
	Hobart (Bart) Rogers, PharmD, PhD	Research Officer and Reviewer, DTPM/OCP/OTS/CDER/FDA

1:30 PM – 1:50 PM	***Oligonucleotide Structure and Innate Immune Activation***	
	Sudhir Agrawal, DPhil, FRSC	Founder and President, ARNAY Sciences; Affiliate Professor, Department of Medicine, University of Massachusetts Chan Medical School
1:50 PM – 2:10 PM	***Assessment of IIRMI for Oligonucleotide Therapeutics***	
	Ha-Na Lee, PhD	Pharmaceutical Scientist, DPQR IV/OPQR/OPQ/CDER/FDA
2:10 PM – 2:30 PM	***Safety Considerations Including Immunogenicity When Developing Generic Oligonucleotides***	
	Filip Kolenc, MS	Senior Global Toxicologist, Sandoz Global Development (Ljubljana, Slovenia)
2:30 PM – 3:00 PM	***Q&A Session with Panel***	
Moderator:	**Deyi Zhang, PhD**	Senior Chemist, DTP I/ORS/OGD/CDER/FDA
Panelists:	**Sudhir Agrawal, DPhil, FRSC**	Founder and President, ARNAY Sciences; Affiliate Professor, Department of Medicine, University of Massachusetts Chan Medical School
	Filip Kolenc, MS	Senior Global Toxicologist, Sandoz Global Development (Ljubljana, Slovenia)
	Ha-Na Lee, PhD	Pharmaceutical Scientist, DPQR IV/OPQR/OPQ/CDER/FDA
	Markham C. Luke, MD, PhD	Director, DTP I/ORS/OGD/CDER/FDA
	Hobart (Bart) Rogers, PharmD, PhD	Research Officer and Reviewer, DTPM/OCP/OTS/CDER/FDA
	Kui Yang, PhD	Senior Research Scientist, DPQR II/OPQR/OPQ/CDER/FDA
3:00 PM – 3:05 PM	***Closing Remarks for Virtual Attendees (End of Hybrid Sessions for Day 2)***	
	Rob Lionberger, PhD	Director, ORS/OGD/CDER/FDA
3:05 PM – 3:35 PM	***Coffee Break***	

Session 6: Small Group Working Sessions (In-Person Only)

Small group working sessions will involve structured activities for in-person attendees, focusing on the areas discussed during Day 2 of the workshop. First, groups will consider the regulatory challenges for recombinantly produced peptide products and possible in vitro strategies for assessing the risk of host cell protein impurities that may be present in such products. Second, the challenges associated with analytical characterization of oligonucleotide-related impurities and the immunogenicity risk assessment of such impurities and other potential IIRMIs will be discussed.

3:35 PM – 4:20 PM	***Small Group Working Session 1***	
	Discussion Topic: Host Cell Proteins and Alternative Models	
4:20 PM – 5:05 PM	***Small Group Working Session 2***	
	Discussion Topic: Synthetic Oligonucleotide Therapeutics	
5:05 PM – 5:10 PM	***Closing Remarks***	
	James Polli, PhD	Co-Director, CRCG

Appendix of Abbreviations

CDER	Center for Drug Evaluation and Research
CRCG	Center for Research on Complex Generics
DARS	Division of Applied Regulatory Science
DTP	Division of Therapeutic Performance
DTPM	Division of Translational and Precision Medicine
DPhil	Doctor of Philosophy
DPQR	Division of Product Quality Research
DVM	Doctorate in Veterinary Medicine
FAAPS	Fellow of American Association of Pharmaceutical Scientists
FDA	U.S. Food and Drug Administration
FRSC	Fellow of the Royal Society of Chemistry
IIRMI	Innate Immune Response Modulating Impurity
Inc	Incorporated
IPDO	Integrated Product Development Organization
Ltd	Limited
MAPPs	MHC-associated Peptide Proteomics
MHC	Major Histocompatibility Complex
MD	Medical Doctorate
Mgmt	Management
MS	Master of Science
MSc	Master of Science
OCP	Office of Clinical Pharmacology
OGD	Office of Generic Drugs
OPQ	Office of Product Quality
OPQR	Office of Product Quality Research
ORS	Office of Research and Standards
OTS	Office of Translational Science
PBMC	Peripheral Blood Mononuclear Cells
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
SCYM	Specialist in Cytometry