Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products

Public Workshop| Nov 6-7, 2024

The focus of the workshop is to review the current research and recommendations on methods for confirmatory testing of NDSRI formation, safety testing methods for NDSRIs, and recommended acceptable intake limits for NDSRIs based on predicted carcinogenic potency and compound-specific data or read-across analysis. The workshop will also discuss strategies to mitigate the risk of NDSRI formation. Another key focus of the workshop is to provide updates on FDA's guidance 'Control of Nitrosamine Impurities in Human Drugs' (Revision 2, September 2024), including recommendations for assessing formulation stability, and approaches to demonstrating bioequivalence when drug developers are considering reformulation. The speakers and panelists will also discuss the regulatory considerations for navigating the implemented changes and share their regulatory experiences in pre- and post-approval changes in ANDA/NDA submissions and supplements illustrated with relevant case studies.

Day 1 November 6, 2024

8:30 AM – 8:40 AM	**Welcome and Opening Remarks**	
	James Polli, PhD	Co-Director, CRCG
8:40 AM – 8:50 AM	**FDA Opening Remarks**	
	Robert Lionberger, PhD	Director, ORS, OGD, FDA
8:50 AM – 9:00 AM	**Workshop Overview**	
	Khondoker Alam, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA

Day 1 Session 1: Safety & Risk Assessment Methods and Recommendations for Acceptable Intake Limit

This session will discuss the current research on safety testing methods for NDSRIs and recommendations on acceptable intake limits for NDSRIs based on predicted carcinogenic potency and compound-specific data or a read-across analysis.

9:00 AM – 9:10 AM	***Introduction to Session and Speakers***	
	Robert T. Dorsam, PhD	Director, DPTR, OSCE, OGD, FDA
	Xin Fu, PhD, DABT	Senior Pharmacologist, DPTR, OSCE, OGD, FDA
9:10 AM – 9:35 AM	***Development and Regulatory Application of the Carcinogenic Potency Categorization Approach (CPCA)***	
	Naomi Kruhlak, PhD	Scientific Lead, CTCS, DARS, OCP, OTS, FDA
9:35 AM – 9:55 AM	***The HESI QSAR-QM Project: Bridging QM methods and the CPCA to Enhance In Silico Hazard Assessment of Nitrosamines***	
	Jakub Kostal, PhD	Associate Professor and MS Program Advisor. Chemistry; Co-Director, MS Environmental Green Chem. Program, GWU.; Co-Founder and Principal, ToxFix
9:55 AM – 10:15 AM	***EMA Mutamind Projects Testing Nitrosamines***	
	Kevin Cross, PhD	Head of Science, Instem
10:15 AM – 10:35 AM	***Coffee Break***	
10:35 AM – 10:55 AM	***FDA Research Updates: Mutagenicity and Genotoxicity Evaluation of NDSRIs***	
	Robert Heflich, PhD	Director, DGMT, OR, NCTR, OCS, FDA
10:55 AM – 11:25 AM	***Summary of the HESI In Vitro Ames (i.e., Ring Trial) and In Vivo Transgenic Rodent Mutation Studies***	
	Joel Bercu, PhD, MPH, DABT	Executive Director, Nonclinical Safety and Pathobiology, Gilead Sciences
11:25 AM – 11:45 AM	***The In Vivo Comet Assay Predicts the In Vivo Mutagenicity of NDSRIs***	
	Maik Schuler, PhD	Head of Genetic Toxicology Group, Pfizer
11:45 AM – 12:05 PM	***EFSA's Risk Assessment on N-nitrosamines in Food***	
	Anna Christodoulidou, PhD	Senior Scientific Officer, FEEDCO Unit, EFSA
12:05 PM – 1:00 PM	***Lunch Break***	
1:00 PM – 2:00 PM	***Panel Discussion***	
Moderators:	**Robert T. Dorsam, PhD**	Director, DPTR, OSCE, OGD, FDA
	Xin Fu, PhD, DABT	Senior Pharmacologist, DPTR, OSCE, OGD, FDA
Panelists:	**Joel Bercu, PhD, MPH, DABT**	Executive Director, Nonclinical Safety and Pathobiology, Gilead Sciences
	Anna Christodoulidou, PhD	Senior Scientific Officer, FEEDCO Unit, EFSA
	Kevin Cross, PhD	Head of Science, Instem
	Robert Heflich, PhD	Director, DGMT, OR, NCTR, OCS, FDA

	Sruthi King, PhD	Deputy Director, DPTR, OSCE, OGD, FDA
	Jakub Kostal, PhD	Associate Professor and MS Program Advisor. Chemistry; Co-Director, MS Environmental Green Chem. Program, GWU.; Co-Founder and Principal, ToxFix
	Naomi Kruhlak, PhD	Scientific Lead, Computational Toxicology Consultation Service, DARS, OCP, OTS, FDA
	Govindaraj Kumaran, PhD	Chemist, DPQA XIX, OPQA III, OPQ, FDA
	Kristi Muldoon Jacobs, PhD	Director, OFCSDSI, FDA
	Maik Schuler, PhD	Head of Genetic Toxicology Group, Pfizer
2:00 PM – 2:10 PM	***Session Closing Remarks***	
	Robert T. Dorsam, PhD	Director, DPTR, OSCE, OGD, FDA
	Xin Fu, PhD, DABT	Senior Pharmacologist, DPTR, OSCE, OGD, FDA

Day 1 Session 2A: NDSRIs: Risk Factors of Formation, Confirmatory Testing, and Risk Mitigation

This session will discuss the risk factors for the formation of NDSRIs, considerations for risk assessment and confirmatory testing, and current advances and challenges with the analytical methods to quantify nitrosamine impurities. The speakers and panelists will also discuss strategies to mitigate the risk of NDSRI formation.

2:10 PM – 2:20 PM	***Introduction to Session and Speakers***	
	Andre Raw, PhD	Associate Director, Science and Communication, OPQA I, OPQ, FDA
	Dan Snider, PhD	Head of Global Quality Compliance, Viatris
2:20 PM – 2:40 PM	***Mitigation Strategies to Reduce the Risk of Nitrosamine Impurities in Pharmaceutical Drug Products***	
	David Keire, PhD	Office Director, OPQR, OPQ, FDA
2:40 PM – 3:00 PM	***Effect of Excipients on N-nitrosodimethylamine (NDMA) Formation in Metformin HCl Drug Products***	
	Martha Essandoh, PhD	Postdoctoral Research Fellow, DPQR V, OPQR, OPQ, FDA
3:00 PM – 3:20 PM	***Coffee Break***	
3:20 PM – 3:40 PM	***NDMA and Beyond: A Biased Kinetic Model to Assess Nitrosation Risk in Solid Drug Products***	
	Ian Ashworth, PhD	Principal Scientist, Chemical Development, PT&D, AstraZeneca
3:40 PM – 4:00 PM	***Multiple Nitrosamines in a Single Drug Product: Root Causes and Determination of Acceptable Intakes***	
	Dan Berger, PhD	Senior Biologist, OPQA I, OPQ, FDA
4:00 PM – 4:20 PM	***Something in the Air: The Contribution of Nitrogen Oxides to the Formation of Nitrosamines from Vulnerable Active Pharmaceutical Ingredients***	
	Joerg Schlingemann, PhD	Director and Principal Expert, EMD Serono, Healthcare Quality Unit, Merck
4:20 PM – 5:00 PM	***Panel Discussion***	
Moderator:	**Andre Raw, PhD**	Associate Director, Science and Communication, OPQA I, OPQ, FDA
	Dan Snider, PhD	Head of Global Quality Compliance, Viatris
Panelists:	**Ian Ashworth, PhD**	Principal Scientist, Chemical Development, PT&D, AstraZeneca
	Dan Berger, PhD	Senior Biologist, OPQA I, OPQ, FDA
	Martin Ehlert, PhD	Vice President, Global API R&D, Apotex Inc.
	Martha Essandoh, PhD	Postdoctoral Research Fellow, DPQR V, OPQR, OPQ, FDA
	David Keire, PhD	Office Director, OPQR, OPQ, FDA
	Joerg Schlingemann, PhD	Director and Principal Expert, EMD Serono, Healthcare Quality Unit, Merck

Day 2 November 7, 2024

Day 2 Session 2B: NDSRIs: Risk Factors of Formation, Confirmatory Testing, and Risk Mitigation

This continuation of the session will discuss the risk factors for the formation of NDSRIs, considerations for risk assessment and confirmatory testing, and current advances and challenges with the analytical methods to quantify nitrosamine impurities. The speakers and panelists will also discuss strategies to mitigate the risk of NDSRI formation.

8:30 AM – 8:40 AM	***Introduction to Session and Speakers***	
	Andre Raw, PhD	Associate Director, Science and Communication, OPQA I, OPQ, FDA
	Dan Snider, PhD	Head of Global Quality Compliance, Viatris
8:40 AM – 9:00 AM	***Discussing the Pitfalls and Challenges of Nitrosamines Confirmatory Testing***	
	Naiffer Romero, MSc, MPH	Principal Scientist, Science Division, United State Pharmacopeia
9:00 AM – 9:20 AM	***Extraction and Quantification of N-Nitro-Ketamine Impurity in Ketamine Drug Products Using Mixed-Mode Solid Phase Extraction and LC/MS/MS***	
	Guozhang Zou, PhD	Research Scientist, DPQR V, OPQ, FDA
9:20 AM – 9:40 AM	***API Fragment NDSRI: Screening Results and Conversion Rate Assessment***	
	Jingyue (Jan) Yang, PhD	Senior Research Scientist, DPQR I, OPQR, OPQ, FDA
9:40 AM – 10:00 AM	***Coffee Break***	
10:00 AM – 10:20 AM	***Fragment Nitrosamine Risks Based on Quantity, Extent of Conversion Rate and CPCA Calculations (Automated)***	
	Xiang Yu, PhD	Senior Biologist, OPQA I, OPQ, FDA
10:20 AM – 10:40 AM	***NDSRI Analysis; Risk Assessment Methodology***	
	Nitish Sharma, PhD	Assistant Professor, Dept of Pharmaceutical Analysis, NIPER-Ahmedabad
10:40 AM – 11:20 AM	***Panel Discussion***	
Moderator:	**Andre Raw, PhD**	Associate Director, Science and Communication, OPQA I, OPQ, FDA
	Dan Snider, PhD	Head of Global Quality Compliance, Viatris
Panelists:	**Naiffer Romero, MSc, MPH**	Principal Scientist, Science Division, United State Pharmacopeia
	Nitish Sharma, PhD	Assistant Professor, Dept of Pharmaceutical Analysis, NIPER-Ahmedabad
	Jingyue (Jan) Yang, PhD	Senior Research Scientist, DPQR I, OPQR, OPQ, FDA
	Xiang Yu, PhD	Senior Biologist, OPQA I, OPQ, FDA
	Guozhang Zou, PhD	Research Scientist, DPQR V, OPQ, FDA
11:20 AM – 11:40 AM	***Session Closing Remarks***	
	Andre Raw, PhD	Associate Director, Science and Communication, OPQA I, OPQ, FDA
	Dan Snider, PhD	Head of Global Quality Compliance, Viatris
11:40 AM – 12:40 PM	***Lunch Break***	

Day 2 Session 3: Update on FDA Guidance and Recommendations for Assessing Formulation Stability and Approaches to Bioequivalence

This session will provide updates on FDA's guidance 'Control of Nitrosamine Impurities in Human Drugs' (Revision 2, September 2024), including recommendations for assessing formulation stability, and approaches to demonstrating bioequivalence when drug developers are considering reformulation. The speakers and panelists will also discuss the regulatory approaches for navigating the implemented changes and share their regulatory experiences in pre- and post- approval changes in ANDA/NDA submissions and supplements illustrated with relevant case studies.

12:40 PM – 12:50 PM	***Introduction to Session and Speakers***	
	Khondoker Alam, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA
	Bing V. Li, PhD	Associate Director of Science, OB, OGD, FDA
12:50 PM – 1:10 PM	***FDA Nitrosamine Guidance 2024: Implementation of Control Strategies and BE Approach***	
	Dongmei Lu, PhD	Deputy Director (Acting), DTP II, ORS, OGD, FDA
	Susan Zuk, MS	Branch Chief, DRGS, OPPQ, OPQ, FDA
1:10 PM – 1:30 PM	***Use of Antioxidants for Reformulation and Implication of Added Antioxidant on Drug Permeability***	
	James Polli, PhD	Professor, University of Maryland, Baltimore; Co-Director, CRCG
1:30 PM – 1:50 PM	***Bridging Pre- and Post-Change Drug Products in Generic Drug Applications Impacted by Nitrosamine Drug Substance-Related Impurities (NDSRIs): Case Studies***	
	Rong Wang, PharmD, PhD	Associate Director, DB I, OB, OGD, FDA

1:50 PM – 2:10 PM	***Pre- and/or Post-approval Case Studies for New Drug Application***	
	Hansong Chen, PharmD, PhD	Senior Interdisciplinary Scientist, DPQA XII, OPQA II, OPQ, FDA
2:10 PM – 2:30 PM	***Nitrosamines Risk Assessment for BCS IV Containing IR Products & MR Products: Use of In Silico Prediction Tools and PBPK Modeling***	
	Sivacharan Kollipara, MPharm	Team Lead, Biopharmaceutics, Dr. Reddy's Laboratories Ltd.
2:30 PM – 2:40 PM	***Managing Bioequivalence Risks for Nitrosamine Impacted Generic Drug Products Containing BCS IV Drug Substances***	
	Qi Zhang, PhD	Lead Pharmacologist, DTP II, ORS, OGD, FDA
2:40 PM – 2:50 PM	***Physiologically Based Pharmacokinetic Modeling for BCS IV Drugs and Case Example***	
	Fang Wu, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA
2:50 PM – 3:10 PM	***Coffee Break***	
3:10 PM – 4:10 PM	***Panel Discussion***	
Moderator:	**Khondoker Alam, PhD**	Senior Pharmacologist, DQMM, ORS, OGD, FDA
	Bing V. Li, PhD	Associate Director of Science, OB, OGD, FDA
Panelists:	**Hansong Chen, PharmD, PhD**	Senior Interdisciplinary Scientist, DPQA XII, OPQA II, OPQ, FDA
	Sivacharan Kollipara, MPharm	Team Lead, Biopharmaceutics, Dr. Reddy's Laboratories Ltd.
	Dongmei Lu, PhD	Deputy Director (Acting), DTP II, ORS, OGD, FDA
	Sumit Madan, PhD	VP, Formulation R&D, Sun Pharmaceutical Industries Ltd.
	James Polli, PhD	Professor, University of Maryland, Baltimore; Co-Director, CRCG
	Bhagwant Rege, PhD	Director, DPQA VI, OPQA I, OPQ, FDA
	Rong Wang, PharmD, PhD	Associate Director, DB I, OB, OGD, FDA
	Fang Wu, PhD	Senior Pharmacologist, DQMM, ORS, OGD, FDA
	Qi Zhang, PhD	Lead Pharmacologist, DTP II, ORS, OGD, FDA
	Liang Zhao, PhD	Professor and Director, Center of Regulatory Science, SOP UCSF
	Susan Zuk, MS	Branch Chief, DRGS, OPPQ, OPQ, FDA
4:10 PM – 4:20 PM	***Session Closing Remarks***	
	Bing V. Li, PhD	Associate Director of Science, OB, OGD, FDA
4:20 PM – 4:30 PM	***Workshop Closing Remarks***	
	David Keire, PhD	Office Director, OPQR, OPQ, FDA

Appendix of Abbreviations

ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BS	Bachelor of Science
CDER	Center for Drug Evaluation and Research
CFSAN	Center for Food Safety and Applied Nutrition
Chem	Chemistry
Co.	Company
CPCA	Carcinogenic Potency Categorization Approach
CRCG	Center for Research on Complex Generics
CTCS	Computational Toxicology Consultation Service
DABT	Diplomate of the American Board of Toxicology
DARS	Division of Applied Regulatory Science
DB	Division of Biopharmaceutics
DB I	Division of Bioequivalence I
DCP	Division of Clinical Pharmacology
Dept	Department
DGMT	Division of Genetic and Molecular Toxicology
DPQA	Division of Product Quality Assessment
DPQR	Division of Product Quality Research
DPTR	Division of Pharmacology Toxicology
DQMM	Division of Quantitative Methods and Modeling
Dr	Doctor
DRGS	Division of Regulations and Guidance
DTP	Division of Therapeutic Performance
EFSA	The European Food Safety Authority
EMA	European Medicines Agency
EMD	Emmanuel Merck, Darmstadt
FDA	Food and Drug Administration
FEEDCO	Feed and Contaminants
GCM	Global Clinical Management
GWU	George Washington University
HESI	The Health and Environmental Sciences Institute
Inc.	Incorporated
IR	Immediate Release
IV	Intravenous
Lab	Laboratories
LC/MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
Ltd.	Limited
MPH	Master of Public Health
MPharm	Master of Pharmacy

MR	Modified Release
MS or MSci	Master of Science
NCTR	National Center for Toxicological Research
NDA	New Drug Application
NDSRIs	Nitrosamine Drug Substance Related Impurities
NDMA	N-nitrosodimethylamine
NIPER	National Institute of Pharmaceutical Education & Research
OB	Office of Bioequivalence
OCP	Office of Clinical Pharmacology
OCS	Office of Chief Scientist
OFAS	Office of Food Additive Safety
OGD	Office of Generic Drugs
OLDP	Office of Lifecycle Drug Product
ONDP	Office of New Drug Product
OPPQ	Office of Policy for Pharmaceutical Quality
OPQ	Office of Pharmaceutical Quality
OPQA	Office of Pharmaceutical Quality Assessment
OPQR	Office of Pharmaceutical Quality Research
OR	Office of Research
ORS	Office of Research and Standards
OSCE	Office of Safety and Clinical Evaluation
OTR	Office of Testing and Research
OTS	Office of Translational Sciences
PBPK	Physiologically Based Pharmacokinetic
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
PK	Pharmacokinetic
PT&D	Pharmaceutical Technology & Development
QM	Quantum Mechanics
QSAR-QM	Quantitative Structure Activity Relationship-Quantum Mechanics
R&D	Research and Development
SOP	School of Pharmacy
UCSF	University of California, San Francisco
USP	United States Pharmacopeia
VP	Vice President