Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics

Public Workshop
June 15, 2023
Agenda

The presence of N-nitrosamines in drug products can be a potential health concern. N-nitrosamines may increase the risk of cancer if people are exposed to them above acceptable levels. Since the findings of N-nitrosamines in some types of drug products, and considering their potential harmful effects to human health, regulatory agencies and drug manufacturers have been working continuously to understand the root causes of N-nitrosamine formation, to assess the risks of N-nitrosamines for human health, and to take appropriate actions to reduce or prevent the presence of N-nitrosamines in active pharmaceutical ingredients (APIs) and drug products. N-nitrosamine drug substance related impurities (NDSRIs) are a class of N-nitrosamines sharing structural similarity to the API (having an API or API sub-fragment in the chemical structures) that are receiving considerable attention among regulatory authorities.

The purpose of this workshop is to discuss the risks of NDSRIs formation in certain drug products, strategies to mitigate these risks, and considerations in assessing the safety of NDSRIs. The workshop will also discuss approaches to prevent or mitigate the formation of such impurities, for example, by adding a suitable antioxidant and/or pH modifier to drug products. Finally, the workshop will discuss the potential impacts of such reformulations on the bioequivalence of generic products, and strategies to efficiently address these issues.

8:30 AM – 8:40 AM	**Welcome and Opening Remarks**	
	James Polli, PhD	Co-Director, CRCG
	Anna Schwendeman, PhD	Co-Director, CRCG
8:40 AM – 8:50 AM	**Opening Remarks**	
	Robert Lionberger, PhD	Director, ORS, OGD, CDER, FDA
8:50 AM – 9:00 AM	**Nitrosamine Drug Substance Related Impurities (NDSRIs) - Workshop Overview**	
	Andre Raw, PhD	Associate Director for Science and Communication, OLDP, OPQ, CDER, FDA

Session 1: Risk of Forming NDSRIs and Strategies to Mitigate These Risks
This session will discuss the risk factors coming from both APIs and excipients in the formation of NDSRIs, and analytical methods used to quantify N-nitrosamines in pharmaceuticals. The speakers and panelists will also discuss the strategies to control impurities during the synthesis of APIs and excipients, and other strategies to prevent the formation of NDSRIs in a drug product during its shelf-life.

9:00 AM – 9:10 AM	***Introduction to Session and Speakers***	
	Andre Raw, PhD	Associate Director for Science and Communication, OLDP, OPQ, CDER, FDA
9:10 AM – 9:25 AM	***Distilling a Complex Problem into Quantitative Tools and Approaches to Address N-nitrosamine Formation Risk in Drug Products***	
	Justin Moser, BS	Principal Scientist, Pharmaceutical Sciences, Merck & Co., Inc.
9:25 AM – 9:40 AM	***Performance Characteristics of Mass Spectrometry-Based Analytical Procedures for Quantitation of Nitrosamines in Pharmaceuticals: Insights from an Inter-laboratory Study***	
	Jingyue (Jan) Yang, PhD	Senior Research Scientist, DPA, OTR, OPQ, CDER, FDA
9:40 AM – 9:55 AM	***Reducing Nitrosamines Without the Use of Scavengers: The Critical Role of Excipients–An Excipient Manufacturer's View***	
	Sander van Gessel, MEng	Director, Oral Solid Dose, DFE Pharma
9:55 AM – 10:25 AM	***Coffee Break***	

10:25 AM – 10:40 AM	***Control Strategies for NDSRIs Originating from Impurity Amines in APIs***	
	Martin Ehlert, PhD	Vice President, Global API R&D, Apotex Inc.
10:40 AM – 10:55 AM	***Effectiveness of Antioxidants in Selected Model Drugs: Mitigation Strategy and Impact of Reformulation in Their Stability***	
	Diaa Shakleya, PhD	Senior Research Scientist (Pharmacologist), DPQR, OTR, OPQ, CDER, FDA
10:55 AM – 11:10 AM	***Assessment of a Diverse Array of Nitrite Scavengers in Solution and Solid State: A Study of Inhibitory Effect on the Formation of Alkyl-Aryl and Dialkyl N-Nitrosamine Derivatives***	
	Marko Trampuž, MPharm, PhD	Scientist, Early Development, SDC Slovenia, Lek d.d., Sandoz
11:10 AM – 11:25 AM	***Determination of Nitrite in Pharmaceutical Excipients: Air as Source for Higher Nitrite Levels***	
	Rok Grahek, PhD	Head, Analytical Research Department, SDC Slovenia, Lek d.d., Sandoz
11:25 AM – 12:30 PM	***Panel Discussion***	
Moderator:	**Andre Raw, PhD**	Associate Director for Science and Communication, OLDP, OPQ, CDER, FDA
Panelists:	**Bhagwant Rege, PhD**	Director, DB, ONDP, OPQ, CDER, FDA
	Diaa Shakleya, PhD	Senior Research Scientist (Pharmacologist), DPQR, OTR, OPQ, CDER, FDA
	Jingyue (Jan) Yang, PhD	Senior Research Scientist, DPA, OTR, OPQ, CDER, FDA
	Justin Moser, BS	Principal Scientist, Pharmaceutical Sciences, Merck & Co., Inc.
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, CDER, FDA
	Marko Trampuž, MPharm, PhD	Scientist, Early Development, SDC Slovenia, Lek d.d., Sandoz
	Martin Ehlert, PhD	Vice President, Global API R&D, Apotex Inc.
	Mrunal A. Jaywant, PhD, PGDMM	Vice President of R&D, USP India
	Rok Grahek, PhD	Head, Analytical Research Department, SDC Slovenia, Lek d.d., Sandoz
	Sander van Gessel, MScEng	Director, Oral Solid Dose, DFE Pharma
	Zdenko Časar, PhD	Head, Early Development, SDC Slovenia, Lek d.d., Sandoz
12:30 PM – 1:30 PM	***Lunch Break***	

Session 2: Safety & Risk Assessment of NDSRIs for Human Health

This session will focus on considerations for assessing the safety of NDSRIs. The speakers and panelists will discuss current efforts by the FDA and drug manufacturers to assess the potential risk of NDSRIs for human health and to predict the activity and potency of NDSRIs by utilizing quantitative structure–activity relationship (QSAR) models or other relevant quantitative tools.

1:30 PM – 1:40 PM	***Introduction to Session and Speakers***	
	Robert T. Dorsam, PhD	Director, DPTR, OSCE, OGD, CDER, FDA
1:40 PM – 2:00 PM	***Nitrosamine Drug Impurities and Nitrosamine Drug Substance Related Impurities: Optimizing Mutagenicity Testing***	
	Robert H. Heflich, PhD	Director, DGMT, NCTR, FDA
2:00 PM – 2:15 PM	***Why Do Nitrosamine Potencies Vary So Widely? Mechanistic Rationales for the Effects of Structural Features on Activity***	
	David Ponting, MA, MSci, PhD	Principal Scientist, Lhasa Limited
2:15 PM – 2:30 PM	***Using Structure-Activity Relationships to Inform Setting Acceptable Intakes for Nitrosamine Impurities***	
	Naomi Kruhlak, PhD	Scientific Lead, DARS, OCP, OTS, CDER, FDA
2:30 PM – 2:50 PM	***Investigations into Nitrosamine Drug Substance Related Impurities – Mechanistic and Safety Science Investigations Across Key Drug Classes***	
	Andrew Teasdale, BSc (Hons), PhD	Senior Principal Scientist, AstraZeneca
	Raphael Nudelman, PhD, ERT	Senior Director Impurity Expert, Teva Pharmaceutical Industries Ltd.
2:50 PM – 3:20 PM	***Panel Discussion***	
Moderator:	**Robert T. Dorsam, PhD**	Director, DPTR, OSCE, OGD, CDER, FDA
Panelists:	**Andrew Teasdale, BSc (Hons), PhD**	Senior Principal Scientist, AstraZeneca
	David Ponting, MA, MSci, PhD	Principal Scientist, Lhasa Limited
	Naomi Kruhlak, PhD	Scientific Lead, DARS, OCP, OTS, CDER, FDA
	Raphael Nudelman, PhD, ERT	Senior Director Impurity Expert, Teva Pharmaceutical Industries Ltd.
	Robert H. Heflich, PhD	Director, DGMT, NCTR, FDA
	Sruthi King, PhD	Deputy Director, DPTR, OSCE, OGD, CDER, FDA

3:20 PM – 3:50 PM ***Coffee Break***

Session 3: Impact of Reformulation on the Bioequivalence of Generic Products and FDA Perspectives on Reformulated Generics

This session will focus on the potential impact of reformulations (e.g., adding a suitable antioxidant to the existing formulation) on the bioequivalence of generic products and strategies to efficiently address these challenges. The speakers and panelists will discuss current and future research efforts to evaluate the effect of an antioxidant in the formulation on the absorption and/or the bioavailability of APIs, and to utilize modeling and simulation approaches to assess the bio-inequivalence risks in the event of a reformulation. The speakers and panelists will discuss perspectives relating to potential bioequivalence approaches for generic products that are reformulated to mitigate NDSRIs formation.

3:50 PM – 4:00 PM	***Introduction to Session and Speakers***	
	Khondoker Alam, PhD	Senior Staff Fellow, DQMM, ORS, OGD, CDER, FDA
4:00 PM – 4:15 PM	***Use of a Novel Technology, the In Vitro Dissolution Absorption System, to Investigate the Effects of Antioxidants on the Intestinal Permeation of BCS Class III Drugs***	
	Chris Bode, PhD	Vice President of Scientific Affairs, Pharmaron
4:15 PM – 4:30 PM	***Effects of Antioxidants in Drugs Products on Intestinal Drug Transporters***	
	Sook Wah Yee, MPharm, PhD	Assistant Adjunct Professor, University of California, San Francisco
4:30 PM – 4:45 PM	***Physiologically Based Pharmacokinetic (PBPK) Absorption Modeling to Evaluate the Impact of Excipients on Bioequivalence of BCS Class III Drug Products***	
	Fang Wu, PhD	Senior Pharmacologist, DQMM, ORS, OGD, CDER, FDA
4:45 PM – 5:00 PM	***FDA Guidance - Control of Nitrosamines in Human Drugs***	
	Dongmei Lu, PhD	Policy Lead, OPPQ, OPQ, CDER, FDA
5:00 PM – 5:30 PM	***Panel Discussion***	
Moderator:	**Khondoker Alam, PhD**	Senior Staff Fellow, DQMM, ORS, OGD, CDER, FDA
Panelists:	**Andre Raw, PhD**	Associate Director for Science and Communication, OLDP, OPQ, CDER, FDA
	Bhagwant Rege, PhD	Division Director, DB, ONDP, OPQ, CDER, FDA
	Bing Li, PhD	Associate Director for Science, OB, OGD, CDER, FDA
	Chris Bode, PhD	Vice President of Scientific Affairs, Pharmaron
	Dongmei Lu, PhD	Policy Lead, OPPQ, OPQ, CDER, FDA
	Fang Wu, PhD	Senior Pharmacologist, DQMM, ORS, OGD, CDER, FDA
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, CDER, FDA
	Sook Wah Yee, MPharm, PhD	Assistant Adjunct Professor, University of California, San Francisco
5:30 PM – 5:35 PM	**Closing Remarks**	
	Lanyan (Lucy) Fang, PhD	Deputy Director, DQMM, ORS, OGD, CDER, FDA

Appendix of Abbreviations

ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
BS	Bachelor of Science
CDER	Center for Drug Evaluation and Research
Co.	Company
CRCG	Center for Research on Complex Generics
DARS	Division of Applied Regulatory Science
DB	Division of Biopharmaceutics
DGMT	Division of Genetic and Molecular Toxicology
DPA	Division of Pharmaceutical Analysis
DPQR	Division of Product Quality Research
DQMM	Division of Quantitative Methods and Modeling
DPTR	Division of Pharmacology and Toxicology
ERT	European Registered Toxicologist
FDA	Food and Drug Administration
Inc.	Incorporated
Ltd.	Limited
MPharm	Master of Pharmacy
MSci	Master of Science
NCTR	National Center for Toxicological Research
NDSRIs	Nitrosamine Drug Substance Related Impurities
OB	Office of Bioequivalence
OCP	Office of Clinical Pharmacology
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
ORS	Office of Research and Standards
OSCE	Office of Safety and Clinical Evaluation
OTR	Office of Testing and Research
PBPK	Physiologically Based Pharmacokinetic
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
PK	Pharmacokinetic
R&D	Research and Development
SDC	Sandoz Development Center
USP	United States Pharmacopeia