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 (NDSRls) 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 NDSRls formation in certain drug products, strategies to mitigate these risks, and considerations in assessing the safety of NDSRls. 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.

### Session 1: Risk of Forming NDSRls and Strategies to Mitigate These Risks

This session will discuss the risk factors coming from both APIs and excipients in the formation of NDSRls, 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 NDSRls in a drug product during its shelf-life.

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8:30 AM - 8:40 AM
**Welcome and Opening Remarks**
James Polli, PhD  
Anna Schwendeman, PhD  
Co-Director, CRCG  
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 (NDSRls) - Workshop Overview**
Andre Raw, PhD  
Associate Director for Science and Communication, OLDP, OPQ, CDER, FDA

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 NDSRls Originating from Impurity Amines in APIs**
Martin Ehler, 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

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  
Panelists: Bhagwant Rege, PhD  
Diaa Shakleya, PhD  
Jingyue (Jan) Yang, PhD  
Justin Moser, BS  
Lanyan (Lucy) Fang, PhD  
Marko Trampuž, MPharm, PhD  
Martin Ehert, PhD  
Mrunal A. Jaywant, PhD, PGDMM  
Rok Grahek, PhD  
Sander van Gessel, MScEng  
Zdenko Časar, PhD  

12:30 PM – 1:30 PM  **Lunch Break**

**Session 2: Safety & Risk Assessment of NDSRls for Human Health**
This session will focus on considerations for assessing the safety of NDSRls. The speakers and panelists will discuss current efforts by the FDA and drug manufacturers to assess the potential risk of NDSRls for human health and to predict the activity and potency of NDSRls 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  **Using Structure-Activity Relationships to Inform Setting Acceptable Intakes for Nitrosamine Impurities**
Naomi Kruhlak, PhD  
Scientific Lead, DARS, OCP, OTS, CDER, FDA

2:15 PM – 2:30 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

2:30 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  
Panelists: Robert T. Dorsam, PhD  
Andrew Teasdale, BSc (Hons), PhD  
David Ponting, MA, MSci, PhD  
Naomi Kruhlak, PhD  
Raphael Nudelman, PhD, ERT  
Robert H. Heflich, PhD  
Sruthi King, PhD  

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 NDSRls 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 II 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

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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ANDA</td>
<td>Abbreviated New Drug Application</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>BS</td>
<td>Bachelor of Science</td>
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<tr>
<td>CDER</td>
<td>Center for Drug Evaluation and Research</td>
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<tr>
<td>Co.</td>
<td>Company</td>
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<tr>
<td>CRCG</td>
<td>Center for Research on Complex Generics</td>
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<tr>
<td>DARS</td>
<td>Division of Applied Regulatory Science</td>
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<tr>
<td>DB</td>
<td>Division of Biopharmaceutics</td>
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<tr>
<td>DGMT</td>
<td>Division of Genetic and Molecular Toxicology</td>
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<tr>
<td>DPA</td>
<td>Division of Pharmaceutical Analysis</td>
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<tr>
<td>DPQR</td>
<td>Division of Product Quality Research</td>
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<tr>
<td>DQMM</td>
<td>Division of Quantitative Methods and Modeling</td>
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<tr>
<td>DPTR</td>
<td>Division of Pharmacology and Toxicology</td>
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<tr>
<td>ERT</td>
<td>European Registered Toxicologist</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>Inc.</td>
<td>Incorporated</td>
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<td>Ltd.</td>
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<td>Master of Pharmacy</td>
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<tr>
<td>MSci</td>
<td>Master of Science</td>
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<tr>
<td>NCTR</td>
<td>National Center for Toxicological Research</td>
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<tr>
<td>NDStis</td>
<td>Nitrosamine Drug Substance Related Impurities</td>
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<tr>
<td>OB</td>
<td>Office of Bioequivalence</td>
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<tr>
<td>OCP</td>
<td>Office of Clinical Pharmacology</td>
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<tr>
<td>OGD</td>
<td>Office of Generic Drugs</td>
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<td>Office of Lifecycle Drug Product</td>
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<td>ONDP</td>
<td>Office of New Drug Product</td>
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<tr>
<td>OPPQ</td>
<td>Office of Policy for Pharmaceutical Quality</td>
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<tr>
<td>OPQ</td>
<td>Office of Pharmaceutical Quality</td>
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<tr>
<td>ORS</td>
<td>Office of Research and Standards</td>
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<tr>
<td>OSCE</td>
<td>Office of Safety and Clinical Evaluation</td>
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<tr>
<td>OTR</td>
<td>Office of Testing and Research</td>
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<tr>
<td>PBPK</td>
<td>Physiologically Based Pharmacokinetic</td>
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<tr>
<td>PharmD</td>
<td>Doctor of Pharmacy</td>
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<td>PK</td>
<td>Pharmacokinetic</td>
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<td>R&amp;D</td>
<td>Research and Development</td>
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<tr>
<td>SDC</td>
<td>Sandoz Development Center</td>
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<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
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