FDA/HESI Research Roadmap Planning on Hazard and Risk Assessment of Nitrosamine Impurities in Drugs

May 31 – June 1, 2023

Meeting Agenda
All Times in US Eastern Time

Program

May 31, 2023

Welcome and Opening Remarks

9:00-9:10am Welcome and Logistics: Karen Davis-Bruno, Ph.D., Associate Director Pharmacology & Toxicology, CDER, Food and Drug Administration

9:10-9:30am Opening Speaker: Peter Stein, M.D., Director of Office of New Drugs, CDER, Food and Drug Administration

Workshop Objective: The goal of the workshop is to engage stakeholders with expertise in the assessment of nitrosamines (NA), including Nitrosamine Drug Substance-related Impurities (NDSRI) in order to achieve the following:

- Provide a high-level synthesis of key areas/objectives of current research on NA detection and evaluation;
- Identify short-term (1-2 years) research needs that can address data gaps required to improve nitrosamine (NA) risk assessments;
- Identify mid-term (3-5 years) and long-term (5+ years) research needs to improve nitrosamine (NA) risk assessments;
- Discuss potential opportunities and forums to realize the identified research gaps *(e.g., FDA-initiated Public Private Partnership, existing or new consortial efforts, grants, private sector research efforts, etc.)*
- Develop a NA-research roadmap in support of an uninterrupted drug supply that is also protective of public health.

Note: In-depth technical discussions of data sets or methodologies are out of scope for this workshop. Similarly, regulatory policy discussions are also out of scope.

9:30am Session 1: Hazard Assessment

This session will focus on research studies that have been conducted, are in progress or planned, to characterize the safety hazards of nitrosamine impurities, and, to identify

additional potential data gaps for understanding the hazards of nitrosamines. Speakers will provide a brief overview of current activities from industry, government, and other research organizations. The presentations will set the stage to discuss the current status of research studies and additional research needs.

Topics to be discussed include Ames testing, other in vitro mutation tests, in vivo studies, DNA adduct assessment, and metabolism (in silico, in vitro, in vivo).

Invited Speakers

	Speaker	**Summary of current hazard identification studies (speakers to highlight what is finalized, ongoing, and planned)**
9:35-9:55am	Dr. Robert Heflich, FDA/NCTR	FDA/NCTR activities; Ames optimization effort and in vitro alternatives
9:55-10:15am	Dr. Maik Schuler, Pfizer	Completed, ongoing and projected research for hazard identification) with industry
10:15-10:35am	Dr. Kevin Cross, Leadscope & Dr. Matthias Vogel, BfArM	Mutamind project including Ames, alternative in vitro assays, DNA adducts, and endogenous NA formation
10:35-10:55am	Dr. Andreas Czich, Sanofi	HESI in vitro and in vivo projects

10:55-11:50am **Facilitated discussion with invited participants related to speaker presentations, NA hazard assessment needs and practices.**

11:50am-12:10pm **Break and Grab Lunch**

12:10-1:20pm **BREAKOUT SESSIONS FOR IN ROOM/INVITED ATTENDEES ONLY – <u>NO WEBCAST AVAILABLE</u>. *In Room Participants/Invited Participants to move to breakout sessions. Lunch available.***

Breakout Session 1 - Data Gaps and Research Needs in NA Hazard Characterization. *Breakout groups to identify and prioritize data gaps and future research needs related to hazard characterization of NA.*

WEBCAST RESUMES AT 1:20PM

1:20-2:20pm **Report out from Breakout Groups from *Breakout Session 1 - Data Gaps and Research Needs in NA Hazard Characterization.*** *Groups to share consensus points and highlight key research needs for more extended discussion on Day 2 (e.g., areas where future research may be needed but the nature of the research needs further discussion).*

2:20-2:40pm **BREAK**

2:40pm **Session 2: Risk Assessment**

This session will focus on research being conducted by different organizations to better understand risk assessment of NA impurities, and to identify potential data gaps for further research on risk assessment of NAs.

Speakers will provide a brief overview of current activities from industry, government, and research organizations. The presentations will set the stage to discuss current status of studies and additional research needs.

Topics to be discussed include structure-activity relationships (SAR), in silico / computational models, quantum mechanics, mode of action (MOA) studies to characterize risk, DNA repair mechanisms, in vitro to in vivo extrapolation and dose-response modelling of in vivo mutagenicity studies.

Invited Speakers

	Speaker	**Summarization of current hazard identification studies; Studies to summarize (finalized, ongoing, and planned)**
2:45-3:05pm	Dr. Joel Bercu, Gilead	Methods to support AI development including SAR / computational modeling / Quantum Mechanics / read-across, LTL assessment
3:05-3:25pm	Dr. David Ponting, Lhasa	SAR Development, MOA to help set AIs
3:25-3:45pm	Dr. Naomi Kruhlak, FDA	Potency categorization of NAs based on structural features
3:45-4:05pm	Dr. George Johnson, Swansea University	In vivo dose-response modelling

4:05-5:00pm Facilitated discussion related to speaker presentations, NA risk assessment needs and practices.

5:00pm Adjourn Day 1

June 1, 2023

8:30-10:00am	**BREAKOUT SESSIONS FOR IN ROOM/INVITED ATTENDEES ONLY – <u>NO WEBCAST AVAILABLE</u>.** ***In Room Participants/Invited Participants to move to breakout sessions.***
	Breakout Session 2 - Data Gaps and Research Needs in NA Risk Assessment. *Breakout groups to identify and prioritize data gaps and future research needs related to risk assessment of NA.*

<u>DAY 2 Webcast Begins</u>

10:00-11:00am	**Report-out from Breakout Groups for Session 2 -** ***Data Gaps and Research Needs in NA Risk Assessment.*** *Groups to share consensus points and highlight key research needs for more extended discussion in pm session (e.g., areas where future research may be needed but the nature of the research requires further discussion).*
11:00-11:15am	**Break**
11:15-11:30am	**Review Future Research Areas Identified in Day 1/Day 2 and Review of Goals for Breakout Session 3**
11:30am-1:00pm	***In Room Participants/Invited Participants to be in breakout sessions – <u>NO WEBCAST AVAILABLE</u>.***
	Breakout Session 3 – New initiative Resource and Collaboration. *Breakout groups to discuss all topics identified as Near-term priorities / midterm priorities from Day 1 and 2 and identify which stakeholders might be engaged in providing resources, data, ownership, etc. to help advance these needs.*
1:00-1:45pm	**BREAK FOR LUNCH**

<u>WEBCAST RESUMES</u>

1:45-2:30pm	***Report from Breakout Groups from Session 3 - Identifying possible resources and stakeholders to address near/mid-term priorities.***
2:30-3:30pm	**Synthesis of Workshop Discussions/Outcomes: Towards Building a Research Roadmap**
3:30-3:45pm	**Closing Comments:** Aisar Atrakchi, Ph.D., Pharmacology/Toxicology Supervisor, CDER, Food and Drug Administration
3:45pm	**Adjourn**