AGENDA
FDA Virtual Public Workshop

Nitrosamines as Impurities in Drugs; Health Risk Assessment and Mitigation Workshop

March 29 – 30, 2021

Scope/Objectives:

The objectives of this workshop is to gather scientific information on nitrosamines. A panel of national and international experts is invited to discuss the current thinking on the toxicity and chemistry of nitrosamines and, to deliberate on the most appropriate approaches to the safety assessment when nitrosamine formation and presence in drug products cannot be avoided. In addition, the experts are asked to identify data gaps and / or research needs to address the uncertainties in nitrosamine safety assessment.

Day 1 Agenda

9:00-2:45pm ET

Time	Topic	Speaker(s) and Affiliation
9:00 AM – 9:10 AM	Purpose and Goals of the workshop	Dr. Aisar Atrakchi, FDA
9:10 AM – 9:50 AM	N-Nitroso compounds in the human environment: Lessons and issues	Dr. Gerhard Eisenbrand, University of Kaiserslautern, Germany
9:50 AM – 10:10 AM	Nitrosamine Contamination of Drug Products	Dr. Sruthi King, FDA
10:10 AM – 11:30 AM	**Questions for the Panelists** Exposure and Risk Assessment 1. What are the endogenous levels of nitrosamine formation in humans and rodents? Once formed, what is the	Panelists

	rate/kinetics of elimination? What are the conversion rates in the liver, circulation levels in blood, and, normal variations? If this information is not available, can it be determined experimentally? 2. Can nitrosamines be classified? If yes, what is the basis of their classification? e.g. could they be classified based on: ➢ Carcinogenic potency? ➢ Chemical structure e.g. aliphatic vs. cyclic? ➢ Chemical reactivity? Direct alkylating agents vs. indirect (require metabolism)? Adduct formed e.g. O6- , N7-methylation? ➢ Other ➢ Why would you choose this basis of classification? If classification is not possible, is it feasible to calculate a "single" Acceptable Intake (AI) value for nitrosamines i.e. Class Specific Limit, using the existing carcinogenicity study results of 110+ nitrosamines (irrespective of study quality)?	
11:30 AM – 11:40 AM	**Break**	
11:40 AM – 12:30 PM	3. The carcinogenic potential of nitrosamines is dose and duration dependent; ➢ Is there an in vivo exposure level for nitrosamines that could define low vs high risk for carcinogenicity? Is it appropriate to calculate a NOEL dose for carcinogenicity? What are the	Panelists

	criteria to do so (Ames negative, in vivo mutation assay negative, other)? ➢ Can a less than lifetime (LTL) approach as described in ICH M7 Guidance be used to determine the AI, of a nitrosamine if a drug is indicated for a short duration of use?	
12:30 PM – 1:00 PM	**Lunch**	
1:00 PM – 2:45 PM	4. How would the risk assessment change when multiple nitrosamines are present in a drug product? What are the key variables to consider when conducting such risk assessment? (nonmutagenic carcinogen + mutagenic carcinogen; nonmutagenic carcinogen + weakly mutagenic carcinogen; multiple mutagenic carcinogens, etc.)	Panelists
2:45 PM	Adjourn	FDA

Day 2 Agenda

9:00-2:30pm ET

Time	**Topic**	**Speaker(s) and Affiliation**
9:00 AM – 9:05 AM	Welcome/Introduction to Day 2	Aisar Atrakchi, FDA
9:05 AM – 11:00 AM	Exposure and Risk Assessment 5. Should the regulatory limits for nitrosamines listed for food and water or, amount formed endogenously, be considered in determining AI of nitrosamines in drugs?	Panelists

	Chemistry 6. In the absence of data and based on identified differences in nitrosamine chemistries and reactivities, can read-across for structural similarity to related compounds be used for nitrosamines? What are the key parameters to consider when conducting (Q)SAR assessment for nitrosamines?	
11:00 AM – 11:10 AM	**Break**	
11:10 AM – 12:30 PM	7. Nitrosamines can be formed during manufacturing of the Active Pharmaceutical Ingredient (API), and/or Drug Product (DP). What are possible approaches to consider in order to reduce nitrosamine formation during manufacturing? Can nitrosamines be eliminated completely from API and/or DP?	Panelists
12:30 PM – 1:00 PM	**Lunch**	
1:00 PM – 2:00 PM	Continue Discussions	Panelists
2:00 PM	Questions from Attendees, Summary and Conclusion	FDA
2:30 PM	Adjourn	FDA

Speaker slides and other workshop materials can be found here before and after the meeting (please check for regular updates): https://www.fda.gov/drugs/news-events-human-drugs/nitrosamines-impurities-drugs-health-risk-assessment-and-mitigation-public-workshop-03292021

Meeting Platform Links:

DAY I:

When: Mar 29, 2021 09:00 AM Eastern Time (US and Canada)

Topic: Nitrosamines as impurities in Drugs; Health Risk Assessment and Mitigation Workshop Day 1

Please click the link below to join the webinar:

https://fda.zoomgov.com/j/1607725099?pwd=Y3J3bHRLeWk1ZTh2bTEzWGNKMDFQZz09

Passcode: @8hKiE

Or iPhone one-tap:

US: +16692545252,,1607725099# or +16468287666,,1607725099#

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Webinar ID: 160 772 5099

International numbers available: https://fda.zoomgov.com/u/a5uMqU5hF

DAY II:

When: Mar 30, 2021 09:00 AM Eastern Time (US and Canada)

Topic: Nitrosamines as impurities in Drugs; Health Risk Assessment and Mitigation Workshop Day 2

Please click the link below to join the webinar:

https://fda.zoomgov.com/j/1609885470?pwd=aDNxSU9VK3I6K3BId09PMEF0czk0QT09

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