

Overview of US FDA guidance: “Control of Nitrosamine Impurities in Human Drugs”

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Disclaimer

- The content of this presentation reflects the opinions of the speaker, and does not necessarily represent the official position of CDER, the FDA, or the Federal Government

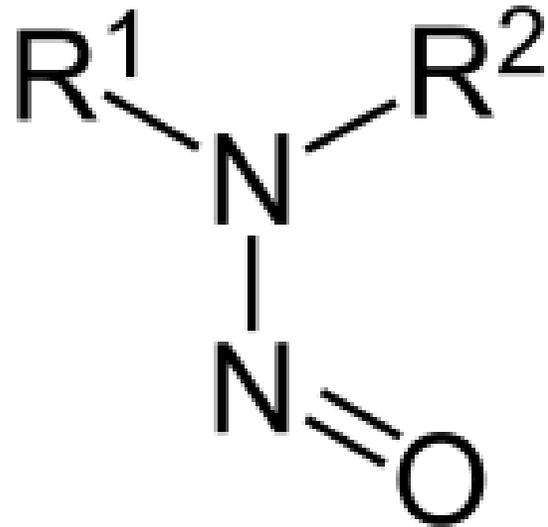
Outline

- The role of the FDA and the genesis of the concern
- The response from FDA
- Future directions

FDA Mission

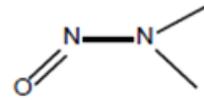
- ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices
- ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation
- helping to speed innovations that make medical products more effective, safer
- helping the public get the accurate, science-based information they need to use medical products

What are Nitrosamines ?

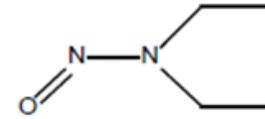


- Nitroso functional group (NO⁺) bonded to an amine
- Five initially identified as being detected in drug substances and drug products
 - NDMA (N-Nitrosodimethylamine)
 - NDEA (N-nitrosodiethylamine)
 - NMBA (N-nitroso-N-methyl-4-aminobutyric acid)
 - NIPEA (N-nitrosoisopropylethyl amine)
 - NMPA (N-nitrosomethylphenylamine)

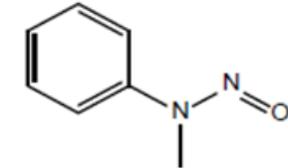
Chemical structures of seven potential nitrosamine impurities in active pharmaceutical ingredients and drug products



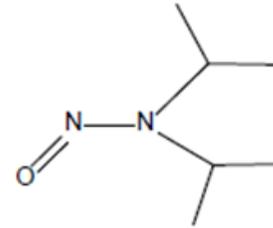
N-Nitrosodimethylamine (NDMA)



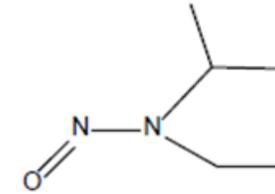
N-Nitrosodiethylamine (NDEA)



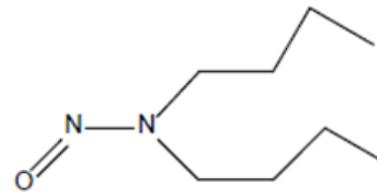
N-Nitrosomethylphenylamine (NMPA)



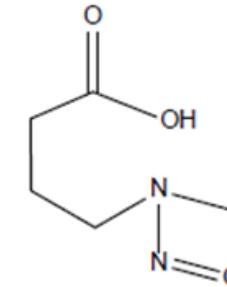
N-Nitrosodiisopropylamine (NDIPA)



N-Nitrosoisopropylethylamine (NIPEA)



N-Nitrosodibutylamine (NDBA)



N-Nitroso-N-methyl-4-aminobutyric Acid (NMBA)

Single Dose Carcinogens

Histochemical Profile of Mouse Hepatocellular Adenomas and Carcinomas by a Single dose of Diethylnitrosamine. Hacker, H.J., et al. (1991) *Cancer Research* 51:1952–1958

Association between Intake of NDMA and Subsequent Occurrence of Colorectal Cancer*

- Occurrence of colorectal cancer was associated with:
 - Intake of NDMA relative risk (RR = 2.12)
 - Intake of smoked and salted fish (RR = 2.58)
 - Intake of cured meat (RR = 1.84)
- *Knekt, P et al. (1999) Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study. *Int. J. Cancer*. 80(6):852–6

First Signs

- 13 July 2018 Press Release
- European Medicines Agency reviewed medicines containing valsartan following detection of N-nitrosodimethylamine, in medicines from Zhejiang Huahai Pharmaceutical Co Ltd, Linhai, China
- Recalls of valsartan products in dozens of European countries, Hong Kong, Pakistan, Canada, US

Chronology

- July 2018: FDA Office of Generic drugs notified of NDMA in valsartan
 - September/October 2018: Losartan and irbesartan recalled due to NDEA
 - February 2019: NMBA detected in losartan
 - Sept 2019: Ranitidine recalled due to NDMA
 - Dec 2019: NDMA reported in metformin
 - Jan 2020: Nizatidine recalled due to NDMA
 - April 2020: FDA requests the recall of all Ranitidine products
 - June 2020: Metformin extended-release product recalled due to NDMA
 - August 2020: Rifampin reported to contain MNP* and Rifapentine, CPNP**
 - July 2021: CHANTIX[®] (Varenicline) tablets recalled due to N-Nitroso varenicline
- *1-methyl-4-nitrosopiperazine ** 1-cyclopentyl-4-nitrosopiperazine

FDA Response

- Established FDA Nitrosamine Task Force
- Developed and published testing methods for regulators and industry
- FDA Virtual Public Workshop. Nitrosamines as Impurities in Drugs; Health Risk Assessment and Mitigation. March 29–30, 2021
- Published Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs, September 2020
- Regular Meetings with other US government agencies, other stakeholders and International Regulators
- Mitigation, Regulatory Discretion and Recalls as needed

CDER Nitrosamine Task Force

- FDA Experts advance and evaluate strategies to mitigate risk while maintaining drug supply
- Meet regularly with international regulators to facilitate a harmonized approach
- Office of the Center Director-Drug Shortage Staff
- Office of Pharmaceutical Quality
- Office of Compliance
- Office of Generic Drugs
- Office of New Drugs
- Office of Communications
- Office of Surveillance and Epidemiology
- Office of Executive Operations

Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs

- Potential sources of nitrosamine impurities in active pharmaceutical ingredient (API)
- Potential sources of nitrosamine impurities in drug products
- Recommendations to API manufacturers
- Recommendations to drug product manufacturers
- Recommended timelines for risk assessment, testing and reporting

Guidance: Recommendations

- Assess the risk of nitrosamine impurities in APIs, marketed products, and products under approved and pending applications
- Manufacturers do not need to submit risk assessment documents to the Agency, but they should retain these documents so that they are available if requested
- Conduct confirmatory testing when there is any risk for the presence of nitrosamine impurities
- Report changes implemented to prevent or reduce nitrosamine impurities in APIs and drug products to FDA

Sources of Nitrosamine Impurities

- Under acidic reaction conditions, nitrite salts may form nitrous acid, which can react with secondary, tertiary, or quaternary amines to form a nitrosamine
- The API, degradants, intermediates, or starting materials may contain secondary or tertiary amine functional groups. Tertiary and quaternary amines may also be added intentionally as reagents or catalysts
- Recovered solvents, reagents, and catalysts may contain residual amines (such as trimethylamine or diisopropylethylamine). If the recovery process involves a quenching step (i.e., nitrous acid used to decompose residual azide), nitrosamines could form during solvent recovery

Recommendations: API Manufacturers

- Optimize the manufacturing process to minimize or prevent the formation of nitrosamine impurities
- Consider removing quenching steps to avoid nitrosamine formation
- Audit supply chains and monitor for at-risk raw materials, starting materials, and intermediates
- Avoid cross-contamination of solvents, reagents, and catalysts
- Reprocess or rework API batches to control the level of nitrosamine impurities as provided in ICH Q7 (Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Sept. 2016, rev. 1) for amending and controlling such operations
- Develop a strategy to ensure that the nitrosamine level remains within the AI limit

Recommendations: Drug Product Manufacturers

- Conduct risk assessments to determine the potential for nitrosamine impurities in drug products
- Test representative samples of all incoming components, including lots of at-risk API, prior to use, as required under 21 CFR 211.84
- Evaluate whether nitrites could be present during manufacturing processes where at-risk APIs are used
- Evaluate whether nitrosamines could form in a finished drug product over the drug product's shelf life

FDA Guidance: Timelines

- Approved drugs
 - Manufacturers should conclude a risk assessment of approved or marketed products within seven months of publication of the original guidance, with a recommended completion date of on or before March 31, 2021
- Pre-NDA
 - Applicants should conduct a risk assessment for nitrosamine impurities in APIs and proposed drug products and conduct confirmatory testing as needed prior to submission of an original application
- Pending applications
 - Applicants with pending applications should conduct the risk assessment expeditiously and inform FDA if confirmatory testing finds nitrosamine levels above the AI limit and amend the application as appropriate

Risk Assessment: Acceptable Intake

- The AI limit is a daily exposure to a compound that approximates a 1:100,000 cancer risk after 70 years of exposure
- The term *acceptable intake* (AI) is used in ICH M7(R1) to indicate the maximum limit for the impurity to be associated with negligible risk of carcinogenicity or other toxic effects
- FDA recommends the following acceptable intake limits for the nitrosamine impurities NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA. We further recommend that manufacturers use these AIs when determining limits for nitrosamine impurities in APIs and drug products

Acceptable intake limits

NDMA (N-Nitrosodimethylamine),

NDEA (N-Nitrosodiethylamine),

NMBA (N-Nitroso-N-methyl-4-aminobutyric Acid),

NMPA (N-Nitrosomethylphenylamine),

NIPEA (N-Nitrosoisopropylethylamine),

NDIPA (N-Nitrosodiisopropylamine)

Nitrosamine

AI limit
(ng/day)

NDMA

96

NDEA

26.5

NMBA

96

NMPA

26.5

NIPEA

26.5

NDIPA

26.5

Determining Compound-Specific Acceptable Intake Limits-NDMA

- NDMA TD₅₀ values: 0.0959 mg/kg/day (rat) and 0.189 mg/kg/day (mouse).
- For the AI calculation, the lower, more conservative value for the rat is used

- $$\frac{\text{TD}_{50}}{50,000} \times 50 \text{ kg bodyweight} \quad \text{or} \quad \frac{0.096 \text{ mg/kg/day}}{50,000} \times 50 \text{ kg bodyweight} = \underline{96 \text{ ng/day}}$$

- A daily lifelong intake of 96 ng/day NDMA corresponds to a theoretical cancer risk of 10⁻⁵ and therefore represents an AI when present as an impurity

See Appendix B of Nitrosamines guidance

Use of surrogates-

ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk

- 2018: FDA became aware of rifampin containing 1-methyl-4-nitrosopiperazine (MNP) and rifapentine containing 1-cyclopentyl-4-nitrosopiperazine (CPNP) above the acceptable limits
- TD_{50} values available for MNP and CPNP not considered reliable
- Per ICH *M7(R1)*, a surrogate compound with carcinogenicity data may be used to derive an acceptable intake if scientifically justified
- Another structurally related compound N-Nitrosodimethylamine (NDMA, AI 96 ng/day) was used as a surrogate to estimate the AI for both MNP and CPNP

AI for CPNP in Rifapentine (ppm)

- Applying the AI for the surrogate NDMA of 96 ng/day, the task force considered the lifetime (70 years) AI for CPNP to be 96 ng/day
- To determine the acceptable intake in ppm, a maximum dose of 900 mg/day was used in the following calculation
- $$\text{AI (ppm)} = \frac{\text{microgram/day}}{\text{Maximum dose (g/day)}} \quad \text{or} \quad \frac{0.096 \text{ microgram/day}}{0.9 \text{ g}} = 0.1 \text{ ppm}$$

Nitrosamine Impurities in Rifampin and Rifapentine

- Nitrosamine levels exceeded AI for Rifampin and rifapentine, but both are used to treat tuberculosis
- 1.4 million deaths from TB in 2019 and 10 million people sickened
- Given the vital importance of this drug and the potential consequences of not treating TB, patients were advised to continue taking their current medicine and consult with their health care professional about any concerns
- Calculated an Interim AI is a short-term strategy to maintain patient access while process changes are instituted to remove or reduce nitrosamine formation
- Offer flexibility when patient access to medically necessary drugs may be affected if all product is recalled

FDA Response: Rifampin and Rifapentine

- Regulatory Discretion
- To help avoid shortages and -ensure access to these medicines, FDA does not intend to object to certain manufacturers temporarily distributing rifampin containing MNP below five parts per million (ppm) or rifapentine containing CPNP below 20 ppm until they can reduce or eliminate the impurities
- Manufacturers should contact the Center for Drug Evaluation and Research's Drug Shortages Staff when their testing of rifampin or rifapentine shows levels of nitrosamines that exceed the acceptable intake limits of 0.16 ppm for MNP and 0.1 ppm for CPNP. FDA will determine on a case-by-case basis whether those drugs should be released for distribution
- FDA will permit exposures above lifetime AI on a case-by case basis to maintain patient access to medically necessary drugs. FDA physicians and scientists make these case-by case decisions based on the severity of disease, the potential impact of a drug shortage for the medication, and discussions with a manufacturer as to their ability to reduce or eliminate these impurities.

Multiple Nitrosamine Impurities

- Above limits are applicable if a drug product contains a single nitrosamine
- If more than one of the nitrosamine impurities is detected and the total quantity of nitrosamine impurities exceeds 26.5 ng/day (the AI for the most potent nitrosamines) based on the maximum daily dose (MDD), the manufacturer should contact the Agency for evaluation

Does the Duration of Dosing Matter ?

Histochemical Profile of Mouse Hepatocellular Adenomas and Carcinomas by a Single dose of Diethylnitrosamine. Hacker, H.J., et al. (1991) *Cancer Research* 51:1952–1958

Risk from Less-than-Lifetime Exposure

The Agency is not currently considering an AI based on a less- than-lifetime (LTL) duration for the following reasons:

- Nitrosamines are listed in the cohort of concern (CoC) in ICH Guidance M7(R1) as a group of highly potent mutagenic carcinogens, classified as probable human carcinogens
- Several nitrosamines cause tumors in animal models at relatively low doses and after short dosing durations, including single doses
- The LTL approach could result in high acute nitrosamine intake, particularly for medicines administered in high doses for short durations.
- There is uncertainty about how the cancer risk of CoC carcinogens change with shorter duration of exposure i.e., unclear dose response at low exposure

Testing Method to Detect Nitrosamine Impurities in Rifampin and Rifapentine

- The link below is to an FDA-published testing method to provide an option for regulators and industry to detect nitrosamine impurities in rifampin and rifapentine drug substances and drug products
- Method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission
- LC-ESI-HRMS method: an LC-MS method for the detection of MNP in rifampin and CPNP in rifapentine drug substance and drug products
- LC-ESI-HRMS method

International Regulatory Agencies

- Imposing similar measures to regulate the distribution of nitrosamine-contaminated drugs
- Meet regularly with FDA to discuss and share scientific ideas for solutions
- Maintain confidentiality of information where appropriate

Publications



- King, F.J. et al. (2020) Ranitidine-Investigations into the Root Cause for the Presence of N-Nitroso-N,N-dimethylamine in Ranitidine Hydrochloride Drug Substances and Associated Drug Products. *Org. Process Res. Dev.* 2020, 24, 2915–2926
- Kim, S. et al. (2021) Effect of Ranitidine Intake on the Risk of Gastric Cancer Development. *Healthcare* 9, 1071
- Yokoo H, et al. (2021) N-Nitrosodimethylamine (NDMA) Formation from Ranitidine Impurities: Possible Root Causes of the Presence of NDMA in Ranitidine Hydrochloride. *Chem Pharm Bull (Tokyo)*. 69(9):872–876.
- Bodiwala KB, et al. (2021) Simultaneous Estimation of Six Nitrosamine Impurities in Valsartan Using Liquid Chromatographic Method. *J AOAC Int*. Epub ahead of print. PMID: 34338773
- Gomm W, (2021) N-Nitrosodimethylamine [NDMA]-Contaminated Valsartan and the Risk of Cancer. *Dtsch Arztebl Int*. 118(21):357–362.

The Work Continues

- Improving drug manufacturing and quality control technologies
- Sharing scientific approaches to the reduction/elimination of nitrosamines with drug manufacturers
- Understanding of the relative potencies of individual nitrosamines
- Better understanding of the relative importance other sources of nitrosamines such as endogenous formation, food or water

The Work Continues

- More harmonized approaches for structural/reactivity assessment
- Developing an optimized Ames assay for nitrosamines
- Role of follow-up *in vivo* mutagenicity testing
- Appropriate limits for non-mutagenic nitrosamines given remaining concern for carcinogenic potential
- Nitrosamine drug substance-related impurities

Acknowledgements

- Hanan Ghantous
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- FDA encourages all interested parties to discuss adverse reactions or quality problems with any human drugs with the review division and/or the agency's MedWatch Adverse Event Reporting Program
- Thank you
- Questions?



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