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Nitrosamine Impurities in Human Pharmaceuticals

Responding to a Global Risk Issue through Effective Risk Mitigation and Regulatory Cooperation

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IGBA Annual Meeting
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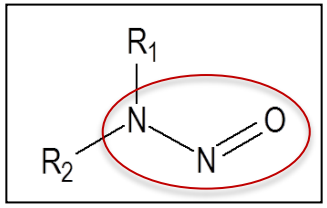
YOUR HEALTH AND SAFETY... OUR PRIORITY.

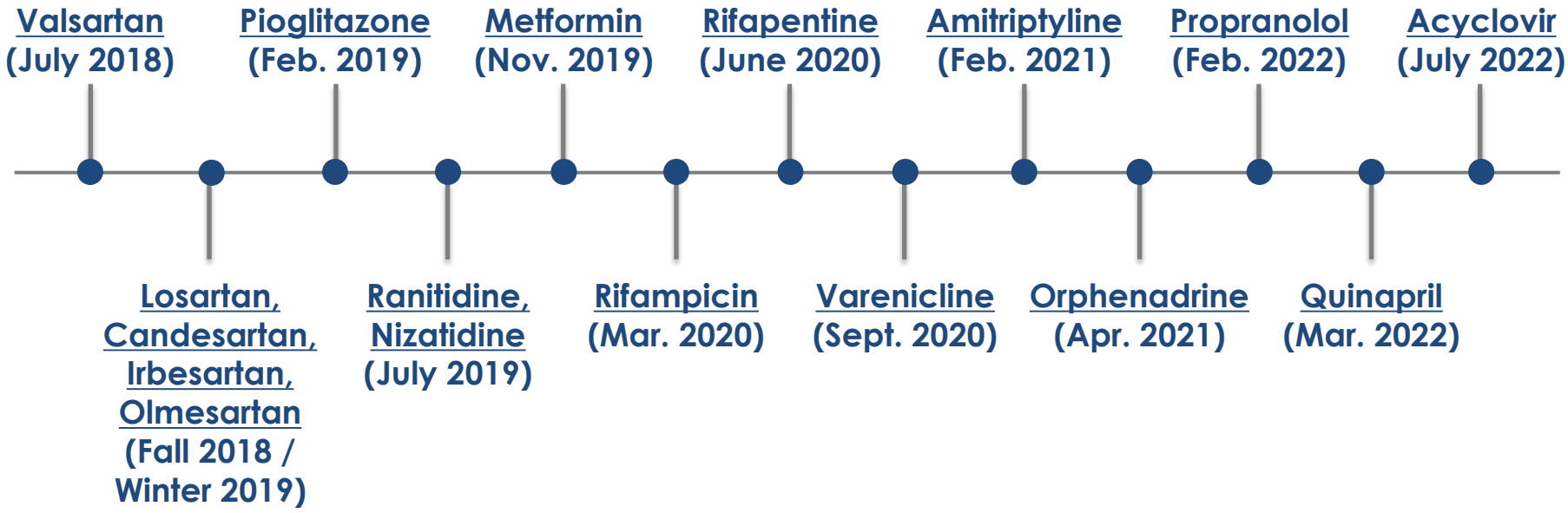
N-Nitrosamines



e.g.,
NDMA: $R_1=R_2=CH_3$
NDEA: $R_1=R_2=CH_2CH_3$

- *N*-Nitrosamines (commonly called nitrosamines) are a class of chemical compounds which are:
  - Structurally characterized by a nitroso (NO) functional group covalently bonded to the nitrogen atom of an amine;
  - Probable human carcinogens based on known carcinogenic effects observed in animals (animal data for 228 low molecular weight nitrosamines reveals that 82% are considered in-vivo carcinogens)
  - Clearly identified in ICH's M7 Mutagenic Impurities guideline as part of the "cohort of concern", a group of highly potent mutagenic carcinogens)
- Commonly, *N*-nitrosamines are formed by reaction of **amines** with a **nitrosating agent** under **appropriate conditions** (e.g., temperature, pH, concentration, catalyst)

Examples of Affected APIs/Drug Products
(with dates of regulatory actions or communications in Canada)



Why is contamination of pharmaceuticals with nitrosamines an on-going issue?

The potential for the formation of nitrosamine impurities was **generally not recognized by regulators and industry until mid 2018.**

Assessment and analysis for nitrosamines requires **specially trained staff** and **specific/highly sensitive test methods** not used for typical impurity testing (capable of detection at ppm and sometimes ppb levels).

Investigations by industry and regulators for nitrosamines continue to identify new nitrosamines, where some are API-related nitrosamines, called **nitrosamine drug substance related impurities (NDSRIs).**

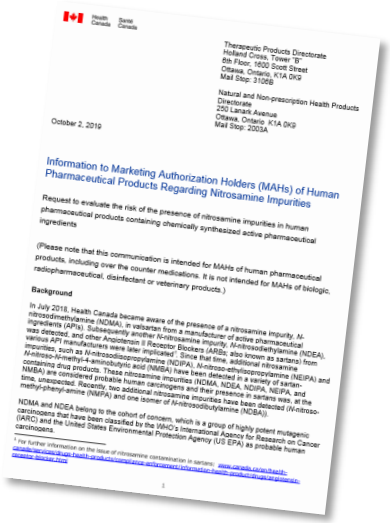
Scientific understanding continues to evolve on these complex issues (e.g., safety information may not be available to establish qualified limits).

Responding to Challenges and Experiences
(heard from applicants/MAHs, external stakeholders, internally)

- **Considerable investment in time/resources**, some sponsors have large portfolios;
- **Capacity issues** internally or third-party availability (e.g., CROs/CMOs, labs);
- Development of **highly sensitive methods** (and procurement of **reference standards**);
- **Availability of proprietary information** from suppliers (e.g., API manufacturers);
- Challenges conducting **robust risk assessments** and determining **risk factors**;
- Identification of which nitrosamines to assess and **establishing Acceptable Intake limits**;
- An **evolving issue with knowledge gaps**, a better understanding is required;
- Continued benefits for **international coordination and alignment**.

Request to All Marketing Authorization Holders (MAHs) for Risk Evaluations ("Call for Review")

- Aligned with EMA's approach, HC issued a **Call for Review in October 2019** to all MAHs:
  - human prescription and non-prescription medications
  - initially, drug products containing chemically-synthesized APIs (later expanded in Dec. 2020 to biologicals and radiopharmaceuticals)
- Similar requests have subsequently been issued by other regulators (e.g., US FDA, Japan's MHLW/PMDA)
- The Call for Review is a **three-step approach** for MAHs to evaluate and address the presence of nitrosamines:



Therapeutic Products Directorate
Holland Cross, Tower "B"
6th Floor, 1600 Scott Street
Ottawa, Ontario, K1A 0K9
Mail Stop: 3109B

Natural and Non-prescription Health Products Directorate
250 Lamarr Avenue
Ottawa, Ontario K1A 0K9
Mail Stop: 2003A

October 2, 2019

Information to Marketing Authorization Holders (MAHs) of Human Pharmaceutical Products Regarding Nitrosamine Impurities

Request to evaluate the risk of the presence of nitrosamine impurities in human pharmaceutical products containing chemically synthesized active pharmaceutical ingredients

(Please note that this communication is intended for MAHs of human pharmaceutical products, including over the counter medications. It is not intended for MAHs of biologic, radiopharmaceutical, disinfectant or veterinary products.)

Background

In July 2018, Health Canada became aware of the presence of a nitrosamine impurity, N-nitrosodimethylamine (NDMA), in valsartan from a manufacturer of active pharmaceutical ingredients (APIs). Subsequently another N-nitrosamine impurity, N-nitrosodiethylamine (NDEA), was detected, and other Angiotensin II Receptor Blockers (ARBs; also known as sartans) from various API manufacturers were later implicated[1]. Since that time, additional nitrosamine impurities, such as N-nitrosodiisopropylamine (NDIPA), N-nitroso-ethylisopropylamine (NEIPA) and N-nitroso-4-methyl-4-aminobutyric acid (NMBA) have been detected in a variety of sartan-containing drug products. These nitrosamine impurities (NDMA, NDEA, NDIPA, NEIPA, and NMBA) are considered probable human carcinogens and their presence in sartans was, at the time, unexpected. Recently, two additional nitrosamine impurities have been detected (N-nitroso-methyl-phenyl-amine (NMPA) and one isomer of N-nitrosodibutylamine (NDBA)).

NDMA and NDEA belong to the cohort of concern, which is a group of highly potent mutagenic carcinogens that have been classified by the WHO's International Agency for Research on Cancer (IARC) and the United States Environmental Protection Agency (US EPA) as probable human carcinogens.

[1] For further information on the issue of nitrosamine contamination in sartans: www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-products/drugs-pharmaceutical-products.html

Step	Action	HC's Deadline for Pharmaceuticals (chemical entities)	HC's Deadline for Biologicals and Radiopharmls.
Step 1	Conduct **RISK ASSESSMENTS** for the possible presence of nitrosamines	by Mar. 31, 2021	by Nov. 30, 2021
Step 2	In the event a risk is identified, conduct **CONFIRMATORY TESTING** using validated and sensitive methods	by Oct. 1, 2022	by Nov. 30, 2023
Step 3	Implement **CHANGES TO THE MARKET AUTHORIZATION** (e.g., control strategy, manufacturing procedures, formulation, testing specifications)	by Oct. 1, 2023	by Nov. 30, 2023

Request to All Marketing Authorization Holders (MAHs) for Risk Evaluations ("Call for Review")

- Provided HC's initial recommendations in 2019 for performing risk assessments for the presence of nitrosamines in drug products and components
  - Included recommendations to consider nitrosamine formation due to the presence of secondary and tertiary amines within the structures of APIs, API intermediates, synthetic impurities, and degradants (nitrosamines later collectively referred to as NDSRIs)
  - Included recommendations to consider nitrosamine formation during drug product manufacturing and packaging when APIs and excipients containing nitrite are present together, especially in solutions, suspensions, or at elevated temperatures

➢ **Recognition of the wide scope of drug products that were potentially implicated**

Key Communications

- **HC's Guidance on Nitrosamine Impurities in Medications:**
  - Initially published as a **Q&A document** in November 2019, several updates with the most recent being Sept. 2022
  - ***Safety:*** established AI limits for 21 nitrosamines (including those for NDSRIs), options where multiple nitrosamines are detected
  - ***Quality:*** risk factors and root causes, considerations for analytical methodologies and specifications, control strategy options
  - https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities/medications-guidance.html

- **HC Stakeholder Events and Meetings** - Nitrosamines in Pharmaceuticals:
  - Webinars (Jan. 2020, Feb. 2021, Oct. 2021)
  - Conferences (e.g., DIA, PSG, IGBA)
  - Many meetings with Industry Associations (e.g., IMC, CGPA, GPIM, self-care product associations) and applicants

- **HC webpage** for Nitrosamines:
  - Communicating information on context, test methodologies, affected drug products, guidance document
  - https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities.html

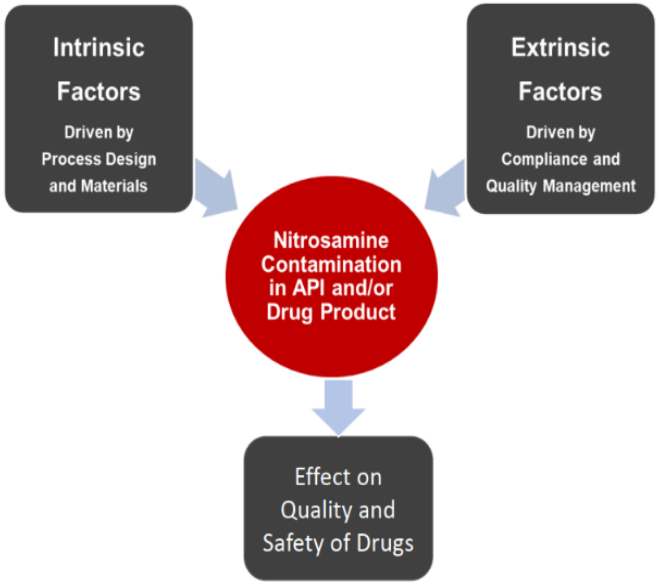
Guidance for New Applications (NDSs, ANDSs, and Supplements)

- As of April 1, 2021, applicants of NDSs (brand products), ANDSs (generic products), and Supplements (PACs) are expected to include a summary of the risk assessment for nitrosamines in the drug application
  - Similar step-wise approach and principles should be applied as for marketed products
  - The summary of the risk assessment is expected to include sufficient detail to allow Health Canada to assess the adequacy and robustness of the assessment (e.g., including the risk factors considered specific to the manufacturing processes and conditions for the API and drug product as well as other potential risk factors).
  - Risks for the potential presence of nitrosamines continue to be inadequately addressed and deficient risk assessments continue to be observed leading to a significant number of major deficiencies in drug applications

- Risk Assessments
- Risk Factors/Root Causes
- Risk Mitigation

Risk Assessments (RAs) – Gaps Observed

- The approach being taken for the RA is unstated or unclear (e.g., delegation of RA activities to third parties) … applicants/MAHs are responsible for ensuring that personnel involved have acceptable expertise, training, knowledge
- "Checklist style" summary of RA:
  - missing discussion on the rationale, scientific basis, or justification for the overall risk determination
- A "silo approach" to the RA:
  - e.g., absence of a holistic approach is observed with separate, unlinked drug substance and drug product RAs
- The RA is not robust, e.g., potential risk factors which have been noted by regulators or in literature are not adequately addressed



Risk Assessments (RAs) – Gaps Observed

- Data/scientific justification to support the conclusions of the RA is missing (e.g., purge factors, solubility data, nitrite content in excipients)
- Confirmatory testing results were not provided when applicable
- Proposed Acceptable Intake limits were not satisfactorily qualified
- Tertiary amines, API related compounds are not adequately addressed as risk factors
- The potential for increases in nitrosamine levels over the retest period or shelf-life is not considered in the assessment

Some Commonly Observed Potential Risk Factors and Root Causes

- Nitrosation of an amine present in the structure of an API, starting material, intermediate, reagent, or degradant during drug substance or drug product manufacturing, and during storage
- Presence of nitrosating agent precursors, such as nitrite found in water, excipients, and reagents
- Oxidation of a hydrazine functional group present in an API, starting material, intermediate, reagent or degradant
- Certain manufacturing operations that may:
  - facilitate contact between nitrosamine precursors (e.g., wet granulation steps), particularly if the process step occurs in an optimal pH range
  - introduce nitrosating agents/precursors (e.g., nitrogen oxides during fluid bed drying)
  - impart energy into solid state drug matrices (e.g., roller compaction)
- Presence of nitrocellulose in packaging components

Risk Mitigation

- Products and processes should be designed at the outset to avoid the formation or introduction of nitrosamine impurities as much as possible, based upon:
  - A thorough understanding of the chemistry, risk factors, and root causes associated with nitrosamine impurity presence in APIs and drug products
  - An effective Pharmaceutical Quality System (PQS)[1]
    - Effective PQS governance includes aspects relevant to the control of nitrosamine impurities consistent with compliance and GMPs, including but not limited to: acceptability of quality attributes of drug products and their components; continuing acceptability of supply chain partners over the product lifecycle; oversight of outsourced activities such as the recovery and reuse of process materials; training of personnel appropriate to their responsibilities.

[1] International-Council-for-Harmonisation-of-Technical-Requirements-for-Pharmaceuticals-for-Human-Use ICH Harmonised Tripartate Guideline: Pharmaceutical Quality System Q10. https://database.ich.org/sites/default/files/Q10%20Guideline.pdf

Risk Mitigation

- It is understood that remediation of approved/marketed products is a significant undertaking
- Important to first gain a scientific understanding for nitrosamine presence from root cause investigations which can facilitate CAPAs and justified control strategies
    - Such investigations may include:
        - Impurity identification, characterization and physicochemical property evaluation
        - Sampling and analytical testing of drug product components
        - Stability / forced degradation / excipient compatibility studies
        - Impurity fate and purge studies
- Due to multiple risk factors and root causes potentially being applicable, several strategies and tactics could be leveraged to mitigate nitrosamine risks to patients

Potential Risk Mitigation Approaches - Drug Substances

- Sequencing synthetic steps to minimize carry-over of nitrosamine precursors across steps and convergence (e.g., amines with nitrosating agents, hydrazines with oxidants)
- Positioning any unavoidable nitrosation chemistry well upstream of the drug substance
- Employing an inorganic base or a primary amine as a base, instead of secondary and tertiary amines, where possible
- Avoiding the use of reagents/solvents which are known to contain, or that may generate, secondary/tertiary amines, where possible
- Modification of relevant process parameters (pH, temperature, concentration, addition rates, processing times)

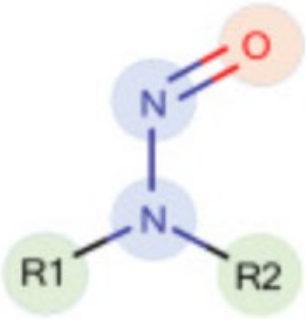
Potential Risk Mitigation Approaches - Drug Products

- Judicious selection of excipients and excipient suppliers[2]
- Well designed stability / forced degradation / excipient compatibility studies
- Control pH ranges of drug formulations to avoid nitrosating conditions
- Suppression of nitrosamine formation when nitrosating conditions are unavoidable (e.g., incorporation of antioxidants into formulations[3])
- Avoidance of certain manufacturing operations that could facilitate contact between nitrosamine precursors (e.g., wet granulation steps) or introduce nitrosating agents (e.g., nitrogen oxides during fluid bed drying), where possible

[2] Boetzel R, Schlingemann J, Hickert S, Korn C, Kocks G, Luck B, Blom G, Harrison M, François M, Allain L, Wu Y, Bousraf Y. A Nitrite Excipient Database: A Useful Tool to Support N-Nitrosamine Risk Assessments for Drug Products. *J Pharm Sci* 2022, in press.

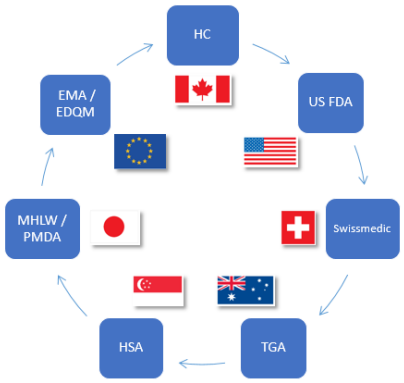
[3] Nanda KK, Tignor S, Clancy J, Marota MJ, Allain LR, D'Addio SM. Inhibition of N-Nitrosamine Formation in Drug Products: A Model Study. *J of Pharm Sci* 2021; 110(12): 3773-3775.

- International Regulatory Cooperation on Nitrosamines



Working Actively with International Regulatory Partners on Nitrosamines

- ***Nitrosamines International Strategic Group (NISG)*** and ***Nitrosamines International Technical Working Group (NITWG)***:
  - Both Chaired by Health Canada
  - Initially, regulatory partners from US FDA, Europe's EMA and EDQM, Japan's MHLW/PMDA, Health Canada, Switzerland's Swissmedic, Singapore's HSA, and Australia's TGA
  - Expanded in 2021 to include the WHO and Brazil's ANVISA
  - Sharing of information on technical issues (e.g., root causes/risk factors, testing results, regulatory actions, communications, establishing Acceptable Intakes)
- Interactions/collaborations:
  - Regular meetings (teleconference calls)
  - Within the NITWG:
    - Safety and Quality sub-groups



NITWG Quality

- ***Regulatory Experiences with Root Causes and Risk Factors for Nitrosamine Impurities in Pharmaceuticals***

  (available online 1 January 2023)

  – Background / Chemistry of Nitrosamines
  – Collation of key guidances and communications from the regulators of the NISG/NITWG
  – Root Causes and Risk Factors:
    - API, DP, other sources
  – Sources of Nitrosatable Amines and Nitrosating Agents
  – Control Strategies and Risk Mitigation Strategies
  – References

- Horne S, Vera M, Nagavelli L, Sayeed V, Heckman L, Johnson D, Berger D, Yip YY, Krahn C, Sizukusa L, Rocha N, Bream R, Ludwig J, Keire D, Condran G.
- *J Pharm Sci*, 2023, in press. https://doi.org/10.1016/j.xphs.2022.12.022

NITWG Safety

- Approaches for establishing Acceptable Intakes (AIs)
  - e.g., use of read-across
- Work towards alignment on established AIs
  - once finalized, AIs will be added to HC's guidance document on nitrosamines
- Interactions with Health and Environmental Sciences Institute (HESI)
  - a HESI sub-team looking at developing recommendations for study protocols for an optimized Ames assay to assess the potential mutagenicity of nitrosamines

Regulatory Strategies

Thinking globally, acting locally

Internal Collaboration and Capacity Building:
- Inter-and intra-Branch
- Case Management
- In-House training

Regulatory Actions:
- Terms and Conditions
- Stop sales
- Product recalls

Regulatory Tools:
- Guidance documents
- Questions and Answers
- Requests for Risk Assmnts.

Communications:
- Public
- Healthcare Professionals
- Patient Groups

Stakeholder Engagement:
- Industry
- Interested parties
- Webinars/workshops

International Regulatory Cooperation:
- Safety, Quality, Multi-disciplinary topics

Before being authorized for sale in Canada, Health Canada verifies that therapeutic products meet the safety, efficacy and quality requirements of the Food and Drugs Act and its Regulations.

Marketing Authorization Holders (MAHs) are responsible for ensuring the ongoing safety, efficacy and quality of marketed pharmaceuticals in Canada.

Acknowledgements…

Stephen Horne (Quality SME),
Alisa Vespa (Safety SME),
HC's Nitrosamines Case Management Team and the Review and Compliance Communities within HC

Enquiries relating to Nitrosamines:

bpsenquiries@hc-sc.gc.ca (for pharmaceuticals)
brdd.nitrosamines.dmbr@hc-sc.gc.ca (for biologicals and radiopharmaceuticals)

HC webpage for Nitrosamines:

https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities.html