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Health Canada Stakeholder Information Webinar

Nitrosamines in Pharmaceuticals

31 January 2020

Ottawa, ON, Canada

YOUR HEALTH AND SAFETY... OUR PRIORITY.

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Nitrosamines in Pharmaceuticals

Opening and Introductory Remarks

Linsey Hollett,
A/Director General,
Health Product Compliance,
Regulatory, Operations and Enforcement Branch (ROEB)

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AGENDA

- Nitrosamine Impurities - Context and Experience to Date
- Health Canada's Question and Answer (Q&A) document
- Industry Associations Experience and Feedback
- *Health Break*
- Question Period
- Closing Remarks

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Nitrosamines in Pharmaceuticals

Context and Experience to Date

Gary Condran
Manager,
Bureau of Pharmaceutical Sciences,
Therapeutic Products Directorate,
Health Products and Food Branch (HPFB)

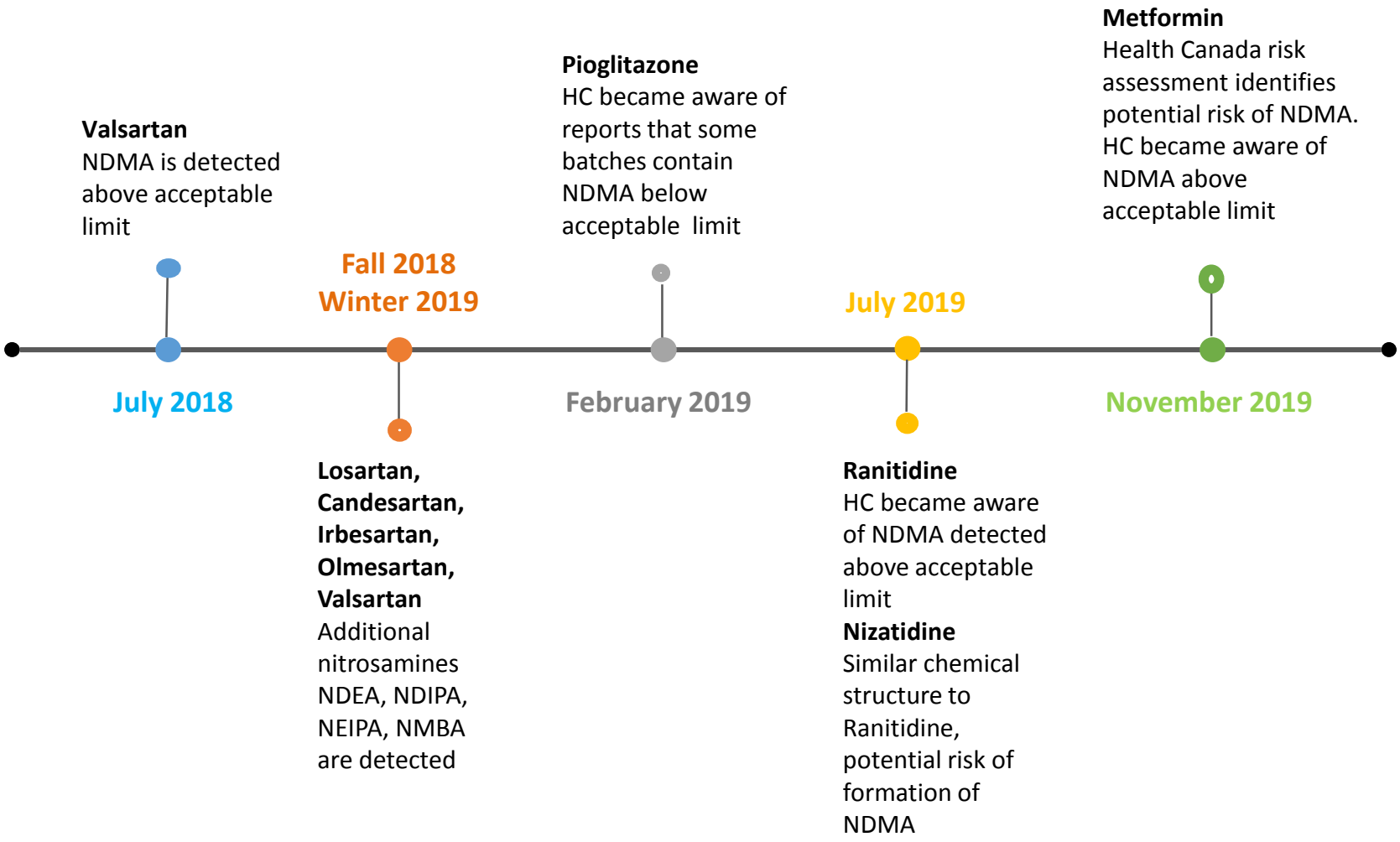
Background

- Summer 2018:
  - Several **Valsartan** products were recalled in Canada and worldwide due to the presence of the nitrosamine impurity, **N-nitrosodimethylamine (NDMA)**, found in the active pharmaceutical ingredient.

- Fall 2018/Winter 2019:
  - Additional nitrosamine impurities were found in Valsartan and four other Angiotensin Receptor Blockers (ARBs or “Sartans”), **Candesartan, Irbesartan, Losartan, and Olmesartan**, including:
    - N-nitrosodiethylamine (NDEA)
    - N-nitrosodiisopropylamine (NDIPA)
    - N-nitroso-ethylisopropylamine (NEIPA) and
    - N-nitrosomethyl-n-butylamine (NMBA)

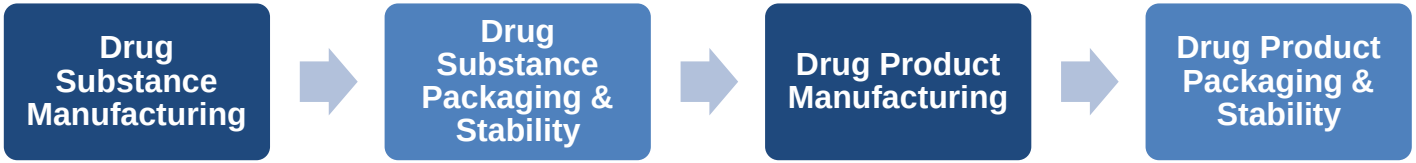
- Regulatory actions taken to date have included import restrictions, stop sale/distribution, product recalls, regulatory letters, and public communications.

Timeline of Products Impacted to Date



Potential Root Causes of Nitrosamine Contamination

- The formation of nitrosamine impurities is potential across several points in the manufacturing process and production chain:



- Some of the challenges:
  - Detection of nitrosamines is challenging for both regulators and industry given the multiple potential root causes, the expanding scope of impacted products and the need to develop highly sensitive detection methods.
  - Nitrosamine impurities which may form during drug product manufacturing have fewer opportunities to be purged than those within drug substance manufacturing processes.
  - Use of third party facilities for some activities.

Why is this an issue now?

The potential for formation of nitrosamine impurities at such low levels during manufacturing processes was not recognized by regulators and industry until recently

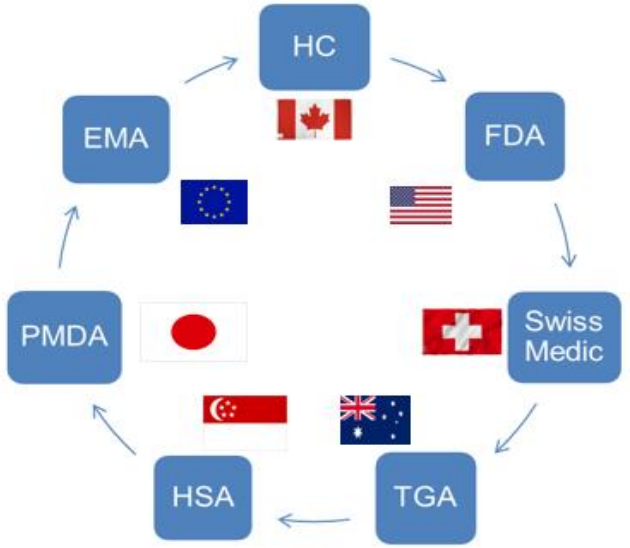
Assessment and analysis for nitrosamines require specially trained staff, specific test methods not used for “normal” impurity testing, and highly sensitive instrumentation capable of detection at parts-per-million (ppm) and parts-per-billion (ppb) levels

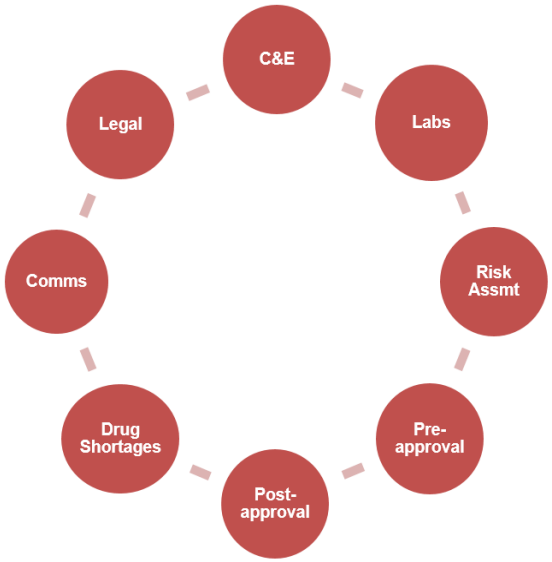
Increase in contracting of certain manufacturing activities has escalated the risk for cross-contamination of impurities such as nitrosamines

Quality Management Systems and Good Manufacturing Practices (GMP) at contract facilities may not be to the same standards as those of the Marketing Authorization Holder

Active Engagement Domestically and Internationally

- **Timely engagement of the Canadian public and stakeholders:**
  - Healthcare professionals (networks and associations)
  - Provincial and Territorial jurisdictions
  - Pharmaceutical industry and associations
- **International Strategic Working Group:**
  - Chaired by Health Canada, includes participants from regulatory partners in the US, Europe, Japan, Australia, Switzerland, and Singapore
  - Timely sharing of information (e.g., inspections, risk assessments, communications, market actions, test results)
- **International consortia:**
  - International Council on Harmonisation (ICH)
  - International Pharmaceutical Regulators Programme (IPRP)
- **Effective, multi-Branch collaboration:**
  - Various Directorates within HPFB, ROEB and CPAB (Communications Branch)





Proactive Measures and Risk Management

Risk Identification and Risk Management

- Evaluation of manufacturing processes of APIs/drug products for potential root causes
- Where a significant risk is identified (e.g. by levels found internationally or based on results of a risk assessment), companies requested to provide information for products on the Canadian market
- Conduct risk assessments and initiate testing where warranted
- Ensuring timely action and risk mitigation when risks are identified

Prevention

- Internal training and information sessions for staff to identify and manage risks (e.g., during submission review)
- Continue working with regulatory partners to coordinate GMP inspections and share information
- Discussions started at international forums (e.g., ICH) around adopting existing guidance/creating new guidance to set limits for impurities

Communication, Transparency & Engagement

- Timely and effective communication to the public and stakeholders:
    - Communicate recalls and regular updates to the public
    - Provide patients and healthcare professionals with risk information to make informed decisions
    - Engagement of healthcare professional associations prior to HC communications
    - Keeping industry stakeholders informed (e.g., updates to the HC webpage, stakeholder webinar)

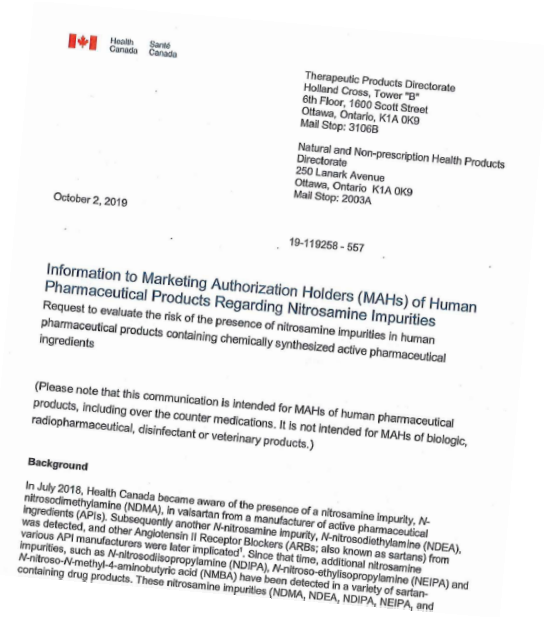
Monitoring

- Testing by Health Canada Labs
    - Developing highly sensitive methods (to ppm and ppb levels) for APIs and drug products on the Canadian market
- Determining interim acceptable limits
    - Interim limits were established by safety experts of the international working group for five nitrosamines (NDMA, NDEA, NDIPA, NEIPA, and NMBA)
- Use of real world evidence to inform on gaps of knowledge

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

- October 2, 2019 letter to all MAHs:
  - Consistent with the approach taken by the European Medicines Agency (EMA), ***HC issued a key communication*** to all MAH's of human prescription and non-prescription medications requesting risk evaluations for the presence of nitrosamines

- Step-wise request for actions:
  - ***Step 1 - Risk assessments:***
    - Conduct risk assessment for the possible presence of nitrosamines within 6 months
  - ***Step 2 - Confirmatory testing:***
    - In the event a risk is identified, immediately test for the presence of nitrosamines (those identified as high priority) or within 2 years (for others)
  - ***Step 3 - Introduce any required changes:***
    - Implement amendments to the manufacturing procedures or testing specifications within 2 years



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Therapeutic Products Directorate
Holland Cross, Tower "B"
6th Floor, 1600 Scott Street
Ottawa, Ontario, K1A 0K9
Mail Stop: 3106B

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

October 2, 2019

19-119258 - 557

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-*N*-methyl-4-aminobutyric acid (NMBA) have been detected in a variety of sartan-containing drug products. These nitrosamine impurities (NDMA, NDEA, NDIPA, NEIPA, and

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Nitrosamines in Pharmaceuticals

Potential Root Causes of Nitrosamines and Considerations During Pharmaceutical Development and Submission Review

Stephen Horne
Senior Evaluator,
Bureau of Pharmaceutical Sciences,
Therapeutic Products Directorate,
Health Products and Food Branch (HPFB)

Potential Root Causes of N-Nitrosamines in Human Pharmaceuticals

Intrinsic Factors

Driven by

Process Design and Materials

Extrinsic Factors

Driven by

Compliance and Quality Management

Nitrosamine Contamination in API and/or Drug Product

e.g.

- Nature of the selected chemistry and manufacturing operations
- Unrecognized impurities in raw materials, excipients
- Structural elements and properties of the starting materials, intermediates, and API

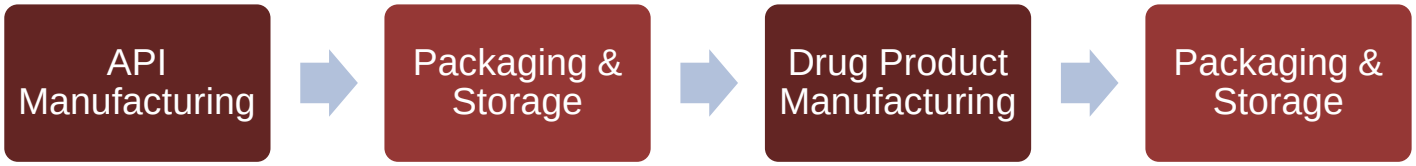
➢ **Gaps in Pharmaceutical Development, Control Strategy**

e.g.

- Use of contaminated recovered or recycled materials
- Use of third party contract recovery/recycling facilities, contractor qualification
- Cross-contamination in multi-purpose facilities

➢ **Gaps in Quality Oversight**

Scope of Nitrosamine Risk



- Nitrosamine formation is potential across many stages of manufacture, and therefore a wide scope is necessary during development/review

- Our current (and still growing) knowledge base comes from HC internal risk assessments and sample testing, information shared by international regulatory partners, results of manufacturer hypotheses/root cause investigations, and peer-reviewed literature

- Many factors inherent to the manufacturing process for API and drug product appear to be relevant, including
  - raw material and excipient quality attributes
  - Route of synthesis for the API
  - manufacturing process conditions
  - structural elements in the API/API intermediates/starting materials
  - packaging material attributes
  - API degradation profile

Considerations During Pharmaceutical Development and Submission Review

- Personnel/Capability
  - Personnel should have the requisite knowledge and practical experience necessary to develop manufacturing processes and/or to conduct critical assessments which address nitrosamine risks.

- Development Approach
  - Preferably, select materials and design manufacturing processes to avoid formation/introduction of nitrosamines at the outset, whenever possible; when not possible, design-in specific operations and establish controls which are demonstrated to reliably purge nitrosamines to acceptable levels.

- Chemistry
  - Nitrosamines are typically formed when nitrosation agents react with an amine under appropriate conditions. Commonly used nitrosation agents include nitrous acid (HNO_2) or its anhydride (N_2O_3), usually formed *in-situ* from a nitrite salt (e.g. $NaNO_2$) and an acid source (e.g. HCl) and nitrogen oxides (NO_x species) (e.g. in nitrogen gas, nitric acid)
  - Secondary and tertiary amines can lead to the formation of stable nitrosamines and are a major concern. Primary amines can also be reactive to nitrosation agents, however they usually do not lead to stable nitrosamines as the primary product. Reviews and book chapters are available which provide in-depth discussion on formation and reactivity of nitrosamines.

Considerations During Pharmaceutical Development and Submission Review

- API Manufacturing
  - Certain points of contact between **nitrosation agents** and primarily **secondary or tertiary amines**, either introduced or formed *in-situ*.
  - Actual process conditions (e.g. pH, temperature, concentration, etc.) are relevant to the risk for nitrosamine formation
  - The nitrosation agent and amine need not necessarily be introduced/formed within the same step/operation to present a risk of nitrosamine formation (e.g. an amine impurity in a starting material may carry over to a downstream step where a nitrosation agent is present)
  - Due to their large dipole moment, nitrosamines may solubilize in aqueous media as well as organic solvents during liquid-liquid phase separations

- Drug Product Manufacturing
  - Certain operations performed when a nitrosation agent and amine co-exist
    - Considered higher risk for solution / suspensions (e.g. during granulations)
    - Elevated temperatures (e.g. during drying stages)

Considerations During Pharmaceutical Development and Submission Review

- Structural Elements of API, starting materials, excipients
  - Evaluate structural elements of starting materials, intermediates, API, and excipients, for the presence of *N*-nitroso groups and secondary or tertiary amines, e.g.
    - Ranitidine hydrochloride API incorporates dimethylaminomethyl group
    - *N*-nitrosopiperazines used as intermediates for *N*-aminopiperazines
    - Methacrylate co-polymer excipients containing dimethylaminoethyl group

- Raw Material/Excipient Impurities
  - Screen all reagents, solvents, catalysts, processing aids, excipients, packaging components etc. for potential presence of nitrosation agents and secondary/tertiary amines as impurities, e.g.
    - sodium nitrite in sodium azide, process water, or sodium starch glycolate
    - dimethylamine as impurity or as a degradant of *N,N*-dimethylformamide solvent
    - nitrogen oxides present in nitric acid, nitrogen gas
    - nitrocellulose in lidding foil used for blister packaging

- Degradation Pathways
  - Consider the degradation products released during storage and potential for nitrosamine formation, e.g.
    - hydrolysis of APIs bearing amide groups may produce secondary amines

Considerations During Pharmaceutical Development and Submission Review

- Material Recovery/Recycling
  - Non-specific methods/processes used for recovery/recycling of solvents, reagents, spent catalysts may not address formation/separation of nitrosamines or amine impurities
  - Quality standard adhered to by third party facilities used for recovery/recycling may be inadequate to control for nitrosamine impurities
  - Use of shared/multi-purpose equipment in particular may present opportunities for cross-contamination

- Analytical Methodology
  - Photolytic degradation of nitrosamines has implications for sample handling and sample preparation protocol during method development and validation

The above considerations are provided to assist in product development strategies and submission review. Global regulatory understanding of the full extent of all potential root causes for nitrosamine contamination continues to develop. Given the uniqueness of each product/manufacturing process, additional considerations may be required to fully assess the risk of nitrosamine impurities in human pharmaceuticals.

Some Useful References

- Chemistry of N-Nitrosamines:
  - Boysen, M. M. K. Science of Synthesis, Volume 41, K. Banert, ed., Thieme, Stuttgart 2007, pp. 437-448.
  - Williams, D. L. H. Nitrosation Reactions and the Chemistry of Nitric Oxide, Elsevier, 2004.
  - Smith, P.A. et al. J. Am. Chem. Soc. 1967, 89(5), 1147.

- APIs Reported in the Literature to Contain NDMA, Survey of Test Methods:
  - Parr, M.K; Joseph, J.F. Journal of Pharmaceutical and Biomedical Analysis 2019, 164, 536-549.

- Common Excipients Reported to Containing Nitrite:
  - Wu, Y. et al. AAPS PharmSciTech 2011, 12(4), 1248-1263.

- Nitrosamine Test Methods:
  - Health Canada (NDMA,NDEA): https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/angiotensin-receptor-blocker.html
  - US FDA ARB page: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan
  - Link to European OMCL Network and other international regulators' test methods: https://www.edqm.eu/en/ad-hoc-projects-omcl-network

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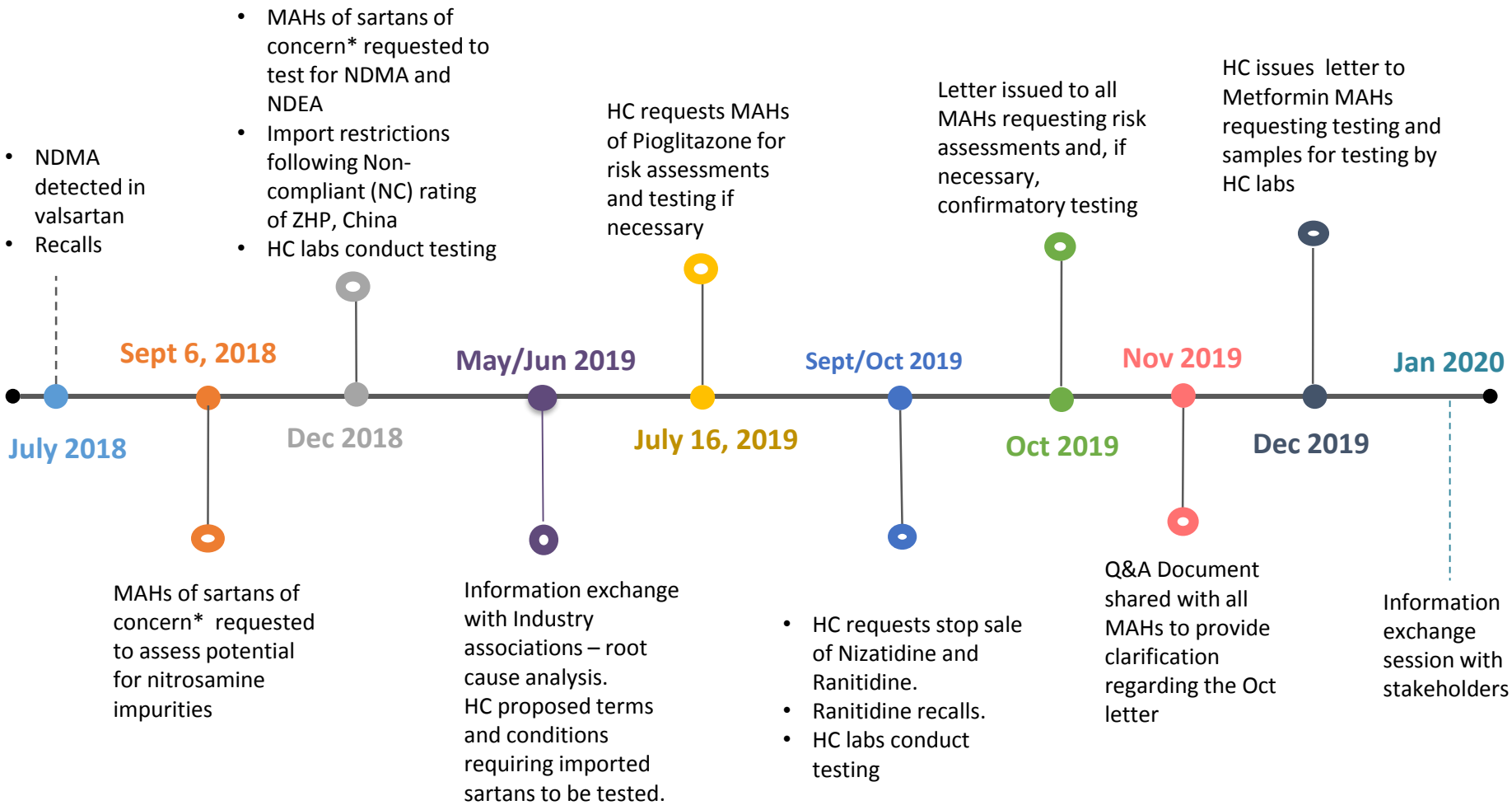
Nitrosamines in Pharmaceuticals

Compliance and Inspection Experience

Salima Rajwani, Case Manager,
Health Product Compliance and Risk Management,
Regulatory, Operations and Enforcement Branch (ROEB)

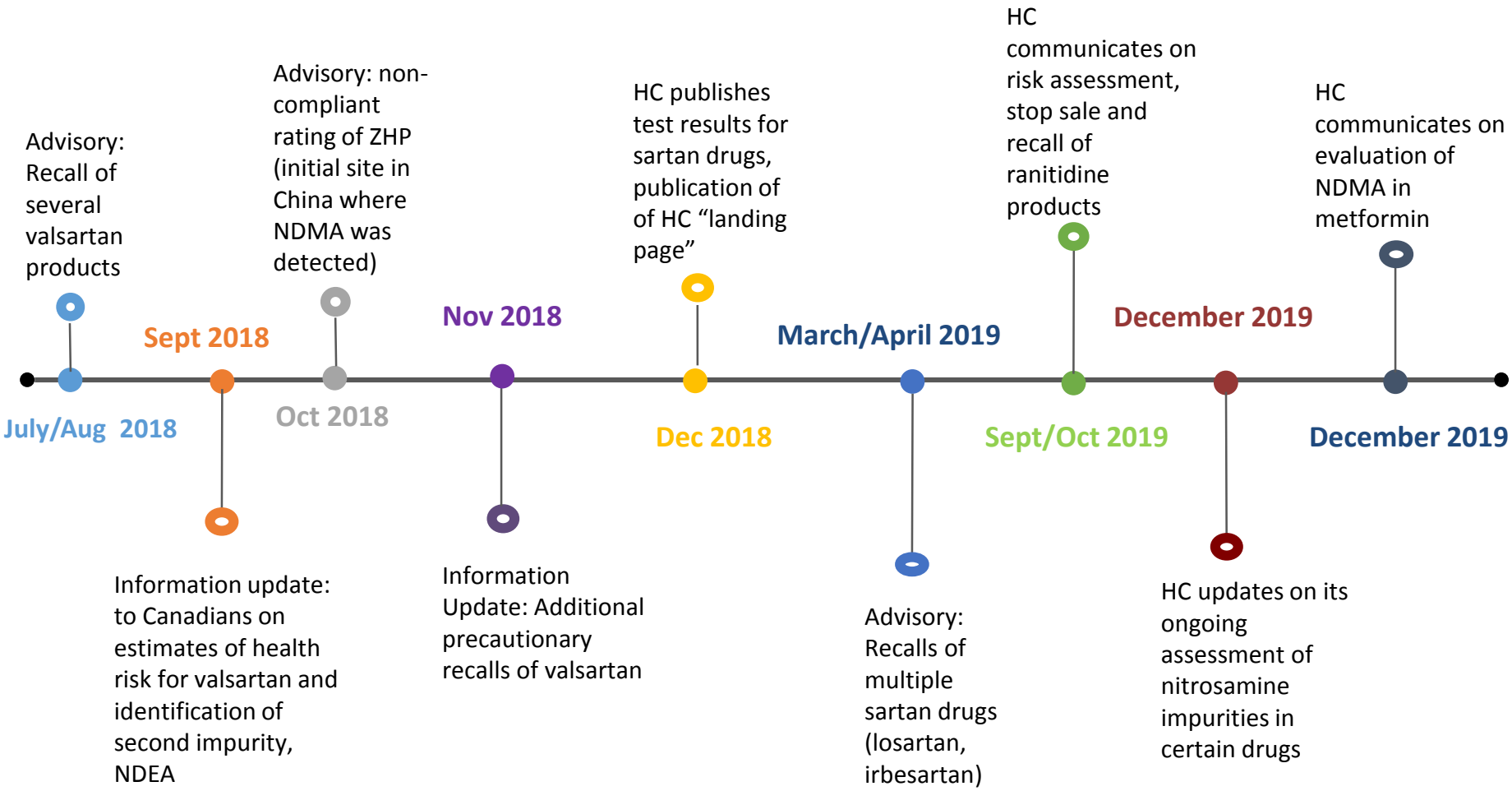
Ann Kourtesis, A/Manager,
Health Product Inspection and Licensing,
Regulatory, Operations and Enforcement Branch (ROEB)

Regulatory Actions



MAH = Marketing Authorisation Holder
* Sartans of concern = valsartan, candesartan, irbesartan, losartan and olmesartan

Communication to Canadians



Inspection Experience / Approach

The scope of GMP Inspections of Canadian DEL Holders may include:

1. Verifying that products are:
   - imported from compliant foreign sites, and
   - tested for nitrosamine impurities, as necessary (e.g., as per Terms and Conditions or if a risk of nitrosamines is identified via MAH risk assessments)
2. Verifying that testing is conducted by a licenced GMP compliant facility
3. Verifying that validated test methods are used
4. Verifying that contamination levels are below acceptable limits
5. Verifying recalls conducted (if any)

Inspection Experience / Approach

Assessment of compliance with Good Manufacturing Practices (GMP), Division 2 of the *Food and Drug Regulations*

- Conducted assessments of foreign buildings' compliance based on evidence submitted as per GUI-0080

- Conducted on-site assessments of foreign buildings
  - Health Canada assessments
  - Joint assessments with other Regulatory Authorities

Progress of testing further to Terms and Conditions on the Drug Establishment Licences (DEL) may be verified through:

- Inspections of Canadian DEL holders
- Proactive risk management projects
- Ad-hoc requests

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Nitrosamines in Pharmaceuticals

Health Canada's Question and Answer (Q&A) document (2019-11-26)

Craig Simon, A/Director, BPS, TPD
Gary Condran, Manager, BPS, TPD
Stephen Horne, Senior Evaluator, BPS, TPD
Alisa Vespa, Office of Risk Management, TPD

Health Canada's Q&A Document - Overview

- 17 Questions and Answers (Q&As) were issued on November 26, 2019 relating to the October 2, 2019 letter from Health Canada to Market Authorization Holders (MAHs)

- These Q&As were issued in response to follow-up questions and areas of ambiguity raised by
  - Industry associations
  - Company enquiries

- HC considers the Q&A document to be a living document, reflective of current thinking and recommendations, and subject to further updates

Q2. Prioritizing Risk Assessments

- Health Canada recognizes that some MAHs hold very large product portfolios, and therefore a risk-based approach to prioritization of products for assessment is critical

- Some important, non-limiting factors to consider:
  - Principles outlined ICH Q9 guideline on Quality Risk Management
  - Maximum daily dose of the drug product
  - Route of administration
  - Duration of use
  - Indication, products used by special populations (e.g. pregnant women and children)
  - Toxicological profile of the API (e.g. mutagenic APIs)
  - Market situation (e.g. product availability and number of patients)
  - Accessible information (e.g. regulatory notices, literature) that an API/drug product class contains nitrosamines
  - Structural elements in the API or manufacturing details that suggest a higher degree of risk (e.g. amine groups, use of nitrites)

Q4. Accessing Information from API Manufacturers

- Health Canada recognizes that MAHs may not have direct access to confidential business information relating to manufacture of the API which is necessary to conduct a thorough risk assessment

- Health Canada also recognizes that MAHs may not possess the internal capability to perform thorough risk assessments on the API

- Use of a third-party (e.g. a consultant) who is provided access to all of the necessary information by the API manufacturer may be appropriate

- Alternatively, delegation of the risk assessment (with respect to the API) to the API manufacturer may be appropriate

- The MAH maintains the responsibility, through appropriate auditing, that risk assessments by third parties / API manufacturer have considered all potential root causes and have been conducted by individuals with acceptable qualifications (e.g. training and practical experience)

Q5: Which nitrosamine impurities should be considered in the risk assessment and confirmatory testing?

Given that each drug substance and drug product manufacturing process is unique, it should be noted that the list of nitrosamines included in Annex 1 of the October 2, 2019 letter may not represent all nitrosamines potentially present in drug substances and drug products. Therefore, MAHs should ensure that the risk assessments consider and identify the possibility of any nitrosamine impurity which may be formed. All nitrosamines that have been determined to be potentially formed should be included within the program for confirmatory testing (Step 2 of the October 2, 2019 letter). For nitrosamines not included in Annex 1, MAHs should follow the principles outlined in the ICH M7(R1) guideline on mutagenic impurities to establish an interim acceptable intake.

Q8: In cases where a risk assessment concludes there is no risk of nitrosamine contamination, is confirmatory testing required?

- MAHs are required to conduct a thorough, robust risk assessment. In the October 2, 2019 letter, Health Canada shared some potential sources of nitrosamine impurities and noted that attention must be given to APIs as well as drug product manufacturing processes. For example, MAHs should evaluate whether secondary amines or nitrites coexist during the manufacturing processes and the potential of contamination through bulk raw materials and potable water.

- MAHs should prepare a report including considerations, steps and conclusions. If it is concluded that a risk does not exist, then confirmatory testing is not expected.

- In the event that a risk of formation or presence of nitrosamines is identified, confirmatory testing should be carried out using appropriately validated and sensitive methods. If one or more nitrosamine impurities are detected in an API or drug product, Health Canada must be informed immediately.

Q11: How will Health Canada respond to notifications of the detection of one or more nitrosamine impurities that are below interim acceptable limit(s)?

In the case where one or more nitrosamine impurities are detected and are below the current interim acceptable limit(s), Health Canada expects that MAHs will:

- Initiate actions to determine the origin of the detected nitrosamine impurity(ies);
- Determine any actions, as necessary, for the batches on the Canadian market;
- Establish a risk mitigation plan to ensure that level(s) will be consistently below the current interim acceptable limit(s) at the end of the shelf-life for the drug product moving forward. Further, measures should be initiated to introduce changes or controls in the manufacturing processes, where possible, to reduce the levels of the nitrosamine impurities to levels below the detectable limits in the longer term.

Q11: How will Health Canada respond to notifications of the detection of one or more nitrosamine impurities that are below interim acceptable limit(s)? (continued)

Health Canada may use such notifications to request documentation describing the company's root cause investigation and risk mitigation plan for the detected nitrosamine impurities. Health Canada may also use such notifications to request additional actions. For example, the origin of nitrosamine impurities may be attributed to the type of process chemistry used and the risk mitigation plan may necessitate the establishment of a control strategy by manufacturers for each detected nitrosamine impurity according to ICH's guidance for mutagenic impurities (i.e. ICH M7(R1)).

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Derivation of Interim Acceptable Intakes (AIs) for Nitrosamine Impurities

Alisa Vespa
Office of Risk Management
Therapeutic Products Directorate,
Health Products and Food Branch (HPFB)

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Interim Acceptable Intakes (AIs) for 5 identified nitrosamine impurities

Nitrosamine	Interim AI (ng/day)*
NDMA	96
NMBA	96
NDEA	26.5
NDIPA	26.5
NEIPA	26.5

*: Limit to be applied to maximum daily dose (MDD) of the drug product

For example,

Interim acceptable concentration limit for NDMA in Metformin

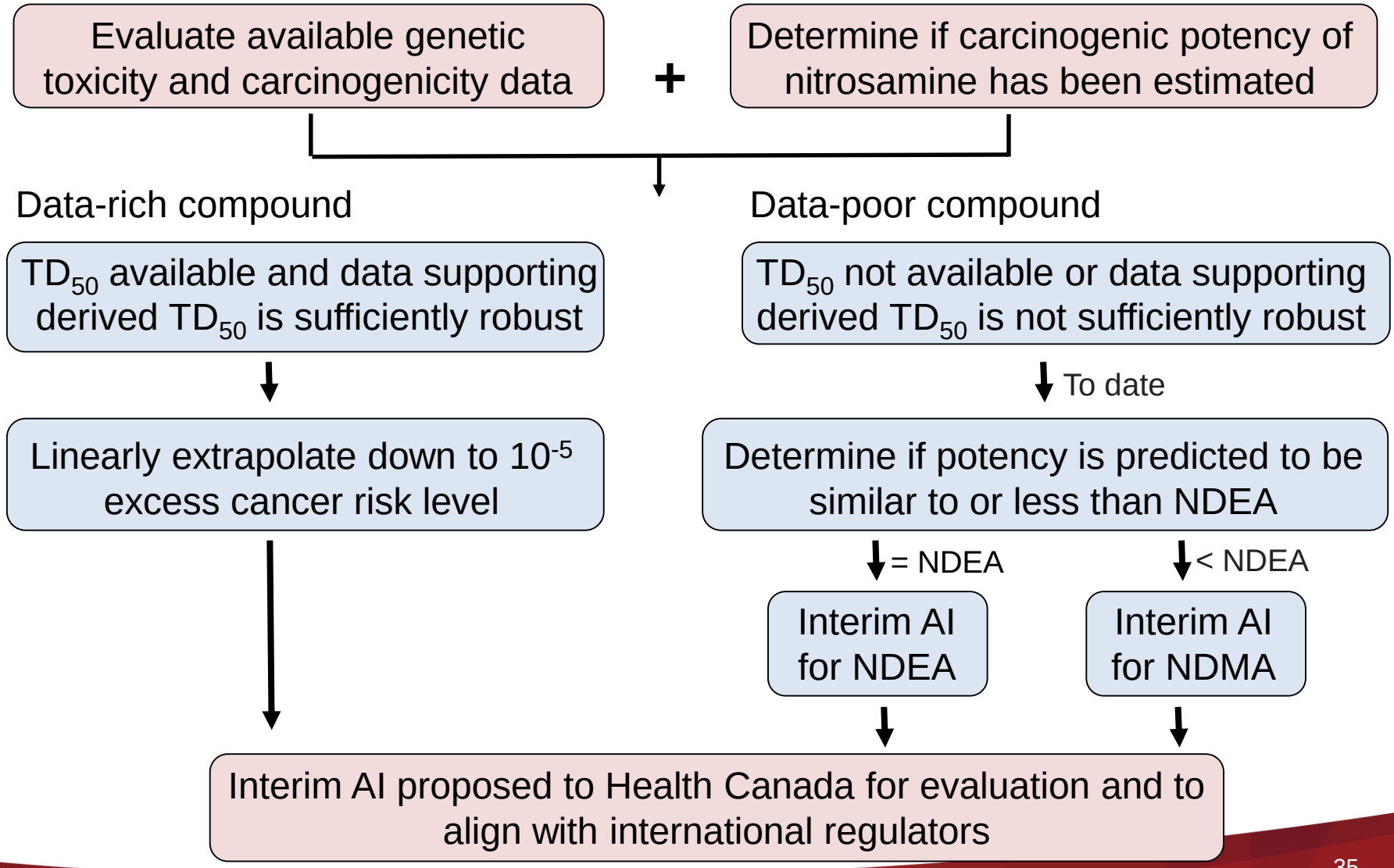
= Interim AI (µg/day) / MDD (g/day)

= 0.096 ug/day / 2.55 g/day

= 0.0376 ppm

= 38 ppb

Derivation of an interim AI for a newly identified nitrosamine impurity



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Industry Associations Experience and Feedback

- Stephen Sampson, IMC
- Jody Cox, CGPA
- Kristin Willemsen, CHPC
- Richard Parcels, CAC (on-line)
- Pierre Morin, GPIM (on-line)
- Luisa Paulo, API Industry (on-line)

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Question Period

Panel:

- Craig Simon, HPFB
- Gary Condran, HPFB
- Stephen Horne, HPFB
- Alisa Vespa, HPFB
- Salima Rajwani, ROEB (on-line)
- Ann Kourtesis, ROEB
- Justin Morin, ROEB (on-line)
- Jennifer Sears, NNHPD

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Closing Remarks

Patrick Stewart
Director General,
Therapeutic Products Directorate,
Health Products and Food Branch (HPFB)

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