

NITROSAMINES- Solving the Puzzle

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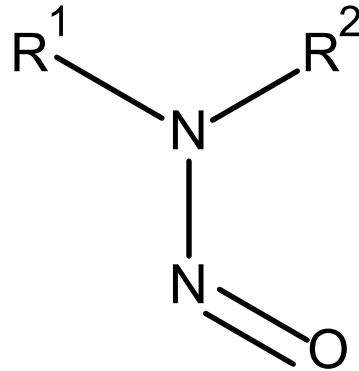
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06 Nov 2020

What are nitrosamines?

Nitroso bonded to amine

amines (secondary, tertiary, or quaternary amines) + nitrous acid (nitrite salts under acidic conditions)



Potent genotoxic agents in several animal species, some classified as probable or possible human carcinogens by the International Agency for Research on Cancer (IARC)

Although present in some foods and drinking water supplies, their presence in medicines is nonetheless considered unacceptable

Origin of the Crisis

July 2018: FDA was notified presence of NDMA in Valsartan + other ARBs; Ranitidine – Sept 19 (Apr 2020, all products withdrawn), Metformin – Dec 19

July 2018, EMA triggered a referral procedure to assess the impact of nitrosamines impurities on sartans with tetrazole ring

Impacted

- ARBs
- Metformin
- Ranitidine
- Clarithromycin & Pioglitazone (Health Canada)
- Nizatidine

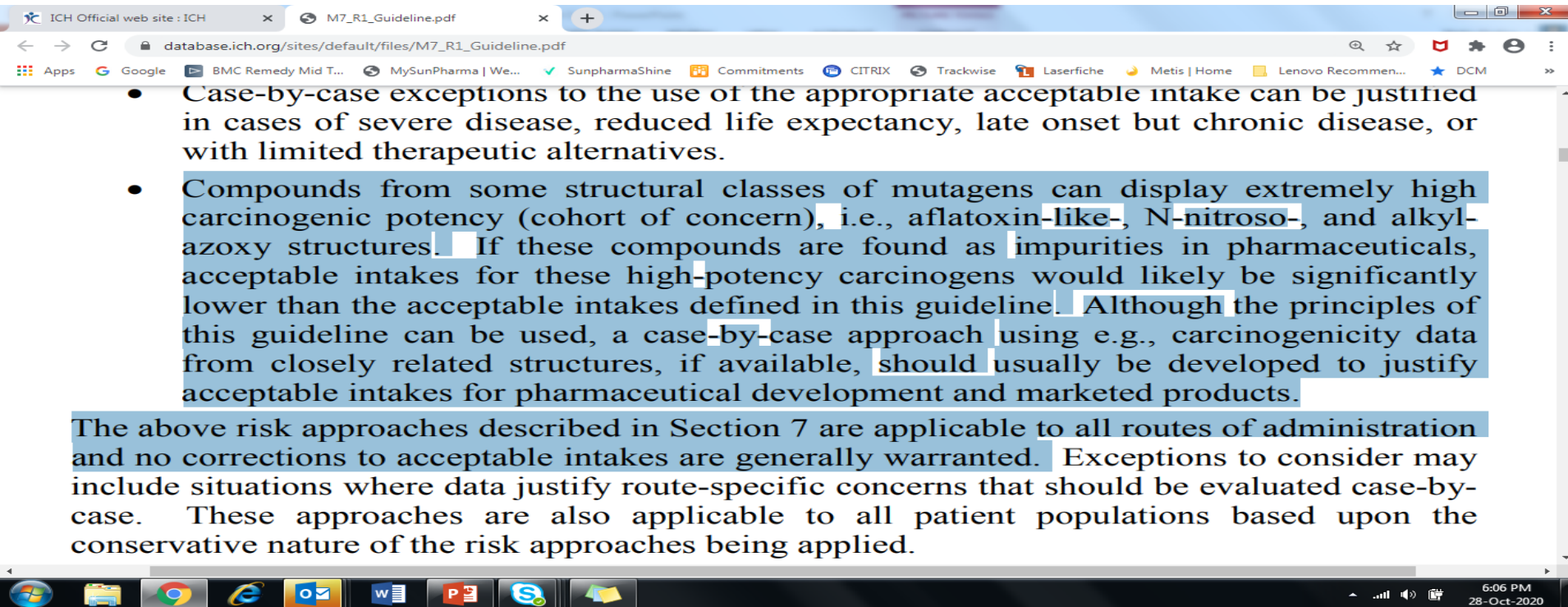
Ask: Evaluate all Drug substances and Drug products for any potential for contamination/presence of Nitrosamines

Industry Impact

- **Recalls** (Teva, Aurobindo, Sun, Mylan, Torrent etc, Zhejiang Huahai faced Import alert)
- **CEP Suspensions** (Till January 2019 11 Ranitidine CEPs were suspended)
- **Cost of testing:**
 - a) Rapid development of very sensitive methods,
 - b) Validations at such low levels,
 - c) Cost of specialized equipment,
 - d) Impact on the timeline for the release of API/DP batches requiring testing,
 - e) Adequately trained manpower.
- **Increased Regulatory Oversight:** Agencies will critically look into the risk assessments and potential for contamination during onsite audits.
- **Increased Quality Oversight:**
 - a) All APIs/Drug Products required to be evaluated for any potential for the formation of any nitrosamines.
 - b) All multipurpose facilities will need to evaluate the APIs/Drug Products for any chance of cross contamination. All time concern, any change need to be scientifically evaluated.
 - c) Use of Recovered solvents/recycled materials and the equipment used therein need scientific evaluation
 - d) Intermediates/Solvents/Reagents sourced from suppliers need oversight

Are Nitrosamines New?

Identified in ICH as a potent class of compounds that have significant risk and are referred to as the “cohort of concern”.



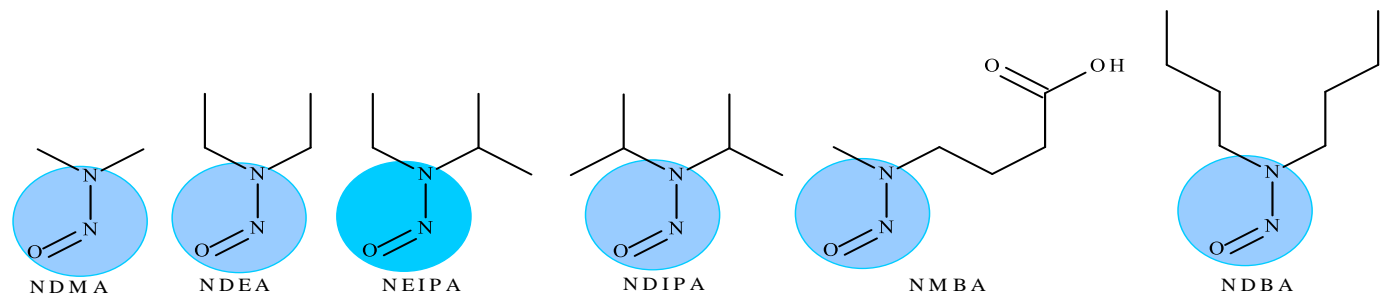
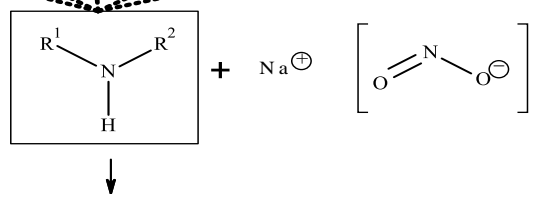
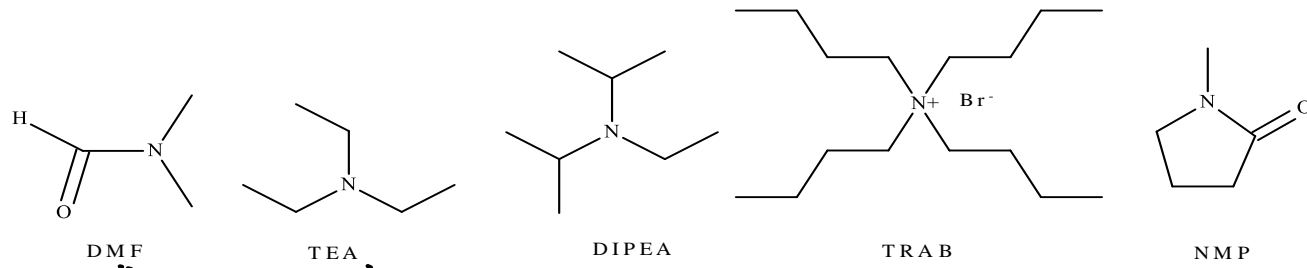
The screenshot shows a web browser window with the address bar displaying "database.ich.org/sites/default/files/M7_R1_Guideline.pdf". The main content area contains two bullet points:

- Case-by-case exceptions to the use of the appropriate acceptable intake can be justified in cases of severe disease, reduced life expectancy, late onset but chronic disease, or with limited therapeutic alternatives.
- Compounds from some structural classes of mutagens can display extremely high carcinogenic potency (cohort of concern), i.e., aflatoxin-like-, N-nitroso-, and alkyl-azoxy structures. If these compounds are found as impurities in pharmaceuticals, acceptable intakes for these high-potency carcinogens would likely be significantly lower than the acceptable intakes defined in this guideline. Although the principles of this guideline can be used, a case-by-case approach using e.g., carcinogenicity data from closely related structures, if available, should usually be developed to justify acceptable intakes for pharmaceutical development and marketed products.

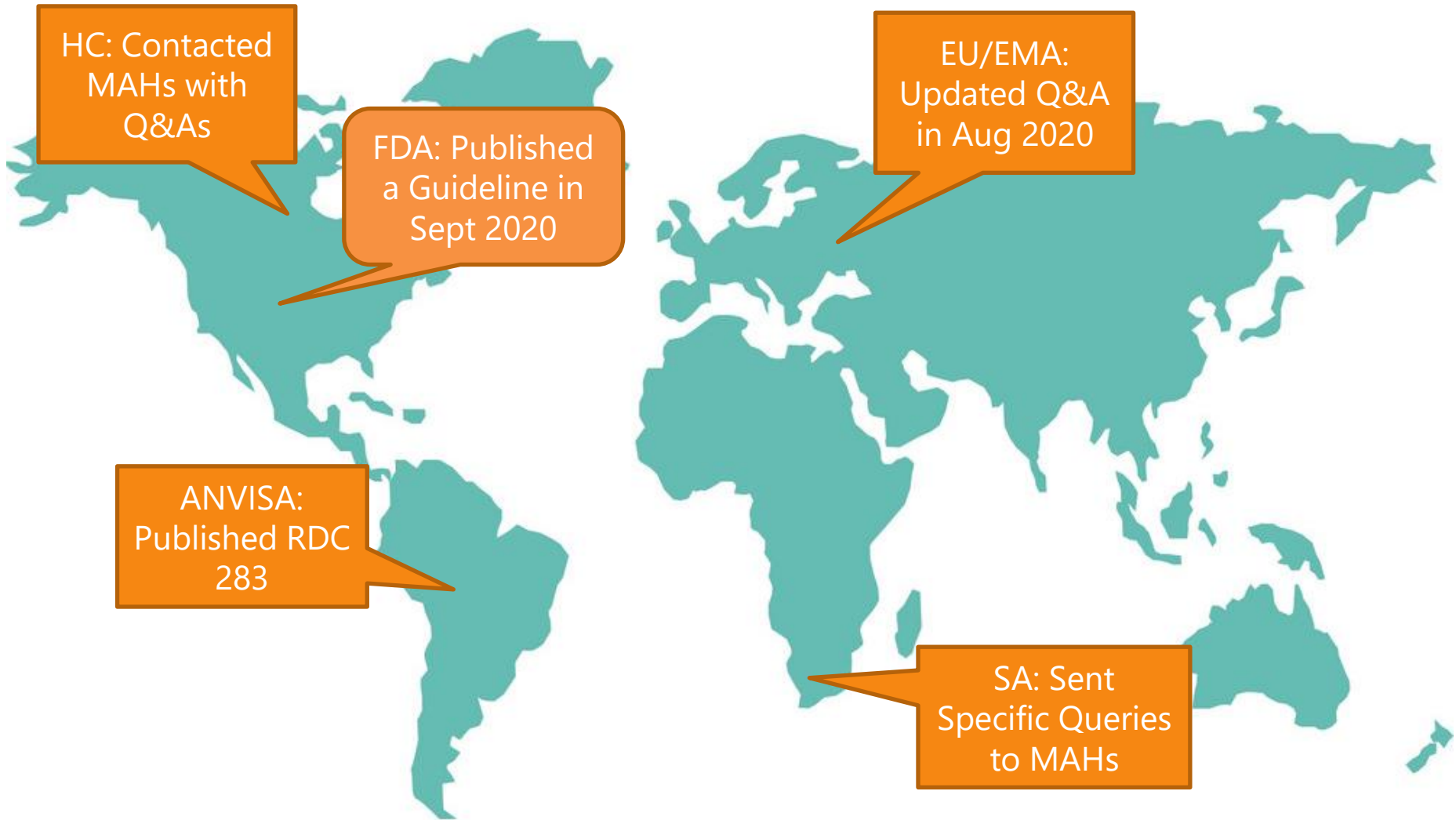
Below the bullet points, a paragraph states: "The above risk approaches described in Section 7 are applicable to all routes of administration and no corrections to acceptable intakes are generally warranted. Exceptions to consider may include situations where data justify route-specific concerns that should be evaluated case-by-case. These approaches are also applicable to all patient populations based upon the conservative nature of the risk approaches being applied."

How do they get into products?

- API Manufacturing Process
 - Nitrous acid used in synthesis
 - Nitrites carried over
- Amines – API, degradants, intermediates/SM, amide solvents
- Vendor sourced RM
- Recovered Solvents, catalyst, reagents
- Quenching process
- Other than API contamination
 - Excipients
 - Degradation in some DPs



Current Regulations



Evolving Expectations : FDA

July 2018: FDA
Notifies of NDMA
in Valsartan



Sept 2018: FDA
Publishes interim
acceptable limits in
ARBs



March 2019:
General Advice Letter

- Testing of DP/API batches
- LoD of the method to be inline with published methods



Sept 2020:
Final Guidance Published

- Acceptable ADIs for 6 Nitrosamines published.
- Concept of Total nitrosamines updated stating that total impurities should be limited with the most stringent ADI



Feb 2020:
General Advice Letter

- Reporting threshold of 0.03 ppm
- Total nitrosamines that can exceed reporting threshold : NMT 1
- Final ADIs of 3 Nitrosamines published

Current Expectations

FDA and EU have published Acceptable Intake (AI) Limits

| Nitrosamine | AI limit (ng/day) (US) | AI limit (ng/day) (EU) |
|-------------|---------------------------|---------------------------|
| NDMA | 96 | 96.0 |
| NDEA | 26.5 | 26.5 |
| NMBA | 96 | 96.0 |
| NMPA | 26.5 | 34.3 |
| NIPEA/EIPNA | 26.5 | 26.5 |
| NDIPA/DIPNA | 26.5 | 26.5 |
| MeNP | - | 26.5 |
| NDBA | - | 26.5 |

These limits are applicable if only one nitrosamine (from the table listed above) is observed.

If more than one nitrosamine is observed, the total limit of nitrosamine should not be more than AI of the most potent nitrosamine.

If a nitrosamine not listed in the table above is observed, 2 approaches are defined*:

- A class specific TTC of 18 ng can be used
- An approach based on SAR considerations to derive an acceptable limit can be used.
- Contact Agency#

* Defined by EMA

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Interpretation

Acceptable Intake (AI) can be converted to the limit (in ppm) by using the following formula:

$$\text{Limit} = \text{AI}/\text{MDD}$$

where MDD is Maximum Daily Dose of an API (in mg)

For Eg: For a Drug Product/API having a dose of 880 mg, the limit of NDMA will be

$$\text{Limit (NDMA) in ppm} = 96 / 880 = 0.109 \text{ ppm}$$

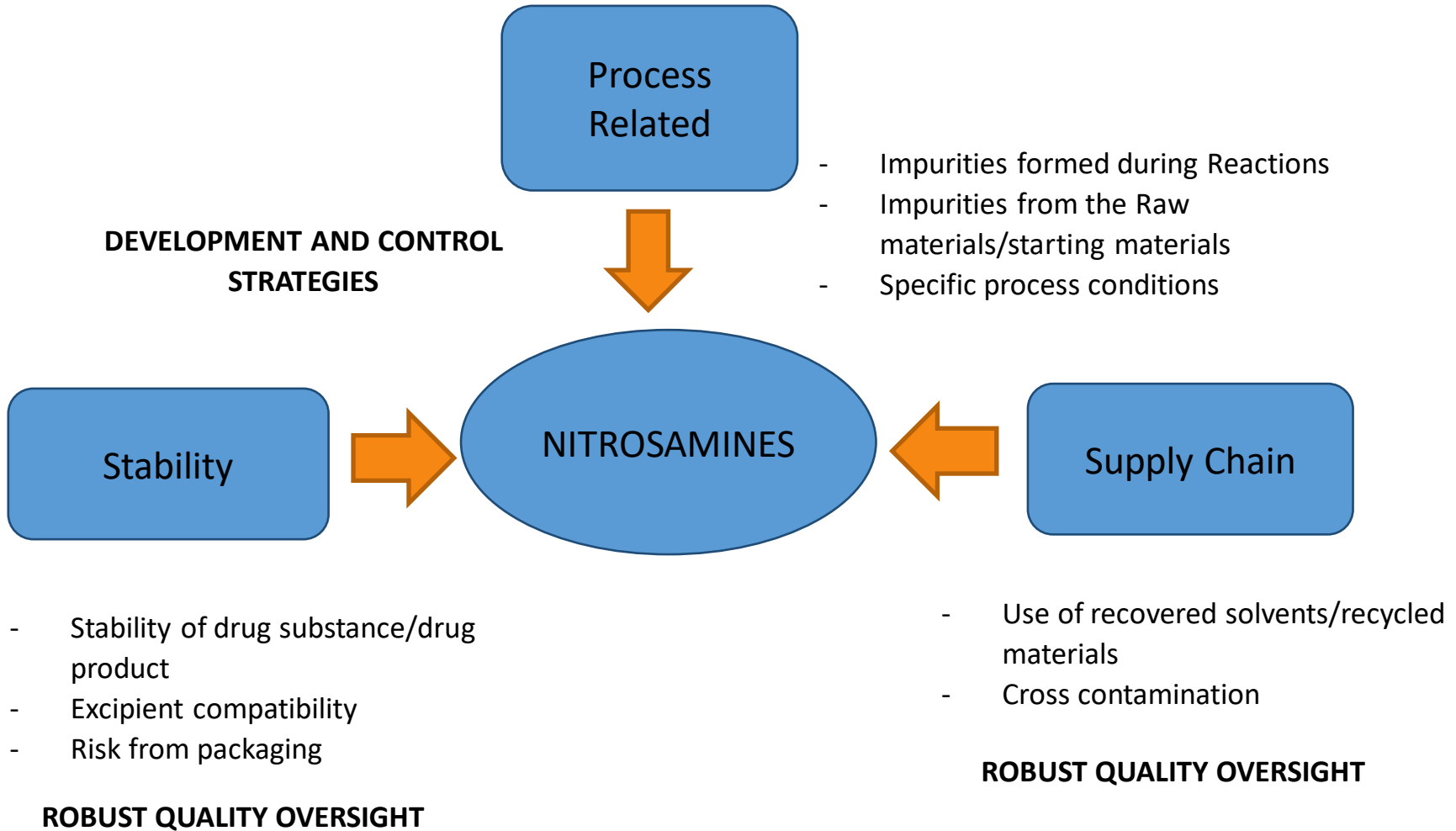
If there are 2 or more nitrosamines observed from the table listed in the last slide, a limit of total nitrosamine also needs to be included. This limit cannot be more than the limit derived using the most stringent nitrosamine.

Eg: If NDMA, NDEA and NDPA are observed in a Drug Product/API having a MDD of 880 mg the limit of total impurities will be calculated as:

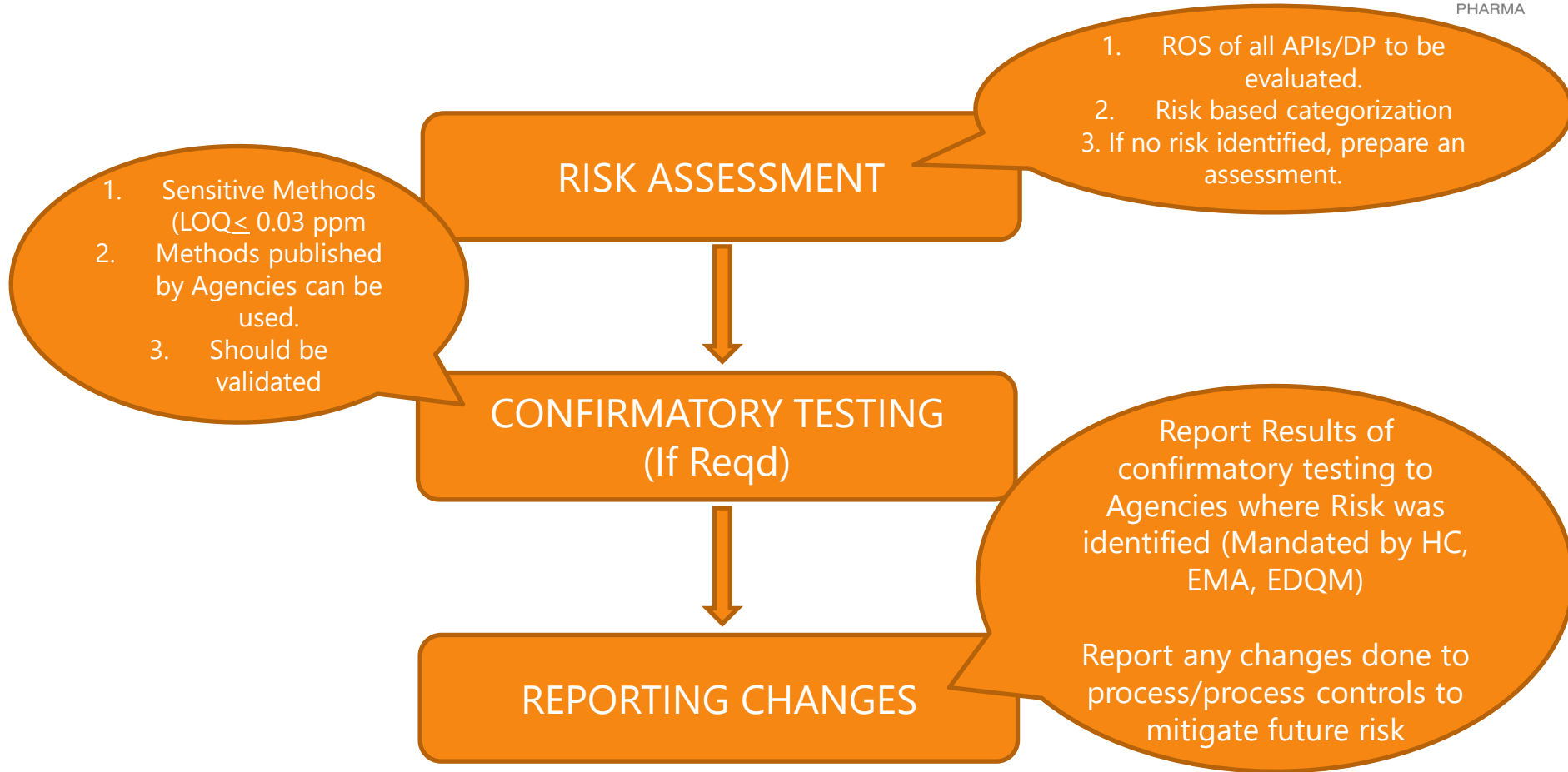
$$\text{Total Impurities (in ppm)} = \text{AI of most stringent nitrosamine (i.e 26.5)} / \text{MDD (880 mg)}$$

$$\begin{aligned} \text{Total Impurities (ppm)} &= 26.5/880 \\ &= 0.03 \text{ ppm} \end{aligned}$$

Control



Marketed Products



Underdevelopment APIs/Products

Aim should be to develop nitrosamine free products

- Use different Solvents (no DMF, TEA, NMP etc)
- Remove sodium nitrite/nitrosating agents
- Change order of steps
- Introduce inprocess controls to check the level of impurities
- Introduce control of Raw materials that may introduce nitrites
- Be careful while using recycled solvents
- API and Product development reports must update include an understanding of the "side reactions".

All Products/APIs that need to be filed must have a robust risk assessment included in the filing.

Under Review APIs/Products

Be Ready for Queries from Agencies!!

- Perform Risk Assessment.

If there is no potential for formation/introduction of nitrosamines in the process : No concern

If there is a risk:

- Confirm
- Include process controls
- Include controls in API/Drug Product specification
- Modify process and amend the file

Implications for Life cycle: Any change of process/process control/even Equipment must be appropriately evaluated for any potential to produce/introduce the nitrosamines.

EDQM has already notified that any revision/renewal of approved CEPs should include this assessment

Way Ahead

How to Ensure there are no future surprises!

- **Robust Development Studies:** Understanding process/Impurity formation (In-depth understanding of process and science based evaluation of the “Not-so-obvious” impurities including potential side reactions or interactions between raw materials or excipients and API)
- **Improved Quality oversight:** Proper Risk Assessment (Change in the process/process controls must be appropriately evaluated and scientifically understood)
- **Cross Contamination/Equipment :** Multipurpose facilities/equipment must be evaluated for any risk to quality
- **Testing:** Appropriate methods must be developed to identify and control the impurities identified. Introduce rigorous testing for impacted APIs/Products.
- **Manpower:** Adequately trained manpower

THANKS