Nitrosamines Impurities – Current Regulatory Status

6th Advanced GMP Workshop, Indian Pharmaceutical Alliance
20-22, October, 2021

Dr. BM Rao
Head – EM QA, ASAT & Corporate Quality control
Dr. Reddy's Laboratories, Hyderabad, India

Nitrosamines Impurities – Available Regulatory Guidance's

- EMA: June 29, 2021 EMA/409815/2020 Rev.4
- FDA: Control of Nitrosamine Impurities in Human Drugs, February 2021
- ANVISA: Public Consultation No. 1050, of May 31, 2021, Guidance No. 50, Version 1
- SWISSMEDIC: Potential nitrosamine contamination, April 16, 2021
- Health Canada: Update 2 of December 15, 2020

Nitrosamines Impurities – Current Regulatory Status

Steps	Type	EMA/409815/2020 / June 29, 2021	FDA / Feb 2021	ANVISA May 31, 2021	SwissMedic April 16, 2021	Health Canada December 15, 2020
Scope		**Human medicinal products**	**Human Drugs**	**Medicines for Human use**	**Human medicinal products**	**HUMAN PHARMACEUTICAL, BIOLOGICAL AND RADIOPHARMACEUTICAL PRODUCTS**
Risk Assessment Scope	Chemical Synthesis Biological API	Drug Product Drug Substance	Drug Product Drug Substance	Drug Product Drug Substance	Drug Product Drug Substance	Drug Product Drug Substance
Step 1: Risk Evaluation	Chemical Synthesis Biological API	31st March 2021 1st July 2021	March 31, 2021	Since date of publication: 9 months-Very high risk products 12 months-High risk products 36 months-All other products	31st March 2021 1st July 2021	March 31, 2021 November 30, 2021
Step 2: Confirmatory testing	Chemical Synthesis Biological API	26th September 2022 1st July 2023	October 1, 2023		26th September 2022 1st July 2023	October 1, 2022 November 30, 2023
Step 3: Changes to the market authorization	Chemical Synthesis Biological API	26th September 2022 1st July 2023	October 1, 2023		26th September 2022 1st July 2023	October 1, 2022 November 30, 2023

Nitrosamines Impurities – Current Regulatory Status

Potential Sources of Nitrosamine (Reference USP<1469>)	
Potential Source	**Risk**
Solvents	1. Residual dialkylamines/Tri-substituted amines can degrade to form intermediate, can further react with Nitrosating agents. 2. Presence of Nitrites, other Nitrosating agents 3. Presence of acid 4. Limited controls/Limits for re-cycled solvents 5. Poor quality of solvents
Water	1. Presence of residual dialkylamines / impurities can degrade to form dialkylamines. 2. Presence of acids and Nitrosating agents
Raw material/Excipients	1. Presence of Nitrites, other Nitrosating agents and/or nitrosamine impurities if applicable
API	1. Use of Sodium Azide/Nitrites in Acid 2. Use of Di/trialkylamines -amides, in presence of nitrites and acid medium 3. Use of Rec. solvents contains Nitrosamines or their precursors. 4. Use of sanitized water ex. Chloramines 5. Insufficient purification 6. Degradation of API
Manufacturing Process	1. Contamination 2. Use of Rec. solvents contains Nitrosamines or their precursors. 3. Presence of Nitrous oxide in air 4. Carry over of relevant reactive species
API-Stability	1. Secondary/Tertiary/Quaternary amine group in molecule of API 2. Presence of nitrate counter ions
Container Closures/ Packing material	1. Containing vulnerable amines

Nitrosamines Regulatory Guidelines - Status

Acceptable Intake (AI) limits of Specific Nitrosamine Impurities							
Impurity	**Code**	**CAS No.**	**EMA (AI - ng/day)**	**FDA (AI - ng/day)**	**ANVISA (AI - ng/day)**	**SwissMedic (AI - ng/day)**	**Health Canada (AI - ng/day)**
N-Nitrosodimethylamine	NDMA	62-75-9	**96.0**	**96.0**	**96.0**	**96.0**	**96.0**
N-Nitroso-4-(methylamino)butyric acid	NMBA	61445-55-4	**96.0**	**96.0**	**96.0**	**96.0**	**96.0**
1-Methyl-4-nitrosopiperazine	MNP/MeNP	16339-07-4	**26.5**	**-**	**26.5**	**26.5**	**96.0**
N-Nitrosodiethylamine	NDEA	55-18-5	**26.5**	**26.5**	**26.5**	**26.5**	**26.5**
N-Nitrosodiisopropylamine	NDIPA/DIPNA	601-77-4	**26.5**	**26.5**	**26.5**	**26.5**	**26.5**
N-Nitrosoethylisopropylamine	NEIPA/NIPEA/ EIPNA	16339-04-1	**26.5**	**26.5**	**26.5**	**26.5**	**26.5**
N-Nitrosodibutylamine	NDBA	924-16-3	**26.5**	**USP**	**26.5**	**26.5**	**26.5**
N-Nitrosomethylphenylamine	NMPA	614-00-6	**34.3**	**26.5**	**34.3**	**34.3**	**-**
N-Nitrosomorpholine	NMOR	59-89-2	**127**	**-**	**-**	**-**	**-**

$$\text{Limit (ppm)} = \frac{\text{Acceptable Intake (ng/day)}}{\text{Maximum Daily Dose (mg/day)}}$$

Nitrosamines Regulatory Guidelines – Status

(Testing Method requirements)

Testing	EMA	FDA	ANVISA	SwissMedic	Health Canada
Method	Validated sensitive method	Validated sensitive method	Validated sensitive method	Validated sensitive method	Validated sensitive method
Testing type	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative
Sensitivity of the method	LoQ should be ≤ of the acceptable limit based on the relevant acceptable intake (AI) for the respective nitrosamine impurity	LoD/LoQ are reasonably practical for products MDD is high (>1 g) If >1 nitrosamine listed, the method LOQ should be <0.03 ppm. If MDD >1 g (e.g. 1200 mg), LOQ should be below 0.02 ppm	LoD or LoQ <10% of limit of AI	LoQ should be < 30 ppb (0.03 ppm)	LoQ should be ≤ to the acceptable limit for most potent nitrosamine detected in an API or drug product

Nitrosamines Regulatory Guidelines – Status

(Control by testing – General recommendation from Confirmatory Testing)

Testing	Omission	Skip testing	Routine control
EMA	the **LoQ of the analytical method employed should be ≤ 10%** of the acceptable limit based on the AI	the **LoQ of the analytical procedure employed should be ≤ 30%** of the acceptable limit based on the AI	the **LoQ should be ≤ of the acceptable limit** based on the relevant acceptable intake (AI) for the respective nitrosamine impurity
FDA	Alternate approaches (e.g., upstream test of an intermediate) should be supported by sufficient process understanding and evidence of adequate statistical control and should be submitted to FDA in a supplement prior to implementation		If a nitrosamine impurity is **detected above the LOQ**
ANVISA	**Admitted the absence of nitrosamines when <10% of the AI limit**	**If results are >10% of AI limit, control must be included. Other approaches can be justified, not exceeding the 30% limit. If the >1 nitrosamine to be controlled, the limits must be adjusted in order to ensure the maintenance of negligible risk**	
SWISSMEDIC	The detection of every nitrosamine impurity must lead to an investigation of the causes, and appropriate CAPAs should be taken in accordance with GMP. As with any case of an identified problematic risk, companies must follow the standard procedure and inform Swissmedic immediately if nitrosamines are detected in APIs or medicinal products – regardless of the quantities – and submit a risk evaluation.		
HEALTH CANADA	**NA**	**NA**	The API specification should include a test and acceptance criterion for each nitrosamine impurity when the risk for nitrosamine presence is considered to be high and/or when the concentration of any nitrosamine is found to be at significant levels (e.g. greater than 30% of the acceptable intake) during confirmatory testing.

Nitrosamines Regulatory Guidelines – Status

(Confirmatory Testing – Already Marketed Products)

Regulations	Specific requirements for batches to be considered for testing
EMA	▪ 10% of annual batches or 3 batches per year (whichever is highest) ▪ If fewer than 3 batches are manufactured annually, then all batches should be tested ▪ If multiple manufacturers, manufacturing processes and/or sources of at-risk raw materials are used, (or were used historically for batches still within expiry date), then testing of additional batches would be necessary to cover these risk factors.
FDA	Based on the risk assessment evaluation
ANVISA	▪ Minimum of 10% of annual batches or 3 batches per year (whichever is greater) ▪ If less than 3 batches are manufactured in the year all the manufactured batches must be tested ▪ If more one manufacturer, manufacturing process and/or sources of major risk – related materials used, more batches should be tested to cover all risk factors ▪ When the possible nitrosamine are degradation impurities, at least 3 representative batches of products shelf life should be tested ▪ Other technically justified approaches may be accepted
SwissMedic	Based on the risk assessment evaluation
Health Canada	• All drug product batches on the Canadian market within expiry should be subjected to confirmatory testing when a risk of nitrosamines is identified. • All drug product lots should be tested as levels may vary from lot to lot. • Testing of the API is also recommended if the risk assessment indicated that the API is a potential source of nitrosamine impurities in the drug product. • The test data should span the approved shelf life of the drug product to ascertain if nitrosamine levels could increase over time due to degradation or other root causes.

Nitrosamines Regulatory Guidelines – Status

(Confirmatory Testing : New Registration or Post-Approval Products)

Regulations	Specific requirements for batches to be considered for testing
EMA	▪ For new and on-going marketing authorisation applications, **the number of batches to be tested as part of any confirmatory testing should be commensurate with the risk in line with ICH M7(R1) guideline.** ▪ The source of risk has to be well understood (e.g. by spike and purge studies) such that impurity levels are expected to be consistent from batch to batch. ▪ **Test results from a minimum of 6 pilot scale batches or 3 production scale batches may be sufficient.** ▪ Depending on the risk factors for nitrosamine presence, e.g. with risk factors being closer to the FP, more batches may need to be tested. ▪ If multiple manufacturers, manufacturing processes and/or sources of at-risk raw materials are used, (or were used historically during development), then testing of additional batches would be necessary to cover these risk factors.
FDA	Based on the risk assessment evaluation
ANVISA	▪ The number of batches to be tested must be consistent with the quantity required by the current legislation ▪ However for petition that required <3 batches the implementation will be conditioned on the companies commitment to test the implementation batches also later, in order to complete the 3 required batches. ▪ The data must be available for presentation to ANIVSA when requested or during inspection
SwissMedic	Based on the risk assessment evaluation (EMA requirements can be considered)
Health Canada	• For NDSs, ANDSs, and Supplements (for Quality changes that may impact the potential presence of nitrosamines in the drug substance or drug product), at least six pilot or three commercial scale batches should be subjected to confirmatory testing where a risk of nitrosamines has been identified. • However, where the risk of nitrosamine contamination is high (e.g. the late stage formation/introduction of a nitrosamine impurity, nitrosamine precursor functional groups in the API, stability concerns exist for nitrosamine formation over the retest period/shelf life etc.), a higher number of batches should be submitted for assessment. • Testing results of stability batches for a nitrosamine impurity should be submitted where there is an identifiable risk that nitrosamine levels could increase in the drug product over time or where the potential for increases over time is unclear. • A minimum of six months of accelerated and long-term stability data in the proposed container closure system(s) should be provided.


Thank you


Any Questions?