Control Strategy Implementation Challenges

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Sanjeeva Chinnakadoori, (PhD)
Amneal Pharmaceuticals

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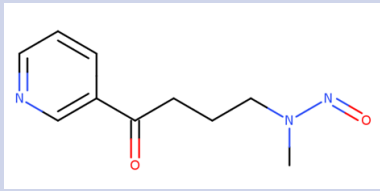
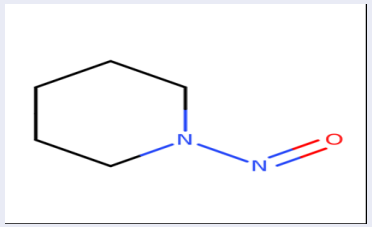
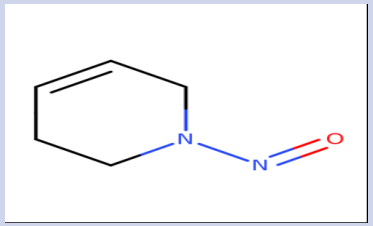
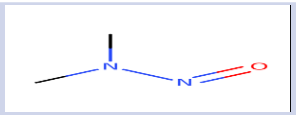
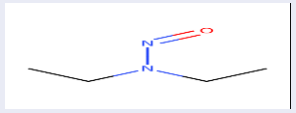
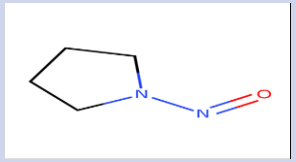
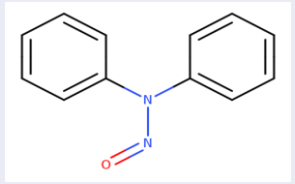
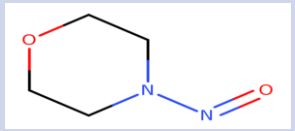
Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

- FDA/other regulatory Authorities published Acceptable Intake (AI) limits for Nitrosamines based on Predicted Carcinogenic Potency Categorization Approach (CPCA) and Compound-Specific Carcinogenicity and Mutagenicity Data or Read-Across Analysis from a Surrogate.
- Minor difference for Potency Category-1 AI- 18 ng/day v/s 26.5 ng/day.
- The following typical Surrogate structures utilized to determine the AI limits for Nitrosamines across Health Authorities.

Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

Surrogate	Structure	AI Limit (ng/day)	Health Authorities Used to determine AI of Nitrosamines
4-(methylnitrosoamino)-1-(3-pyridinyl)-1-butanone (NNK)		100	FDA/EMA/HC
N-nitroso-piperidine (NPIP)		1300	FDA/EMA/HC
N-nitroso-1,2,3,6-tetrahydropyridine (NTHP)		37	FDA/EMA/HC

Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

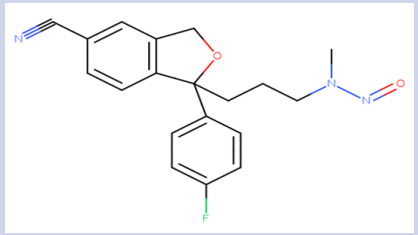
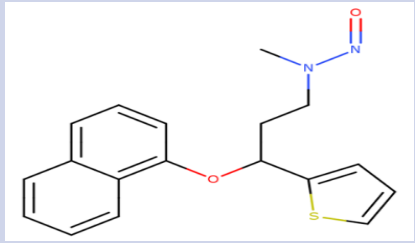
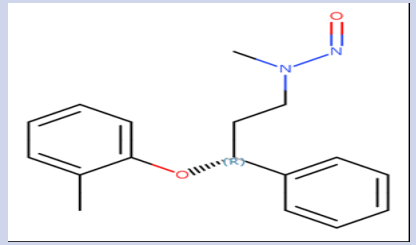
Surrogate	Structure	AI Limit (ng/day)	Health Authorities Used to determine AI limit of Nitrosamines
N-nitroso-dimethylamine (NDMA)		96	FDA
N-nitroso-diethylamine (NDEA)		26.5	EMA/HC
N-nitroso-pyrrolidine (NYPR)		1700	EMA/HC
N-Nitrosodiphenylamine (NDPh)		78000	EMA/HC
N-Nitroso-morpholine (NMOR)		127	EMA/HC

Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

- FDA has published highest number of AI limits for NDSRI's about 279 with ranging from 26.5 ng/day to 1500 ng/day.(except for Interim limits)
- EMA has published about 172 NDSRI's AI limits with ranging from 8 ng/day(NMPEA) to 78000 ng/day (for 4 compounds) and up to NMI (Non mutagenic Impurity- for 10 compounds).
- Health Canada has published about 148 NDSRI's AI limits with ranging from 8 ng/day (NMPEA and NNORT) to 78000 ng/day (for 2 compounds) and up to NMI (Non mutagenic Impurity-for10 compounds).
- Across the Health Authorities difference in Alignment of AI's for structurally same or similar NDSRI's.

Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

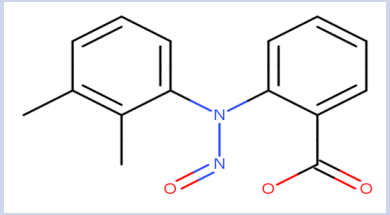
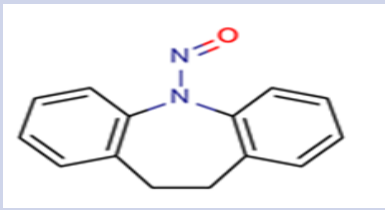
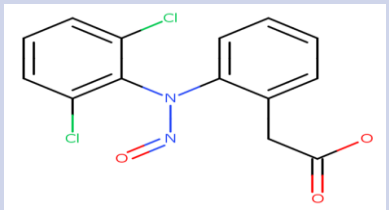
- **Examples of Inconsistency- Case study-1 (NNK Surrogate)**

Source Name	Citalopram	Duloxetine	Atomoxetine
NDSRI Structure			
Name of NDSRI	N-nitroso-Desmethyl-Citalopram	N-Nitroso Duloxetine	N-nitroso-Atomoxetine
Published AI limit	100 ng/day – EMA and HC 26.5 ng/day- FDA	100 ng/day-FDA, EMA and HC	100 ng/day-FDA, EMA and HC
Source of AI	Read Across from NNK-EMA and HC CPCA-FDA	Read across from NNK-FDA,EMA and HC	Read across from NNK-FDA,EMA and HC

- ~ 4 folds difference in published AI limit for Citalopram NDSRI

Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

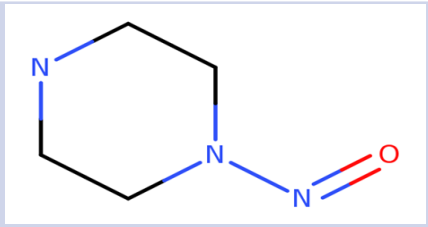
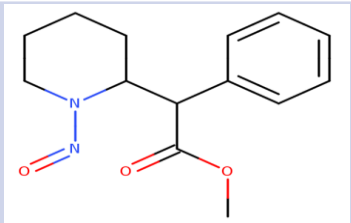
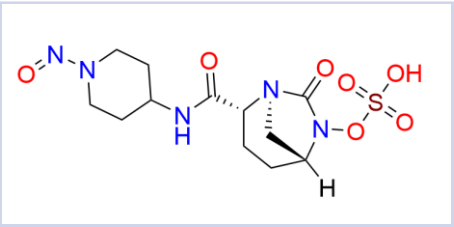
- **Examples of Inconsistency- Case study-2 (N-Nitrosodiphenylamine (NDPh) Surrogate)**

Source Name	Mefenamic Acid	Melipramin	Diclofenac
NDSRI Structure			
Name of NDSRI	N-nitroso-Mefenamic Acid	N-Nitroso Iminodibenzyl	N-nitroso-Diclofenac
Published AI limit	78000 ng/day – EMA and HC Not listed- FDA	78000 ng/day-EMA Not listed- FDA and HC	78000 ng/day-EMA 1500 ng/day-FDA and HC
Source of AI	Read Across from NDPh-EMA and HC N/A-FDA	Read Across from NDPh-EMA N/A-FDA and HC	Read Across from NDPh-EMA CPCA-FDA and HC

- N-Nitroso-diphenylamine is suitable read across substrate for Diclofenac NDSRI
- ~ 52 folds difference in published AI limit for Diclofenac NDSRI

Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

- **Examples of Inconsistency- Case study-3 (N-Nitroso-Piperidine (NPIP) Surrogate)**

Source Name	Ciprofloxacin	Methylphenidate	Relebactam
NDSRI Structure			
Name of NDSRI	N-nitroso-Piperazine	N-Nitroso Methylphenidate	N-nitroso-Relebactam
Published AI limit	1300 ng/day – FDA 400 ng/day – EMA and HC	1300 ng/day-FDA,EMA and HC	400 ng/day- FDA Not listed- EMA and HC
Source of AI	Read Across from NPIP-FDA CPCA- EMA and HC	Read Across from NPIP-FDA, EMA and HC	CPCA-FDA

- ~ 3.25 folds difference in published AI limit.

Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

Specific for Piperidines:

- N-Nitroso-Piperidine (NPIP) Surrogate AI is determined based on Robust Studies.
- Substitutions at 3 and 4 positions of NPIP analogues also proven similar potency to NPIP.
- Substitutions at 2 and 6 positions of NPIP analogues are less potent carcinogens.
- Majority of piperidine Class NDSRIs listed in CPCA Potency Category-3 with AI of 400 ng/day can be suitable for Read Across analysis with NPIP.

Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

Recommendations:

- Align AIs for Structurally related NDSRI's across the Health Authorities.
- Scientific rationale behind differences observed between HA limits for same or similar compounds.
- Streamline the approaches for setting of Interim AI limits.

Nitrosamine Name	Source	Derived AI limit (ng/day)	Recommended Interim AI Limit (ng/day)	Difference from Derived AI
N-Nitroso Ciprofloxacin	Ciprofloxacin	1500	12000	8x
N-Nitroso Duloxetine	Duloxetine	100	600	6x

- Continue to refine and expand activating and deactivating features list for determination of CPCA principles and build structure-based Approach.

Carcinogenic Potency Categorization Approach/Read-Across Analysis from a Surrogate

Recommendations:

- Considerations of NDSRIs with MW>200 Da for-Potency Category-1= 150 ng/day. (Bercu et al., Regulatory Toxicology and Pharmacology https://doi.org/10.1016/j.yrtph.2024.105704)
- Allows for use of multiplier to AI based on real-life exposure durations. Supported by carcinogenicity data for NDEA.(Bercu et al., Regulatory Toxicology and Pharmacology 123 (2021) 104926)
- Harmonization of Global Framework for In Vitro data set that Supports conclusion of an NDSRI is non mutagenic/carcinogenic risk.
- ICH M7 Scientific principles extend to differentiate mutagenic and Non-mutagenic NDSRIs.
- Clear, Transparent and comprehensive similar to other monographs in ICH M7.
- Elaboration of risk assessment and methods to determine control similar to ICH M7 (Options 1-4).

Challenges to Meet Proposed Timelines(August 1,2025) of NDSRI's Testing

- The need to contact the Agency for determined CPCA AI limits for non listed NDSRIs.
- Confusion for implementation of AI limits for Isomers of NDSRIs.
- Require unique and separate method for each NDSRI.
- Lack of recommendation in the guidance for technically not feasible/unstable NDSRI and suitable internal standards.
- Lack of recommendations towards technically not feasible to achieve AI limits and sensitive method LOQ's below 10% of AI for complex dosage forms.
- No Recommendation in the Guidance for Skip testing, if method LOQ's above the 10% of AI.

Reformulation and Bioequivalence Studies Challenges

- FDA has published first ever recommendations in the guidance for Bioequivalence studies for reformulated drug products to mitigate Nitrosamine impurities for IR solid oral or IR Oral Suspension drug products containing of BCS I,II or III class APIs.
- FDA supported research, studied on addition of small amounts of antioxidants like ascorbic acid, α-tocopherol, propyl gallate, or cysteine hydrochloride to formulations inhibit the formation of NDSRIs in drug products.
- The addition of Antioxidants or pH modifiers to control Nitrosamines to bring within the AI limits considered a Level 3 change.
- Most of the instances, the recommendations in the guidance related to the addition of antioxidants or pH adjusters exceed the recommended levels and may not qualify for the recommended BA/BE approach.
- In recent Nitrosamine guidance, Agency expectation is required stability data for 3M ACC (0,1,2 & 3) and long-term (0 & 3M) for three batches, which differs from FDA stability Q&A guidance of one batch is sufficient for post approval changes.
- Other information like methods and AI limits in the NDSRI webpage, recommendations for BA/BE model approaches also make publicly available.