

ICH M7(R2) - Risk-Based Assessment and Control Strategies for Mutagenic Impurities Using Real-World Case Studies (including Manufacturing Processes)

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Disclaimer

- This presentation reflects the personal understanding and opinions of the speaker, and does not represent the official views of International Council for Harmonisation (ICH) as well as the company to which the speaker belongs.
- There is no guarantee of the accuracy of legislative interpretation or the completeness of the information provided.

Overview

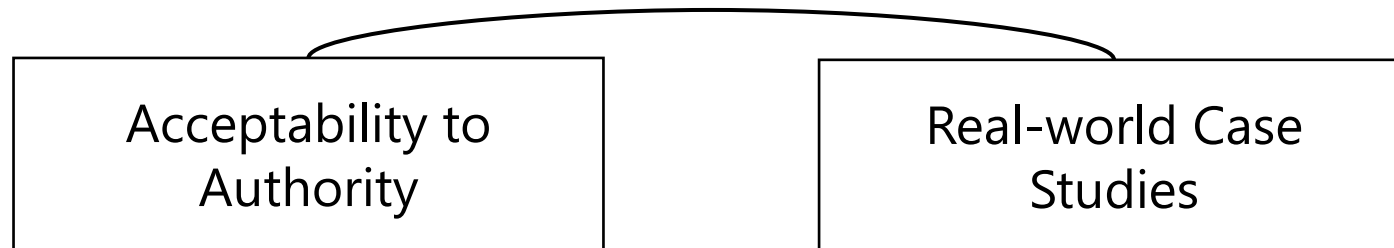
- Purpose and Key Takeaways
 - Enhance understanding of mutagenic impurity control on small molecule and certain biopharma
 - Risk assessment, Control strategy
- Contents
 - Background
 - Process Design and Risk Sources
 - Hazard Assessment (some cases)
 - Control Strategy (some cases)
 - Analytical Procedures and Technologies
 - Preparation of Dossiers and Communication with Authorities
 - N-nitrosamines (some cases)
 - Outlook

Background

- Humans develop cancer due to a variety of factors
- However, it is necessary to reduce cancer risk from pharmaceuticals
 - Carcinogenicity and genotoxicity testing on drug substance
 - Unrealistic to evaluate them of all impurities
- Impurities are trace amounts, then focus on high-risk substances
- Mutagens that act directly on genes are of high concern
- The Ames test: the most accurate in vitro mutagenicity test
 - Outcome can be predicted from structure per correlation studies
 - Guideline is established along with acceptable intakes
- However, there are some kinds of highly mutagenic carcinogens

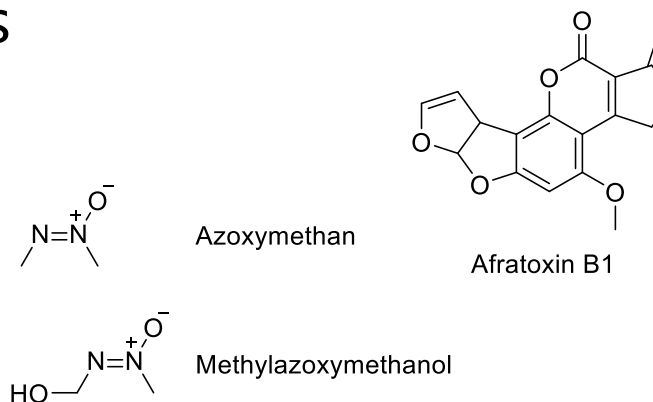
Global Regulatory Landscape (ICH M7)

- Scope
- Impurity classification (Class 1–5)
 - Expert review required
- TTC concept and control options (Option 1–4)
- Latest Q&A (2024) : documentation and interpretation



Mutagens with High Carcinogenic Potency

- ICH M7 specifies following group of compounds
 - aflatoxins (fungi poison)
 - N-nitroso compounds
 - Alkyl azoxy compounds



- <1970's> Detection of N-nitrosamines in Drugs

- Eisenbrand G, Spiegelhalter B, Kann J et al., Carcinogenic N-nitrosodimethylamine as a contamination in drugs containing 4-dimethylamino-2, 3-dimethyl-1-phenyl-3-pyrazolin-5-one (amidopyrine, aminophenazone), *Arzneim-Forsch* 1979;29(6):867-9.
- Gold B, Mirvish SS, N-Nitroso derivatives of hydrochlorothiazide, niridazole, and tolbutamide, *Toxicol Appl Pharmacol*, 1977;40(1):131-6.

- <2018> (post ICH M7) N-nitrosamine in Valsartan and more
- Risk assessment of marketed products begins in earnest

Process Design & Risk Sources

Risk Factors

- Reactive reagents
- Byproduct formation
- Degradation Products

- Changes
 - Impurity identification during route changes
 - Change control and CMC collaboration
 - Integration with ICH Q8/Q9/Q10 principles

What Extent does M7 Apply

- How about biologics?
 - Assessment report, COVID-19 Vaccine Moderna, Common name: COVID-19 mRNA Vaccine (nucleoside-modified), Procedure No. EMEA/H/C/005791/0000
- Control of SM-102 (novel insoluble lipid excipient)
- The applicant will provide an evaluation of mutagenic impurities based on ICH M7

NOT out of consideration

M7 Application Case for Biopharma Processes

- Focus on small molecule components in biopharma
 - Functional additives/excipients
 - Antibody-drug conjugates (ADCs) linker/payload
- Design / Changes requiring (re)evaluation based on ICH M7
 - Each chemical synthesis route/step
 - Degradation products
 - Raw materials
 - Changes alter the structure and properties of by-products
- Explicitly states following are not included
 - Pure protein pharmaceuticals
 - Cell culture-derived products

Hazard Assessment

Assessment whether Impurity is Mutagenic

- Combination of (Q)SAR predictions and actual testing
- (Q)SAR and expert reviews are effective for small molecule impurities with chemical structure
- For biopharmaceuticals, the aforementioned scope is the primary target of assessment
- Recent particular interest :
 - challenges in questioning the reliability of assessments
 - prediction accuracy
 - test system selection
 - regulatory compliance.

(Q)SAR Models & Expert Review

- Scientific support and documentation requirements of prediction
- Model selection: domain applicability and validation
- OECD principles: transparency, applicability, scientific basis
- Expert review: ensure the scientific validity of results
 - Provide practical decision-making
 - Provide knowledge to complement predictions
 - Addressing the limitations of predictive models
 - Supplementing with literature and similar structures
 - Prioritizing actual testing
 - Reflect it in application documents

FDA Expert Review of Impurities under ICH M7

- Review Scope: 1002 impurities evaluated (2017–2019)
- Expert Review Impact: 26% of predictions overturned
- Ambiguous Predictions: 91% clarified by expert review
- Out-of-Domain Predictions: 75% resolved
- Chemical Classes Frequently Reclassified:
 - Aromatic amines (46%)
 - Aldehydes (45%)
 - Michael acceptors (37%)
- Expected Expert Review Contributions:
 - Clarify borderline or equivocal predictions
 - Assess structural analogs and mechanistic plausibility
 - Provide justification for overrides and classification

Foster RS, Fowkes A, Cayley A, Thresher A, Wermer ALD, Barber CG et al., The importance of expert review to clarify ambiguous situations for (Q)SAR predictions under ICH M7. *Genes and Environ* 2020;42:27. <https://doi.org/10.1186/s41021-020-00166-y>

Prediction Competition Case

- Second Ames/QSAR International Challenge Project (2020-2022)
- International efforts to improve the reliability of QSAR models
- Participant tried prediction w/ 12,000 training + 1,589 trial dataset
 - Performance comparisons including deep learning models
- Some models have high sensitivity
- Issue is coverage of chemical space
- Key Points:
 - Limitations and improvements of QSAR models
 - Practical issues in in silico evaluations under ICH M7
 - Regulatory authorities' expectations and outlook

Furuhashi A, Kitazawa A, Yao J, dos Santos CEM, Rathman J, Yang C. Evaluation of QSAR models for predicting mutagenicity: outcome of the Second Ames/QSAR international challenge project. SAR and QSAR Environ Res 2023;34(12):983-1001. <https://doi.org/10.1080/1062936X.2023.2284902>

Improvement of Computational Toxicology

Aspect	Model Performance (Traditional)	Decision Support (Modern)
Focus	Accuracy, statistical performance	Regulatory decision-making, risk assessment
Metrics	Sensitivity, specificity, coverage	Class assignment, TTC application, expert review alignment
Use Case	Model development, academic evaluation	ICH M7 compliance, submission support
Limitations	May not reflect real-world decisions	Requires expert judgment and integration
Evolution	Improving prediction performance	Enhancing transparency and traceability

FDA collaboration
 -ACD/Labs Suite
 - Leadscope Model Applier

Inspired from <https://doi.org/10.1016/j.comtox.2024.100303>

FDA 2024 Poster Summary: Class 4 Impurity Expert Review under ICH M7

- Review Scope: 109 QSAR consultations (2017–2023)
- 13% involved Class 4 impurity discussions
- Common Challenges:
 - Inadequate structural similarity in comparisons
 - Use of positive APIs as reference compounds
 - Insufficient reliability of experimental data
- Expert Review Contributions:
 - Evaluate structural alert location and context
 - Confirm validity of negative comparators (OECD 471 compliance)
 - Assess presence and impact of non-shared alerts

Authority Safety Review Information (1/2)

https://www.ema.europa.eu/en/documents/assessment-report/litfulo-epar-public-assessment-report_en.pdf
(2023/9/18) [Safety]

According to the ICH M7(R1), these impurities would classify as class 3 impurities that need to be controlled below the TTC of 1.5 µg/day. However, for these 5 impurities, no Ames test data were submitted. Instead, the applicant performed a read-across assessment for these impurities (by using structurally similar compounds for which Ames test data were available) and concluded that these 5 impurities possess no mutagenic hazard and can therefore be classified as class 5 impurities.

https://www.ema.europa.eu/en/documents/assessment-report/jeraygo-epar-public-assessment-report_en.pdf-0
(2024/7/24) [Safety]

No risk has been identified and all organic impurities are classified as non-mutagenic (Class 5 according to ICH M7). The applicant submitted missing study reports during the procedure and the reports were assessed to be negative. All studies, with the exception of T-04.072 which relates to impurity ACT-080303, were GLP and OECD guideline 471 compliant. Furthermore, none of other impurities that were tested in GLP AMES tests (ACT-053052, ACT-284043, ACT-056482, ACT-283437, ACT-730960) had an in silico alert but were tested anyway due to suspicious structural properties or as a part of standard company's package.

Authority Safety Review Information (2/2)

https://www.ema.europa.eu/en/documents/assessment-report/balversa-epar-public-assessment-report_en.pdf (2024/8/29) [Quality/Safety (ICH S9)]

, the control and fate of one of these impurities was not sufficiently justified by the applicant and a major objection was raised questioning the control strategy for this impurity. Upon provision of additional comprehensive process-specific data, the major objection was considered resolved. Batch results showed that none of these genotoxic impurities was observed at relevant levels. The depletion of these impurities was demonstrated by the results of spiking studies. In case of a suspected structural alert, an AMES test has been conducted. A following review of human expert knowledge confirmed the final conclusion on mutagenicity (review not presented).

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/215168Orig1s000ChemR.pdf (2024/9/27) [Safety]

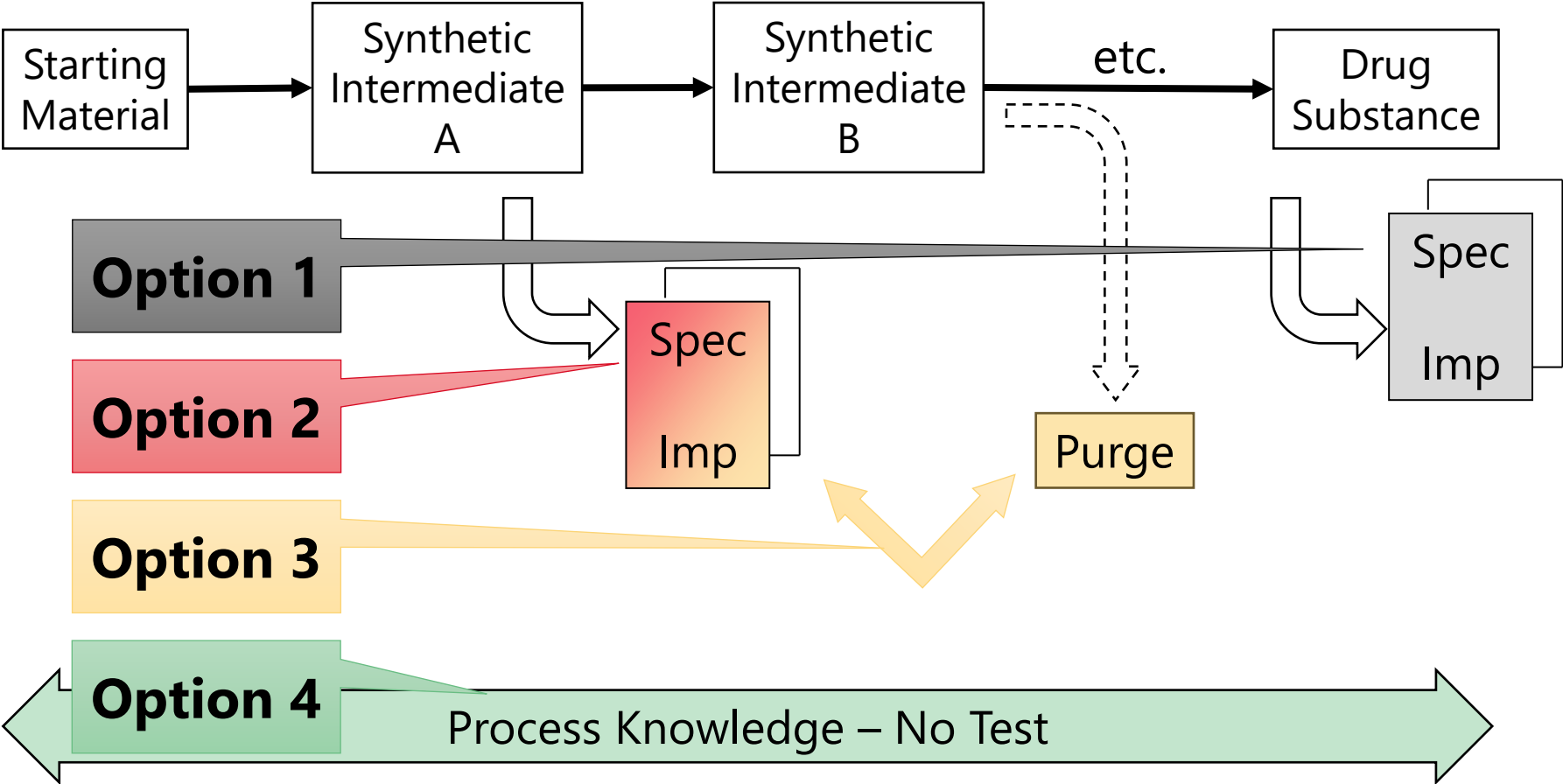
GE justifies the safety of increased impurities levels (both radiochemical and chemical) with biodistribution and PK data in non-clinical analyses as well as the guidance in ICH M7. These issues had been discussed with the FDA division's pharmacology and toxicology team during reviews of amendments to referenced IND 075307 associated with the pre-NDA to NDA 215168; and the P/T team had found the increased levels of all impurities to be acceptable.

Control Strategy

Class-Based Control Options

- Scientific and rational control strategy expected
- TTC or compound specific limit calculation
- Less-than-lifetime exposure consideration
- Options 1–4 control, application conditions and examples

Impurity Control (Strategy) Options



Aspects of Control Strategy Lifecycle

- Material impurity profile control
- Process parameter control
- Product stability and specification
- Change control procedures
- Periodic review and re-evaluation triggers
- Internal processes for regulatory change adaptation

Considerations on Option 4 Control Strategy

- 2. Potential Mutagenic Materials Introduced during Later Processing Stages
 - 2.1. Use of Extraction Partitioning Data to Augment a Purge Rationale
 - 2.2. Use of Spike-Purge to Demonstrate Process Control
 - 2.3. Utilizing Half-Life to Demonstrate Control
- 3. Potential Mutagenic Materials Introduced within Earlier Processing Stages
 - 3.1. Trace Testing for MI in API to Confirm Required Purge Requirements Are Met
 - 3.2. PMI with Insufficient Predicted Purge: How Options 4, 3, 2, or 1 Could Be Justified
 - 3.3. Choosing an Option 3 Control Strategy over an Option 4 Control Strategy
- 4. Measurement of Surrogates for Mutagenic and Potentially Mutagenic Impurities to Justify ICH M7 Option 4 Control
 - 4.1. Routine Testing to Support Last Point of Measurement
 - 4.2. Single Measurement for Multiple Impurities
- 5. Possible Formation of a Potential Mutagenic Impurity in the Final Manufacturing Stage and De-risking Impurity Formation
 - 5.1. De-risking Ethyl Sulfonate Ester Formation in Final Step
 - 5.2. Post Approval Removal of Testing

Urquhart MW, Burns MJ, Clark HF et al., Leveraging ICH M7 Control Options 3 and 4: Discussion and Clarification Using Industrial Case Studies, Org Process Res Dev 2024;28(8):3295-306. <https://doi.org/10.1021/acs.oprd.4c00207>

Purge Prediction Enhancement

- Background
 - Purge is one of the risk management of mutagenic impurities
 - Mirabilis is used in the industry as an in silico purge prediction tool
- Overview of the new method
 - Prediction evolution from traditional structure-based to reaction condition-based
 - Possible judgement closer to a chemist's based on conditions e.g., temperature, reagents, time
- Applicability
 - Risk assessment using purge ratios complies with the ICH M7 Q&A.
 - Supports over 30 impurity types.
- Practical examples
 - High concordance with expert judgment in three cases using Mirabilis.
 - Can also be used for regulatory submissions.

Authority Quality Review Information (1/3)

https://www.ema.europa.eu/en/documents/assessment-report/opzelura-epar-public-assessment-report_en.pdf
(2023/4/20) [Quality]

Upon CHMP's request, another 19 potential impurities were evaluated using Derek Nexus (v 6.1.0) and Sarah Nexus (v 3.1.0). 17 structures were assigned as ICH M7 Class 5 based on absence of a structural alert and will be treated as non-mutagenic impurities. Two structures, MS 305 and INCB042043, were positive in both Derek and Sarah with an alerting structure of potential alkylating agent and assigned ICH M7 Class 3. For all batches of ruxolitinib phosphate drug substance tested, the two impurities were not detected at or above the method detection limit of 1 ppm. Thus, the potential exposure is below the acceptable threshold of toxicological concern (TTC) for mutagenic impurities based on maximum recommended use. Therefore, none of these compounds needed to be further tested for mutagenicity.

https://www.ema.europa.eu/en/documents/assessment-report/vafseo-epar-public-assessment-report_en.pdf
(2023/5/31) [Quality]

It is identified as a metabolite, which is formed in humans, dogs and rats. B504 is not considered of mutagenic potential based on in silico modelling using DEREK Nexus and Leadscope. Several other impurities are identified as mutagenic impurities in the manufacture of vadadustat. However, the Applicant has stated that the impurities are purged in the manufacturing process of the drug substance to levels below the threshold of toxicological concern (TTC) according to ICH M7

Authority Quality Review Information (2/3)

https://www.ema.europa.eu/en/documents/assessment-report/velsipity-epar-public-assessment-report_en.pdf
(2024/2/21) [Quality]

All 7 class 2 or 3 impurities (Bromocyclopentane, AR432054, ethyl 2-oxyacetate, 4 Benzyloxyaniline, AR507614, 5-Me-AR507614, and AR438611) are controlled according to ICH M7 requirements in etrasimod drug substance to not more than 1.5 µg/d patient exposure.
The initially provided nitrosamines risk assessment was not acceptable and a major objection was raised.

https://www.ema.europa.eu/en/documents/assessment-report/obgemsa-epar-public-assessment-report_en.pdf
(2024/7/5) [Quality]

2 major objections as the control strategy for potentially mutagenic impurities had not been adequately justified. Initially, no routine control was proposed and no information on root causes was provided resulting in a major objection. Furthermore, the AI had not been justified in line with latest policy. In response, the applicant proposed a limit of 1500 ng/day based on structural features in line with the carcinogenic potency categorisation approach (CPCA).

Authority Quality Review Information (3/3)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/218808Orig1s000,218820Orig1s000ChemR.pdf
(2024/12/13)

The applicant has used the well-established synthesis for manufacture of the drug substance which adequately controls residual solvents, elemental impurities, and mutagenic impurities as per the applicable ICH guidance. Starting materials are appropriately designated.

https://www.ema.europa.eu/en/documents/assessment-report/beyontra-epar-public-assessment-report_en.pdf
(2025/3/3) [Quality]

some additional mutagenic impurities potentially present in the process related to formation of were omitted from the initial discussion resulting in an MO (major objection). NDMA. While the applicant considered this to be a low risk, the CHMP requested confirmatory testing using a suitably sensitive analytical method as an MO.

Analytical Procedures and Technologies

Application of Analytical Tests

- ICH M7 allows control strategies that do not involve analysis
- Use of analytical techniques
 - Justifying the strategy
 - As part of the control strategy
- Mainstream for trace-level detection: Mass spectrometry
 - Excellent structural elucidation capability
 - Sensitivity, selectivity, quantitation capability
- Analytical method optimization
 - Detect low-level impurities
 - Comply with regulations
- Sample pretreatment
 - Detection accuracy
 - Reproducibility

Sample Preparation & Separation

- For trace impurity detection near quantification limits
- Concentration step
 - Reliably capture components near the lower limit of quantitation
 - Enhance peak detection
- Liquid-liquid extraction (LLE)
 - Effective for selective separation by utilizing polarity differences
 - Recovery is a key. Improve peak shape, interference
- Solid-phase extraction (SPE)
 - Simultaneously remove matrix components and concentrate
 - Recovery is a key. Improve peak shape, interference and detection

Preparation of Dossier and Communication with Authority

Expected Documentations for each Stage

(Background) It is understood that even if in silico assessment is conducted, there would be information not disclosed to authorities.

Phase	Class 1, 2 (Concern)	Class 3 (Alert)	Class 4, 5 (less concern)	in silico info	Ames test
≤14 days Phase 1	Describe efforts to risk mitigation	--	--	--	--
>14 days Phase 1. Phase 2a	(Control strategy)	Include which need analysis control	--	(System info)	--
Phase 2b, 3	(Control strategy)	Provide with plan for control	Provide	System info	Results on actual impurity
Marketing Application	(Control strategy)	(Control strategy)	Supporting info for conclusion	(System info)	Provide study report

(Background) Though there is a mutagenicity database, it is a forward thinking that data will contribute future prediction accuracy.

Points to Address in Regulatory Review of Mutagenic Impurities

- Points to consider
 - Utilize guideline including Q&As on content of application documents
 - Providing scientific evidence and accountability for mutagenic impurities
- Recent point of interest is the reviewer's area of concern
 - Validity of tools and quality of expert review
 - Regulatory authorities may view relatively in expensive commercial systems
e.g., validation perspective
 - Dealing with discrepancies between predictions
 - Dealing with discrepancies between predictions and measurements
 - "why was the prediction positive?" (limitation)
 - "were the Ames test conditions appropriate?" (suitability)

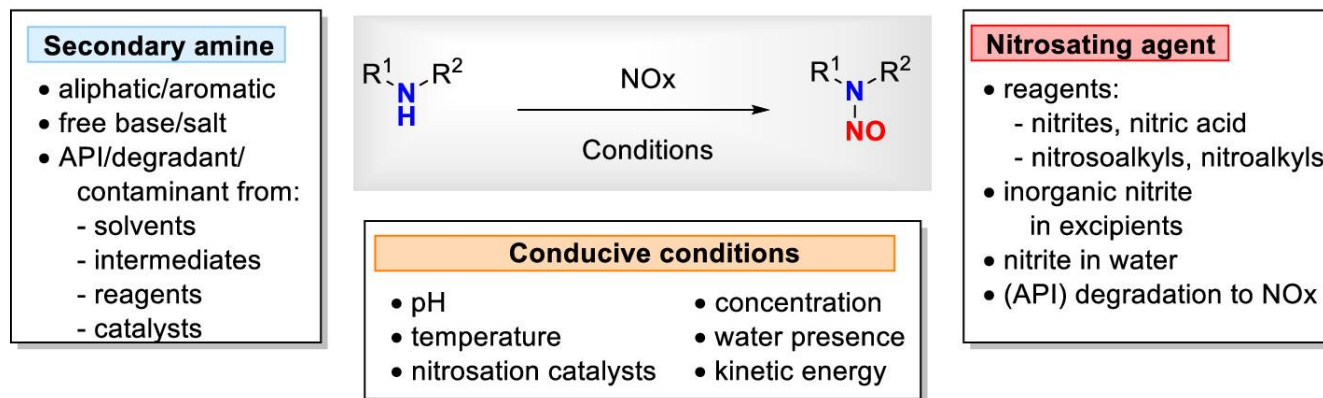
Summary of Regulatory Documentation & Interactions

- Structuring submissions per ICH M7
- Utilizing M7 Q&A for justification
- Reviewer concerns: prediction / calculation vs. experimental results
- Cross-functional collaboration: R&D, QA, RA, Manufacturing

N-nitrosamines

N-nitrosamine Drug Substance Related Impurities (NDSRIs)

N-nitrosamine formation in **drug substance** and **drug product**:
3 risk factors - **ALL** required:



- Review of formation mechanisms and risk factors of NDSRIs
- Emphasizing their complexity and unpredictability in drug products
- Highlight the need for improved scientific understanding and regulatory strategies

Can we Judge N-nitrosamines by Ames test?

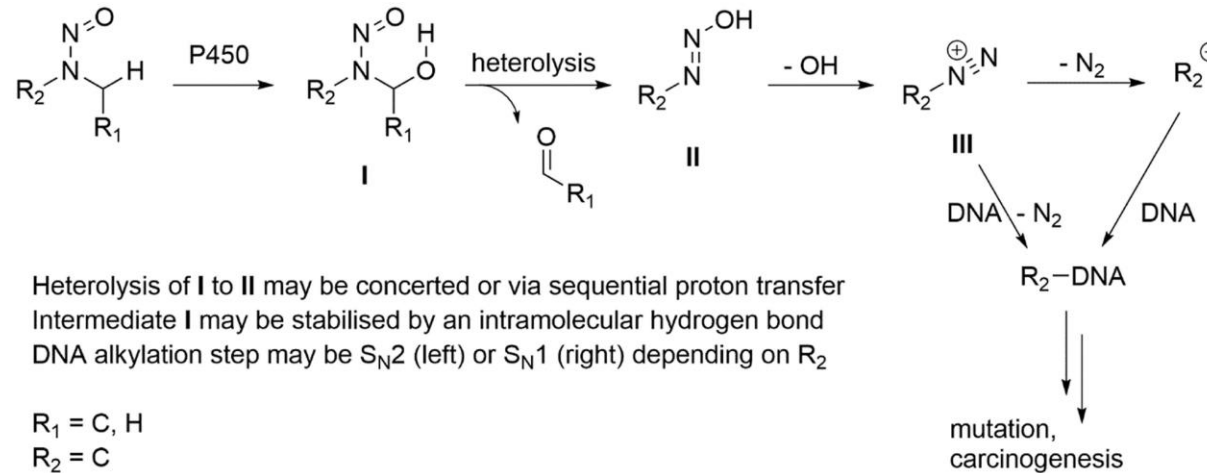
- TA1535 and WP2 uvrA (pKM101) were the most informative tester strains for evaluating the mutagenicity of the set of 29 small-molecule nitrosamines and NDSRIs.
- with hamster liver S9 generally producing greater mutagenic responses than rat liver S9.
- preincubations conducted with S9 mixes containing 30% S9 generally produced greater mutagenic responses than preincubations conducted with S9 mixes containing 10% S9.

Heflich RH, Bishop ME, Mittelstaedt RA. et al., Optimizing the detection of N-nitrosamine mutagenicity in the Ames test. Regul Toxicol Pharmacol 2024;105709. <https://doi.org/10.1016/j.yrtph.2024.105709>

Details are expected to be discussed in ICH M7 sub group activity

Background of CPCA on N-nitrosamines

CPCA: carcinogenic potency categorisation approach



Cross KP, Ponting DJ, Developing structure-activity relationships for N-nitrosamine activity *Comput Toxicol* 2021;20:100186.
<https://doi.org/10.1016/j.comtox.2021.100186>

- Structural features included in the CPCA are those that have been identified as directly impacting the α -hydroxylation pathway and, consequently, carcinogenic potency.
- Evaluated Features : α -Hydrogen, Deactivating (6 types), Activating (2 types), Additional (2 types)

Kruhlak NL, Schmidt M, Froetschl R et al., Determining recommended acceptable intake limits for N-nitrosamine impurities in pharmaceuticals: Development and application of the Carcinogenic Potency Categorization Approach (CPCA). *Regul Toxicol Pharmacol* 2024;150:105640. <https://doi.org/10.1016/j.yrtph.2024.105640>

Applicability of Control Strategy to N-nitrosamines

- Background
 - Attracting global attention especially for commercial products
 - Applicability of Control Option 3 and 4 (purge discussions) through actual cases
- Methodology and Results
 - Eight industrial cases to evaluate the possibility of formation and purge
 - Some initial scientific justifications under control options 3/4 were not accepted
 - These were supported by additional experimental data e.g., spiking studies
- Conclusion
 - Scientifically based purge prediction pre M7 is useful for regulatory submissions
 - Control Options 3 and 4 were shown to be practical and compliant approaches

Urquhart MW, Burns MJ, Bernardoni F, Clark HF, Crochard JP, De Benedetti A et al., Industrial Case Studies Demonstrating Applicability of ICH M7 Control Options 3 and 4 for Nitrosamine Control, Org Process Res Dev 2025;29(4):1152-67. <https://doi.org/10.1021/acs.oprd.5c00042>

- Two nitrosamine case studies were presented last year

<https://www.kobia.kr/imagebox/upload/20241014143112.pdf>

Authority Review Information (1/2)

https://www.ema.europa.eu/en/documents/assessment-report/urneffy-epar-public-assessment-report_en.pdf
(2024/6/27)

Risk assessed considering all suspected and actual root causes in line with the in line with the EMA/409815/2020 and EMA/369136/2020. An MO was raised as the information initially provided was incomplete since it did not fully address risks from all manufacturers involved in the API process and identified the possibility of nitrosation of epinephrine and other amines in the formulation in the slightly acidic solution environment. In response, the applicant provided an updated risk assessment arguing there is no source of nitrosating agents in the formulation. Furthermore, test data demonstrated that none of the tested nitrosamines, including N-nitrosoepinephrine (AI = 100 ng/day based on CPCA), were detected using a suitably sensitive analytical method.

https://www.ema.europa.eu/en/documents/assessment-report/zegalogue-epar-public-assessment-report_en.pdf
(2024/5/30)

The ASMF holder was requested, as MO, to provide a rationale for the risk assessment of nitrosamines presence and carry-over, also taking into consideration starting materials, process reagents and process solvents (low molecular amine precursors are observed during synthesis). Nitrite and nitrate levels of the water are not presented, the applicant indicated that a risk evaluation was conducted and that no risk of presence of nitrosamines was identified. The applicant submitted an additional risk assessment which takes into consideration the active substance manufacturing process, herewith including the evaluation of the impact of reagents and solvents. In this risk assessment the potential presence of nitrites has been identified and analytical tests have been carried out in order to determine the nitrites content and eventual carry-on into dasiglucagon. The risk is considered negligible, but as additional measure, the manufacturer if the finished product will test for nitrites all incoming batches in the future.

Authority Review Information (2/2)

https://www.ema.europa.eu/en/documents/assessment-report/obgemma-epar-public-assessment-report_en.pdf
(2024/4/25)

Risk assessed considering all suspected and actual root causes in line with the EMA/409815/2020 and EMA/369136/2020. N-nitrosovibegron was detected in some batches of finished product below the proposed acceptable intake (AI). Initially, no routine control was proposed and no information on root causes was provided resulting in a major objection. Furthermore, the AI had not been justified in line with latest policy. In response, the applicant proposed a limit of 1500 ng/day based on structural features in line with the CPCA. Further data from stability batches was also provided, demonstrating compliance with the specification throughout the proposed shelf-life. A routine control for N-Vib is included in the finished product specification (20 ppm, equivalent to 1500 ng/day). The applied LCMS/MS analytical method has been suitably validated at the required sensitivity.

https://www.ema.europa.eu/en/documents/assessment-report/litfulo-epar-public-assessment-report_en.pdf
(2023/7/30)

Risk assessed (as requested in a Major Objection) considering all suspected and actual root causes in line with the EMA/409815/2020 and the EMA/369136/2020. Specific details of the expected nitrite level in each component of the finished product have been provided and the details on the analytical procedure (LC-UV/MS) used for the analysis of nitrosamines in WHO NAP test and acetic acid standard conditions, as well as the results of the experiments performed to test the reactivity of the active substance and its impurities towards nitrosation, have been provided. Discussed in the context of the conditions existing in the finished product and are considered extreme / forced degradation conditions. The potential risk of nitrosamine formation from packaging has also been addressed. The overall risk for nitrosamine formation is negligible. The API-specific nitrosamine impurity has been shown to be not detected (LOD < 10% of AI of 18 ng/day), and no further control is considered necessary.

Future Outlook

FDA SafetAI Initiative Summary

- Goal: Support IND safety assessments using AI-based toxicity prediction models.
- AI Models Developed:
 - DeepAmes (Mutagenicity)
 - DeepCarc (Carcinogenicity)
 - DeepDILI (Liver toxicity)
 - Kidney toxicity model
 - DICTrank (Cardiotoxicity)
- Technical Approach:
 - Deep learning models tailored to chemical structure.
 - Improved accuracy and domain applicability.
- Regulatory Applications:
 - Preclinical risk assessment.
 - Supports 3Rs (Replacement, Reduction, Refinement) in toxicology.
 - Potential integration into IND review workflows.

ICH M7 Sub-group Work Plan

Expected future completion date	Milestone
Jun. 2028	Step 1 Consensus reached on draft Technical Documents
Aug. 2028	Step 2a/2b – Confirmation of Technical Document by Assembly and Adoption of draft guideline by Regulatory Members
Dec. 2029	Step 3 Public consultation and address comments
Mar. 2030	Step 4 Finalize Guidance

End

Linker Case

- https://www.ema.europa.eu/en/documents/assessment-report/datroway-epar-public-assessment-report_en.pdf
 - The control strategy for the impurities including organic impurities, stereoisomers, residual solvents, elemental impurities and mutagenic impurities (including nitrosamines) for MAAA-1162a was provided.