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EUROPEAN MEDICINES AGENCY

Stakeholder webinar on

Reflection paper on the qualification of non-mutagenic impurities

06 March 2025

Agenda

- Opening of the Event
- Update of reflection paper: purpose & overview of the content and proposed changes
- Questions & Answers
- Wrap up & closure

Opening of the event

Moderator and speakers

Leon van Aerts
Moderator

Marianne Schmidt
Chair of drafting group

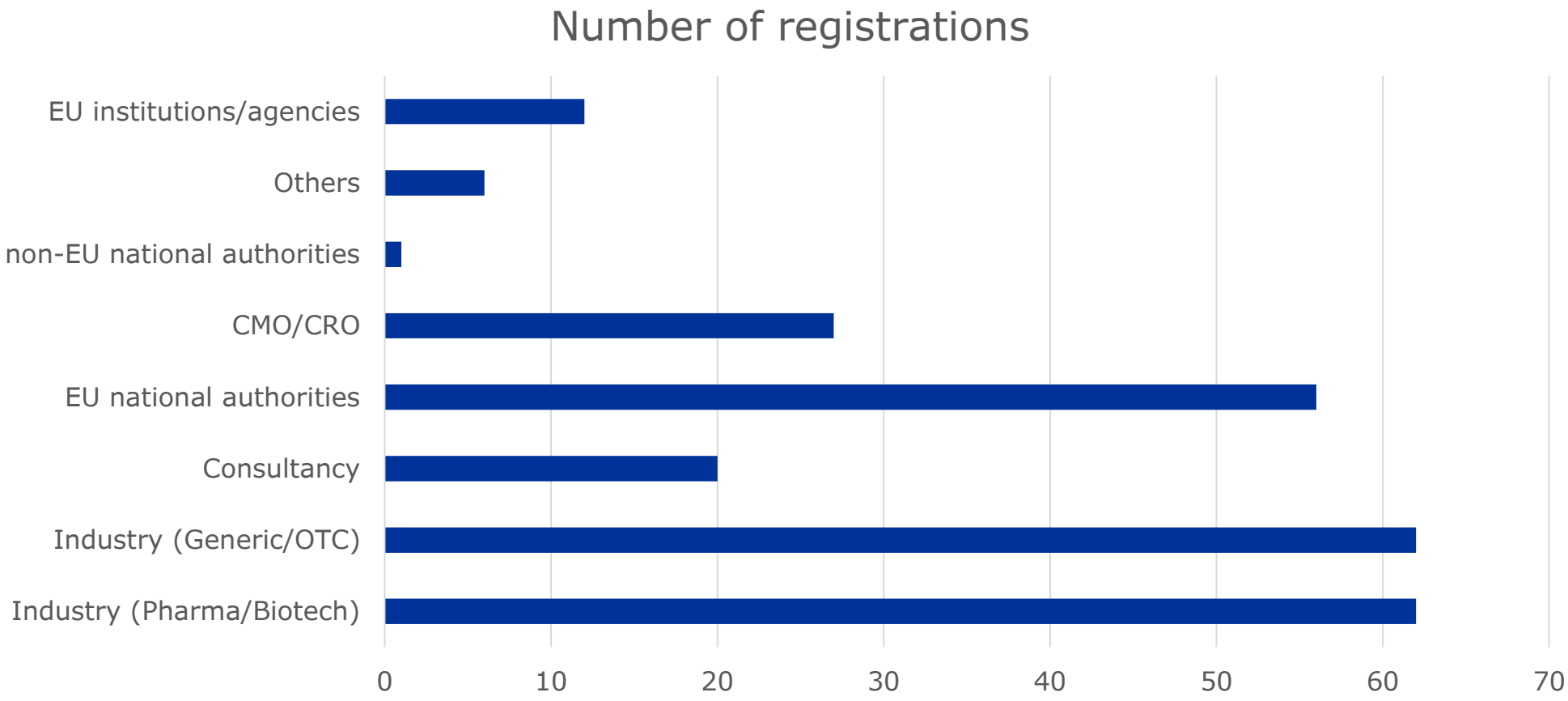
Roland Frötschl

Dominique Masset

Objectives of the webinar

- Explaining the content and main changes implemented in the update draft reflection paper
- Illustrating the ongoing public consultation and providing guidance on how stakeholders can contribute
- Adressing questions and requests for clarification received from stakeholders

Overview of registrants



Update of reflection paper: purpose & overview of the content and proposed changes

Leon van Aerts, Marianne Schmidt,
Roland Frötschl and Dominique Masset

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Scope of the revision

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 November 2018
EMA/CHMP/SWP/545588/2017
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on the qualification of non-genotoxic impurities

Draft

Draft agreed by Safety Working Party	October 2018
Adopted by CHMP for release for consultation	15 November 2018
Start of public consultation	23 November 2018
End of consultation (deadline for comments)	30 September 2019

Comments should be provided using this template. The completed comments form should be sent to SWP-H@ema.europa.eu

Keywords	***Non-genotoxic impurities, pharmacology, toxicology, threshold of toxicological concern, read across, animal testing, in vitro testing, 3R's.***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Stakeholder's comments and scientific publications

New DG after pandemic

Redraft taking into account comments

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

02 December 2024
EMA/CHMP/543397/2024
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on the qualification of non-mutagenic impurities

Draft

Draft agreed by NcWP	09 October 2024
Adopted by CHMP for release for consultation	02 December 2024
Start of public consultation	30 January 2025
End of consultation (deadline for comments)	30 April 2025

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Non-mutagenic impurities, pharmacology, toxicology, threshold of toxicological concern, read across, animal testing, *in vitro* testing, 3Rs.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Main sections of the reflection paper

Introduction

Scope

Key considerations

- General outline for risk assessment of NMIs
- Level of concern considerations
- Acceptable level calculations
- New approach methodologies
- API-like vs non-API-like
- Metabolites
- In vivo quantification studies
- Products under clinical development

Historical background

- A first draft RP was released in 2018
- Main comments from stakeholders concern:
  - *Providing clarity on exceeding Q3A/B limits during early development.*
  - *Use of 1 mg as limit for all drug products under 2g under Q3A/B*
  - *Providing guidance on the acceptance of alternative methods to replace in vivo qualification studies when these are required.*
  - *Maximizing the results from in vivo studies used to show safety of the drug substance for qualifying impurities*
  - *Consideration of risk/benefit of the pharmaceutical for qualification of impurities.*
- The current draft Reflection Paper on the Qualification of Non-Mutagenic Impurities (NMI) addresses all of these comments

Stakeholders publications

Regulatory Toxicology and Pharmacology xxx (2017) 1–8

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Commentary

Management of organic impurities in small molecule medicinal products: Deriving safe limits for use in early development

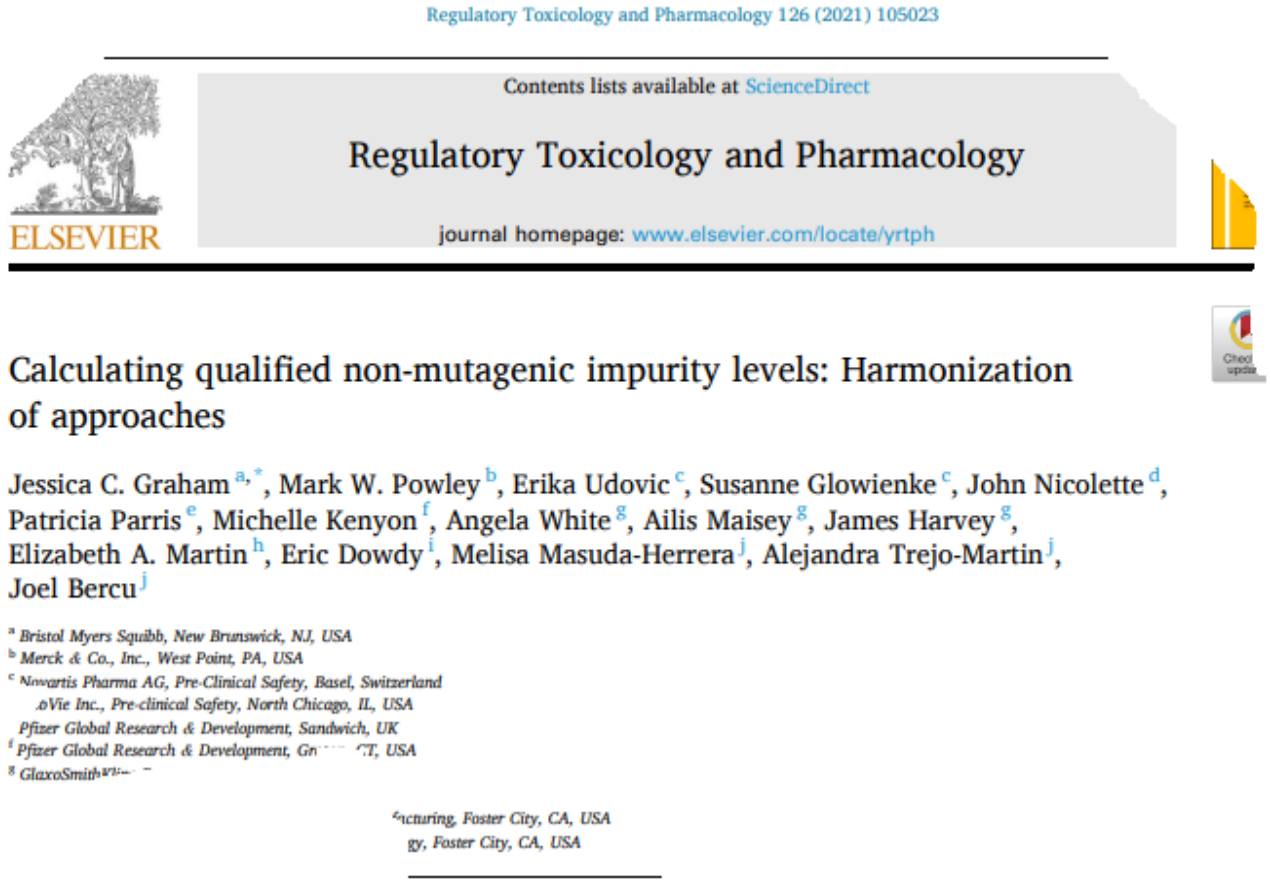
James Harvey [a, *], Andrew Fleetwood [b], Ron Ogilvie [b], Andrew Teasdale [c], Phil Wilcox [a], Steven Spanhaak [d]

[a] GlaxoSmithKline R&D, Park Road, Ware, Hertfordshire, SG12 0DP, United Kingdom
[b] Pfizer, Ramsgate Road Sandwich, Kent, CT13 9N, United Kingdom
[c] AstraZeneca, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NX, United Kingdom
[d] Janssen R&D, Turnhoutseweg 30, 2340 Beerse, Belgium

- Focus on early clinical trials
- Not regulated by Q3A/B ⇔ requests from RAs
- 1 mg/day for NMI in drug substance as QT for DS when DDI >666 mg as defined in Q3A as starting point
- Modified Haber's law to transform to short-term use →5 mg/day as QT for early clinical tyrials

Stakeholders publications

- Pharmaceutical industry-wide survey by IQ Consortium on current impurity qualification practices
- Use of the DS NOAEL
- Does not favor use of BSA/HED conversion
- Data on 181 intermediates and starting materials (‘INTs’)
- When MDD = 2 g (taken from table 2)
  - 18% of cases safety margin is ≤100
  - 53% of cases safety margin is ≤500



Regulatory Toxicology and Pharmacology 126 (2021) 105023

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Calculating qualified non-mutagenic impurity levels: Harmonization of approaches

Jessica C. Graham [a,*], Mark W. Powley [b], Erika Udovic [c], Susanne Glowienke [c], John Nicolette [d], Patricia Parris [e], Michelle Kenyon [f], Angela White [g], Ailis Maisey [g], James Harvey [g], Elizabeth A. Martin [h], Eric Dowdy [i], Melisa Masuda-Herrera [j], Alejandra Trejo-Martin [j], Joel Bercu [j]

[a] Bristol Myers Squibb, New Brunswick, NJ, USA
[b] Merck & Co., Inc., West Point, PA, USA
[c] Novartis Pharma AG, Pre-Clinical Safety, Basel, Switzerland
AbVie Inc., Pre-clinical Safety, North Chicago, IL, USA
Pfizer Global Research & Development, Sandwich, UK
[f] Pfizer Global Research & Development, Gr[illegible]CT, USA
[g] GlaxoSmith[illegible]

[illegible]cturing, Foster City, CA, USA
gy, Foster City, CA, USA

Stakeholders publications

Regulatory Toxicology and Pharmacology 147 (2024) 105559

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Non-mutagenic impurities – Recent industry experience of using dose durational limits in drug development☆

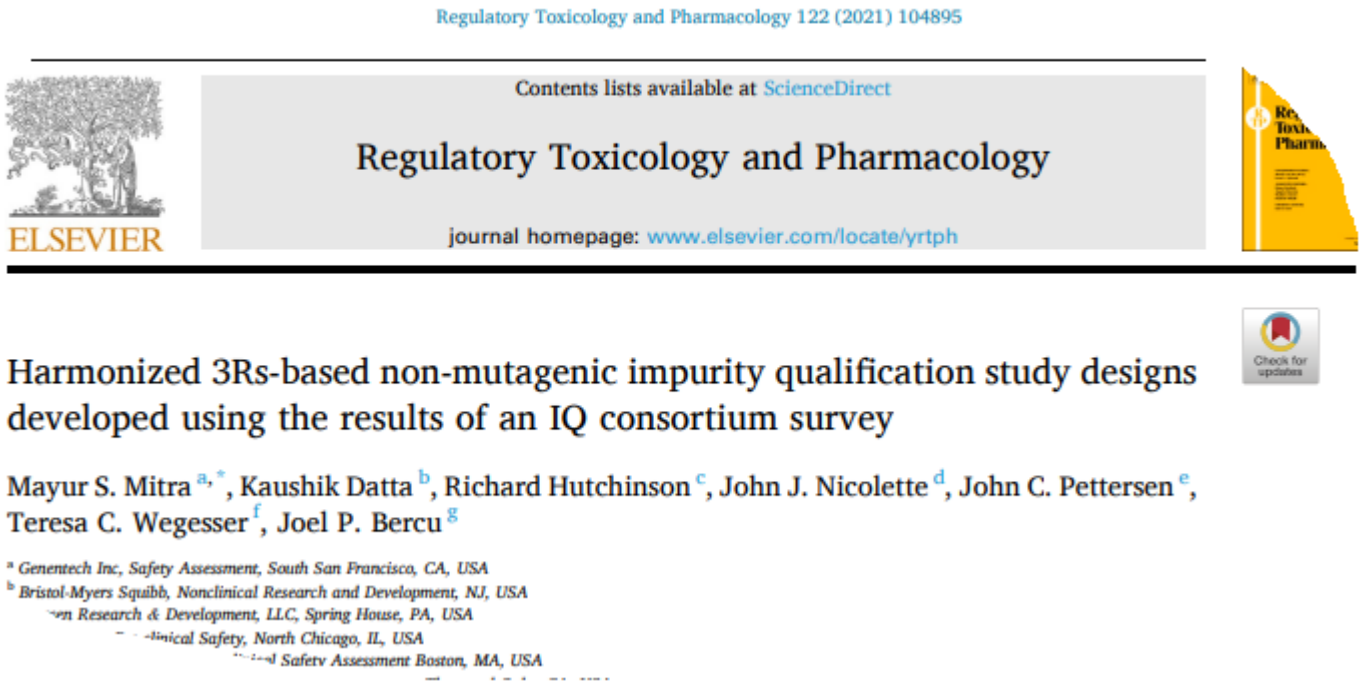
Andreanne Lortie [a,*], Elizabeth A. Martin [b], Kate Arnot [c]

[a] Non-Clinical Drug Safety, Ipsen, Les Ulis, France
[b] Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Cambridge, UK
[c] MC Regulatory Affairs, AstraZeneca, Macclesfield, UK

- Survey from EFPIA on 13 case studies of NMI qualification amongst 6 member companies
- Variations in companies strategies and RAs acceptance evident

Stakeholders publications

- Based on IQ consortium survey (Graham et al 2021)
- Provides recommendations for impurity qualification study design



Regulatory Toxicology and Pharmacology 122 (2021) 104895

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

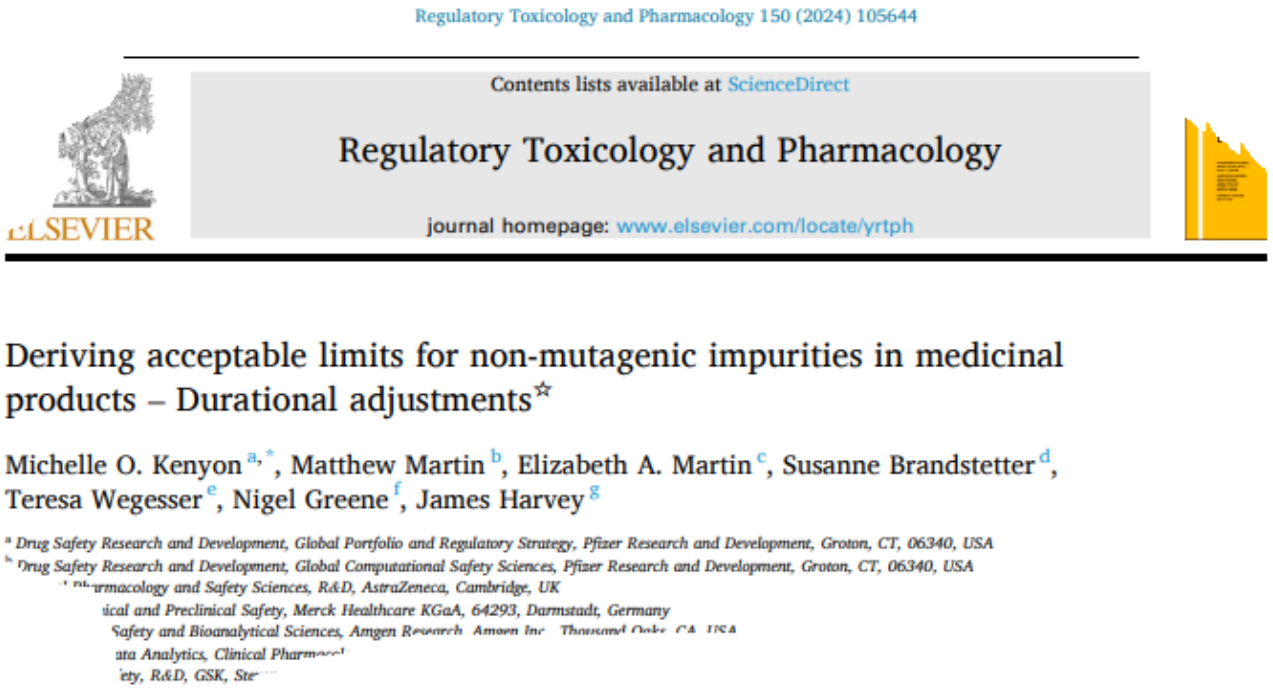
journal homepage: www.elsevier.com/locate/yrtph

Harmonized 3Rs-based non-mutagenic impurity qualification study designs developed using the results of an IQ consortium survey

Mayur S. Mitra [a,*], Kaushik Datta [b], Richard Hutchinson [c], John J. Nicolette [d], John C. Pettersen [e], Teresa C. Wegesser [f], Joel P. Bercu [g]

[a] Genentech Inc, Safety Assessment, South San Francisco, CA, USA
[b] Bristol-Myers Squibb, Nonclinical Research and Development, NJ, USA
[c] ...en Research & Development, LLC, Spring House, PA, USA
... ...inical Safety, North Chicago, IL, USA
... ...l Safety Assessment Boston, MA, USA

Stakeholders publications



Regulatory Toxicology and Pharmacology 150 (2024) 105644

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Deriving acceptable limits for non-mutagenic impurities in medicinal products – Durational adjustments☆

Michelle O. Kenyon [a,*], Matthew Martin [b], Elizabeth A. Martin [c], Susanne Brandstetter [d], Teresa Wegesser [e], Nigel Greene [f], James Harvey [g]

[a] Drug Safety Research and Development, Global Portfolio and Regulatory Strategy, Pfizer Research and Development, Groton, CT, 06340, USA
[b] Drug Safety Research and Development, Global Computational Safety Sciences, Pfizer Research and Development, Groton, CT, 06340, USA
[ ] rmacology and Safety Sciences, R&D, AstraZeneca, Cambridge, UK
ical and Preclinical Safety, Merck Healthcare KGaA, 64293, Darmstadt, Germany
Safety and Bioanalytical Sciences, Amgen Research, Amgen Inc, Thousand Oaks, CA, USA
ata Analytics, Clinical Pharmacol
ety, R&D, GSK, Ste

- Distribution of NOAELs for 4978 chemicals studied
- Argues that data support 1 mg/day as a safe threshold for NMI in pharmaceuticals.
- Suggests that NMI levels < 20 mg/day and < 5 mg/day are considered safe in clinical trials with <1 month and >1 month but <6 months duration, respectively

Stakeholders publications

- Analysis of 2213 chemicals
- 0.6% have PoD <0.02 mg/kg/day (‘very potent’)
- 2.4% have PoD <0.2 mg/kg/day (‘potent’)
- Potent structural classes were identified including organothiophosphates and derivatives, polychlorinated benzenes and polychlorinated polycyclic aliphatics
- Additionally, likely potent classes included cyclic aliphatic organothiols, steroids and derivatives, and inorganic chlorine oxides.
- Considerable number of miscellaneous potent compounds

Regulatory Toxicology and Pharmacology 150 (2024) 105645

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Analysis of non-mutagenic substances in the context of drug impurity assessment – Few are potent toxicants

Catrin Hasselgren [a,*], Michelle Kenyon [b], Lennart T. Anger [a], Paul Cornwell [c], Eric Watt [b], Joel Bercu [d]

...rtment of Safety Assessment, Genentech, Inc., South San Francisco, CA, 94080, USA
...fety Research and Development, Pfizer Research and Development, Groton, CT, 06340, USA
... Assessment, Eli Lilly & Co, Indianapolis, IN, 46285, USA
... Safety and Pathobiology (NSP), Foster City, CA, 94404, USA

Stakeholders publications

ELSEVIER

Regulatory Toxicology and Pharmacology

Volume 150, June 2024, 105647

New limits proposed for the management of non-mutagenic impurities

Anja Slikkerveer [a], Olaf Doehr [b], Nancy Claude [c], Richard Hutchinson [d], James Harvey [e], Steven Spanhaak [f 1]

- EFPIA survey on qualification studies
- 467 NMIs
- Majority of impurities studied in spiked DS batches
- Only 1.3% studied as neat impurity
- These studies do not provide a unique safety signal for these impurities
- Proposes 5 mg/day and 1 mg/day as QT for CTs <6 months and lifelong exposure, respectively

Stakeholders publications

- Strategies for qualification and RAs assessments vary
- 1 mg/day considered as a safe threshold; 5 mg/day for early clinical trials (< 6 months).
- Testing in 28-day rat study with (spiked) DS batch most common
- No concerning signals detected in these studies

- Stakeholder papers provide relevant information and are valuable when considering strategies for qualification of NMI
- NOAEL in animal study considered safe for human exposure without consistent application of modifying factors to allow for interindivual variation, species differences, study duration, seriousness of toxicity, correction when PoD is not a NOAEL, and route-to-route extrapolations
- Studies with (spiked) DS batches are often non-informative
- Qualification still relies on traditional use of animal studies without considering non-animal approaches

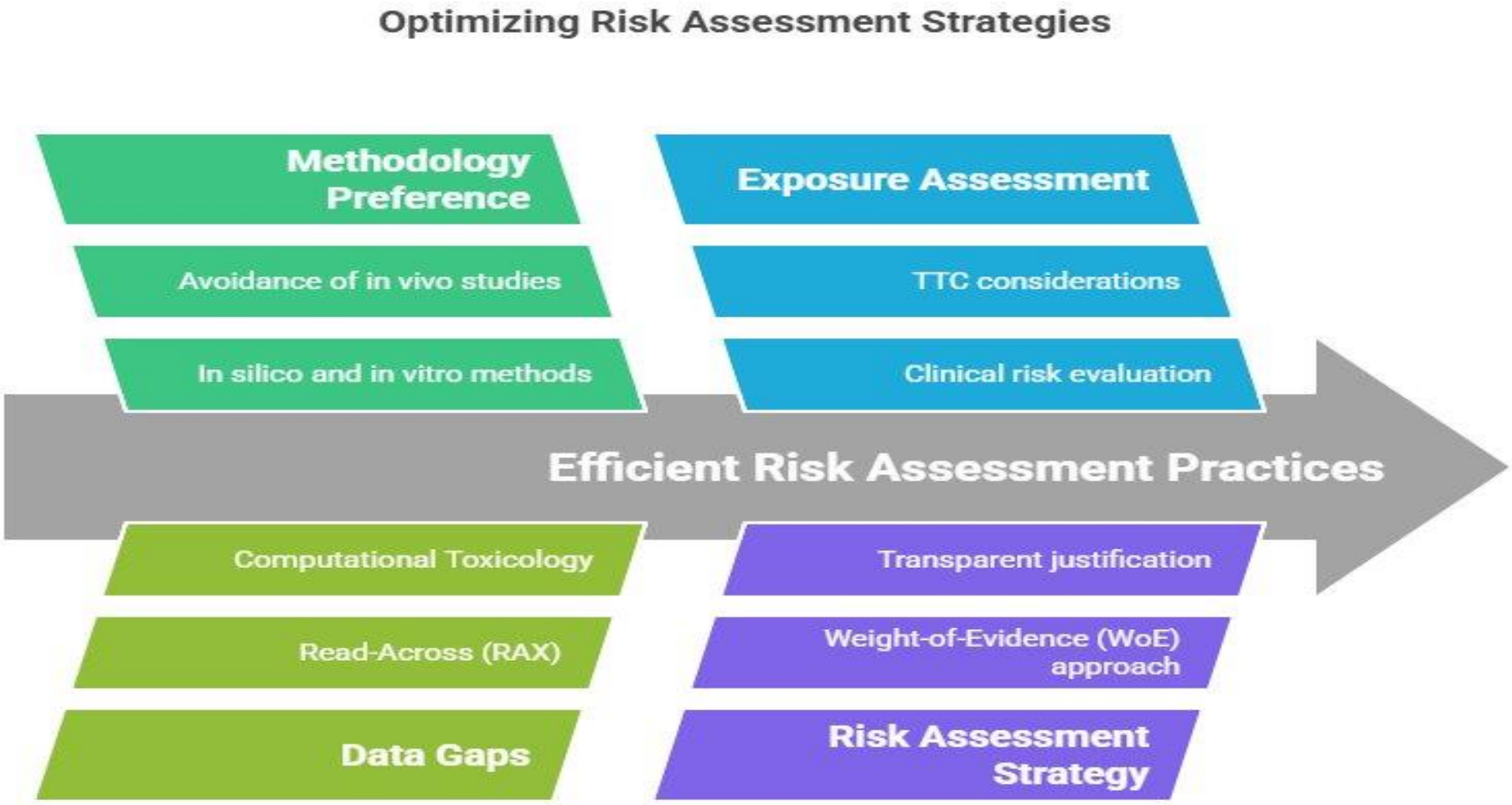
Problem statement

- Presence of impurities in drug substances (DS)/drug products (DP) are inevitable
- ICH Q3A/B are main guidelines providing the requirements for qualification of impurities in DS/DP
- Qualification means providing safety information on the impurity at the proposed specification level
- Impurities present in DS/DP batches at relevant levels in (non-) clinical safety studies are considered qualified
- Separate qualification needed when novel impurities appear or higher specification levels are proposed
- Current practice means testing of DS batches in animal studies
- Such studies never reveal safety concerns, and are of little value to inform on the safety of the novel impurity
- Guidance on compound-specific qualification of impurities when it concerns mutagenic carcinogens (M7), solvents (Q3C), elemental impurities (Q3D) and (in the future) E&L (Q3E)
- Need to move away from animal testing of novel impurities and make a compound-specific assessment

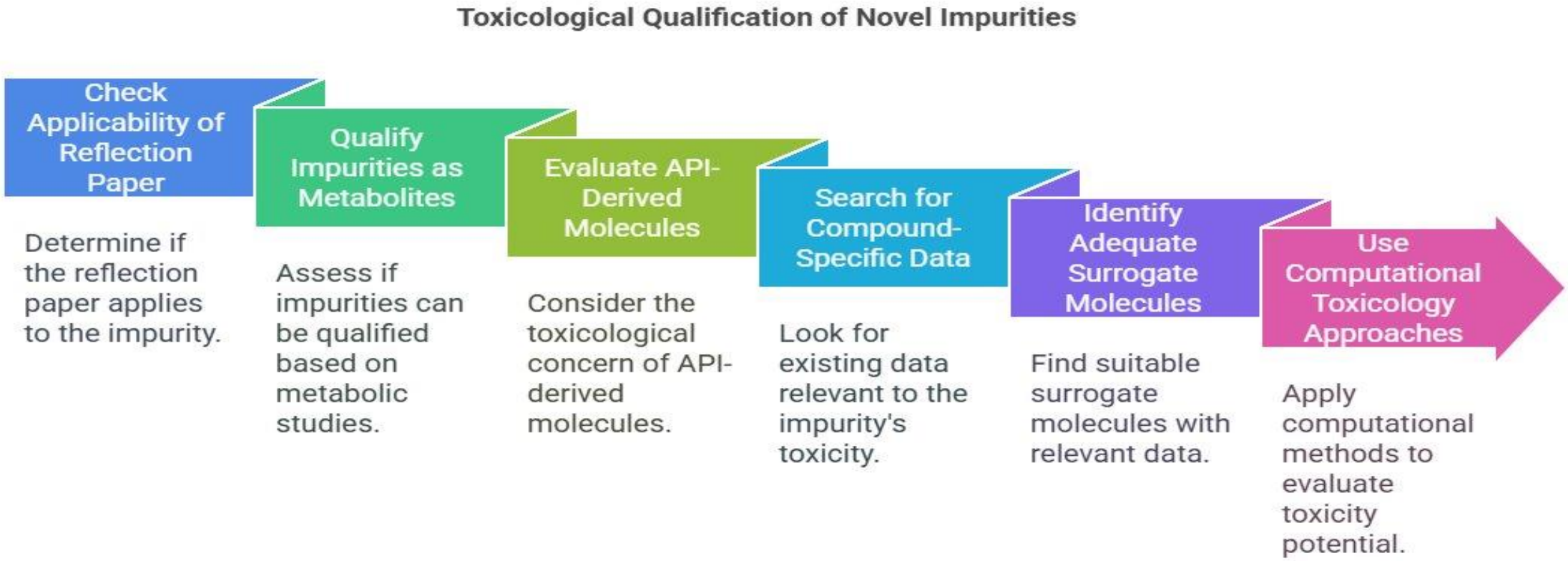
Scope of reflection paper

- Chemically synthesized pharmaceuticals
- When these are not covered by existing guidances
  - Solvents, elemental impurities, E&L (future), oligonucleotides, peptides, radiopharmaceuticals
- Reflection paper aimed at qualifying novel impurities or higher levels of impurities
  - Change of manufacturing process, newly discovered impurities
- Non mutagenic impurity (NMI) considered qualified when adequately tested in safety studies and/or clinical trials
- Not in scope:
  - ATMP, biological and biotechnological derived pharmaceuticals, herbal medicinal products
  - Clinical trials, but principles may be used to guide determination of level of concern and provide qualification data if considered necessary.

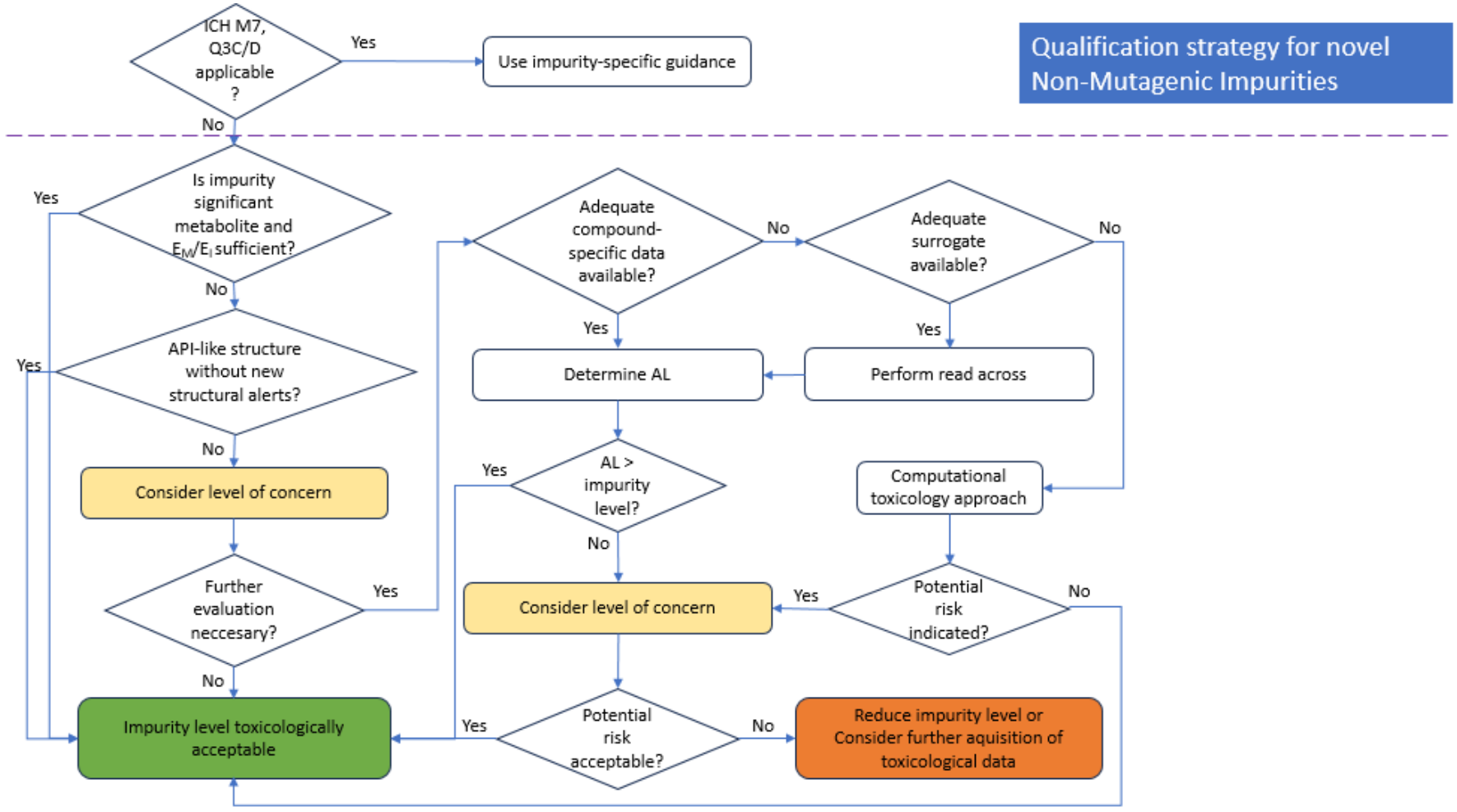
Key considerations: General outline for risk assessment



Key considerations: General outline for risk assessment



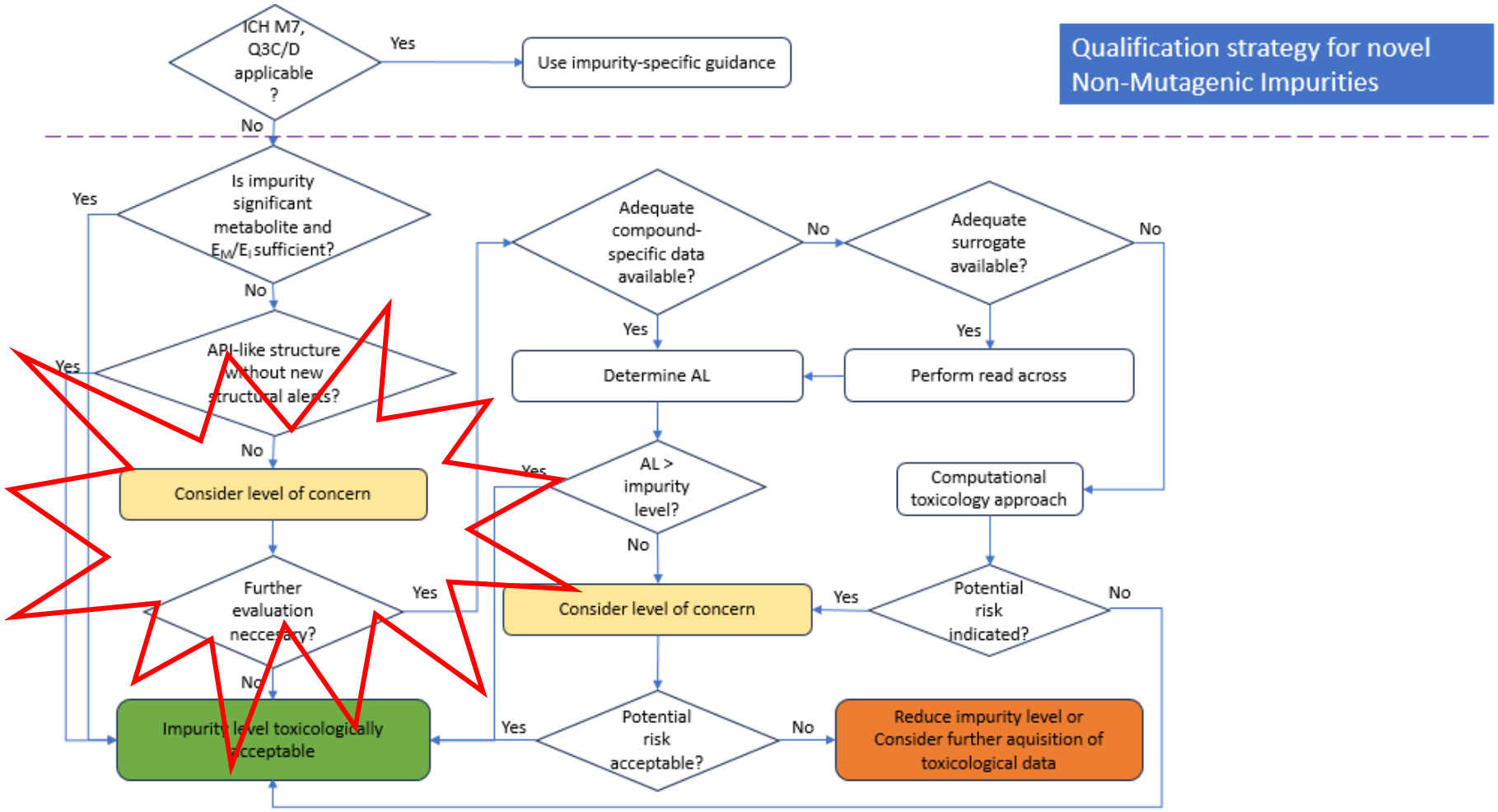
Key considerations: General outline for risk assessment



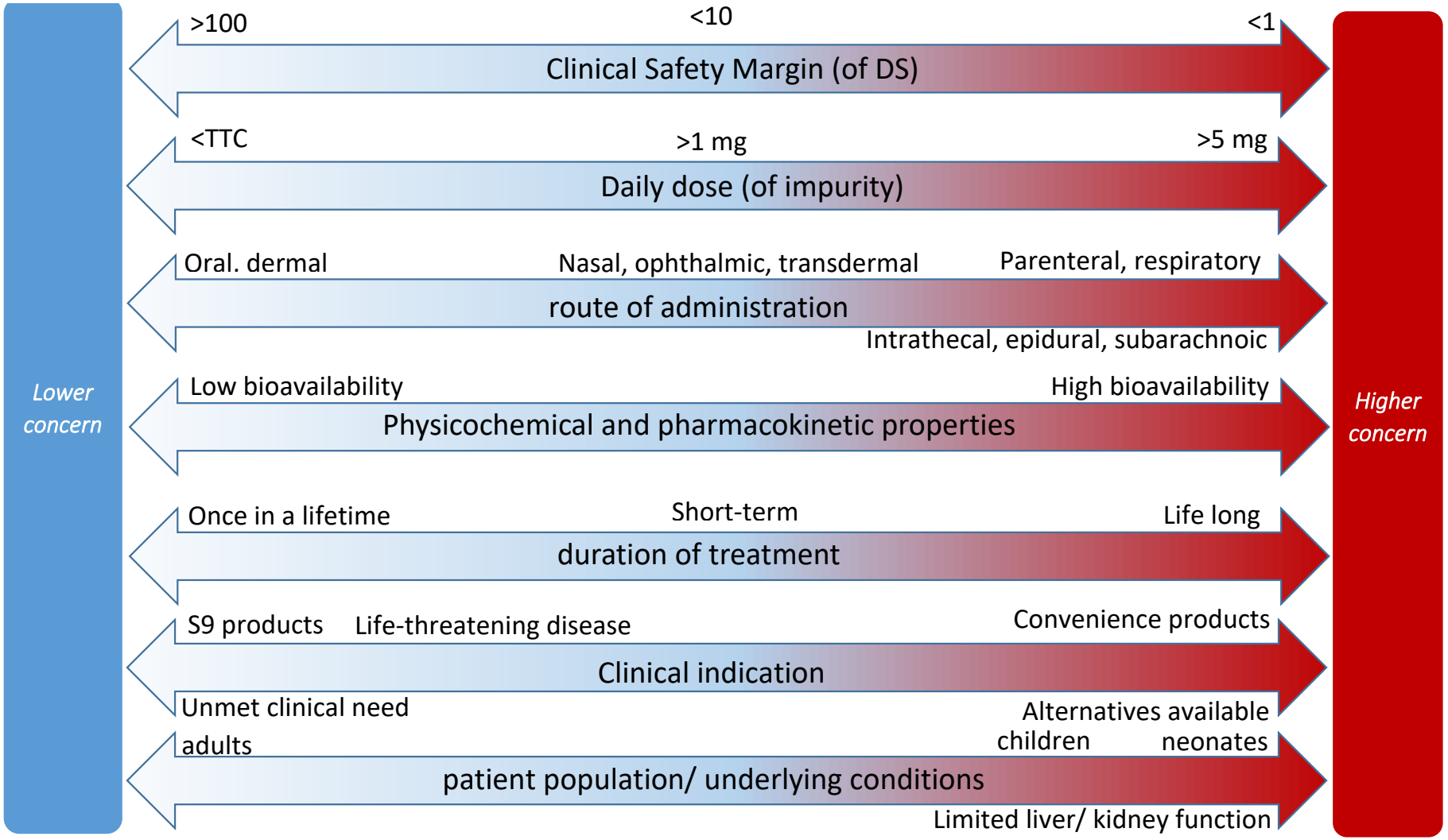
Applicability Q3A/B, Q3C/D/E & ICH M7

Q3A/B	Q3C/D/E and M7 (for PDE)
Mixture of impurities in DS/DP is tested	Compound-specific assessment
Impurity levels in non-clinical study are qualified → levels at NOAEL are acceptable	NOAEL in non-clinical study is PoD
No Assessment Factors used (Some RAs use HED derived from NOAEL)	F1-F7 as assessment factors to account for (potential) differences between animal study data and patient safety
Generic qualification thresholds (e.g. 0.15% or 1 mg whichever is lower)	No generic qualification thresholds in Q3C/D, only compound- or class specific PDEs Qualification thresholds in Q3E under development in µg/d range TTC of 1.5 µg/d applied for mutagenic compounds in M7, but only compound-specific PDEs for carcinogens with threshold-related mechanism

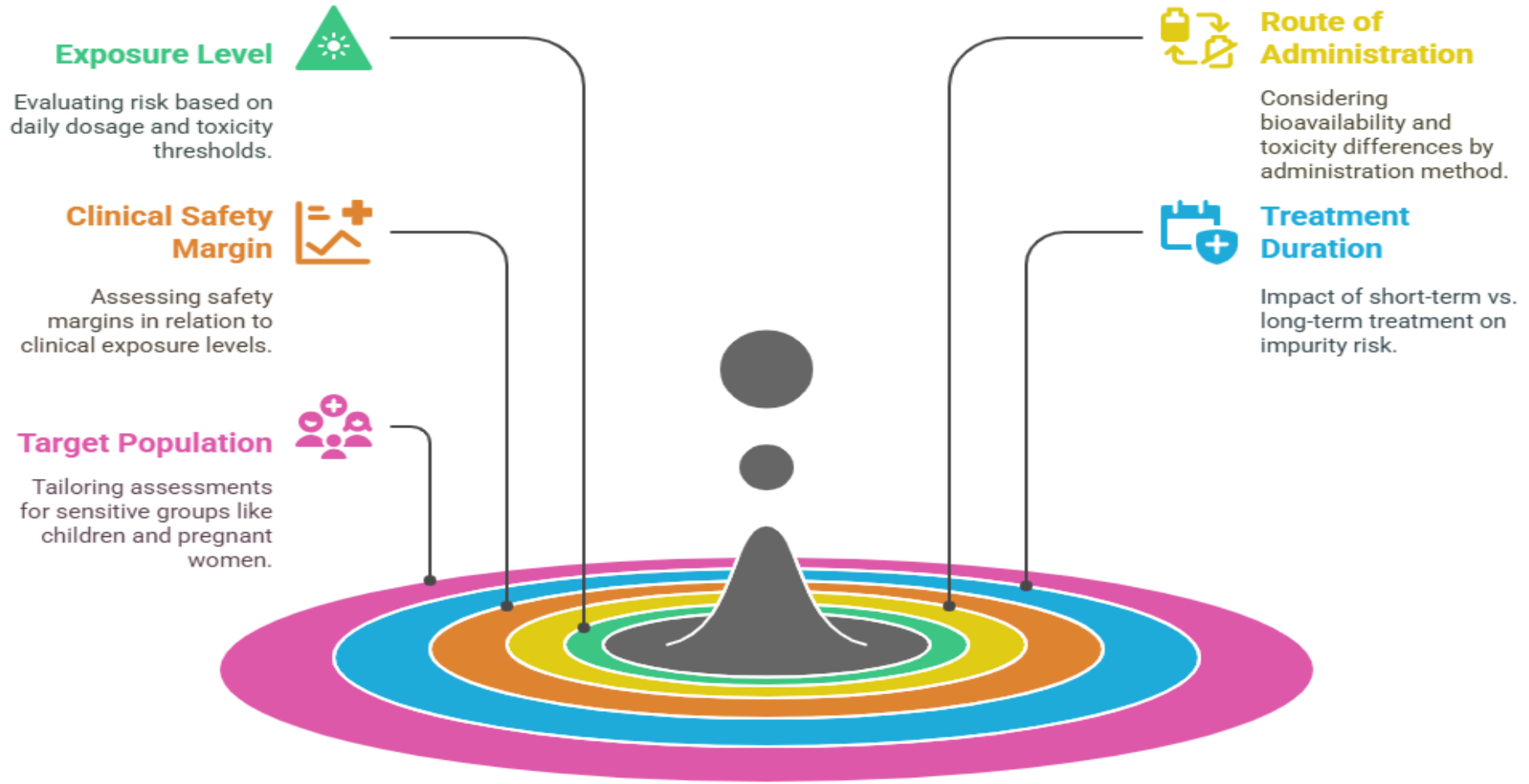
Key considerations: Level of concern considerations



Key considerations: Level of concern considerations



Impurity Assessment in Pharmaceuticals

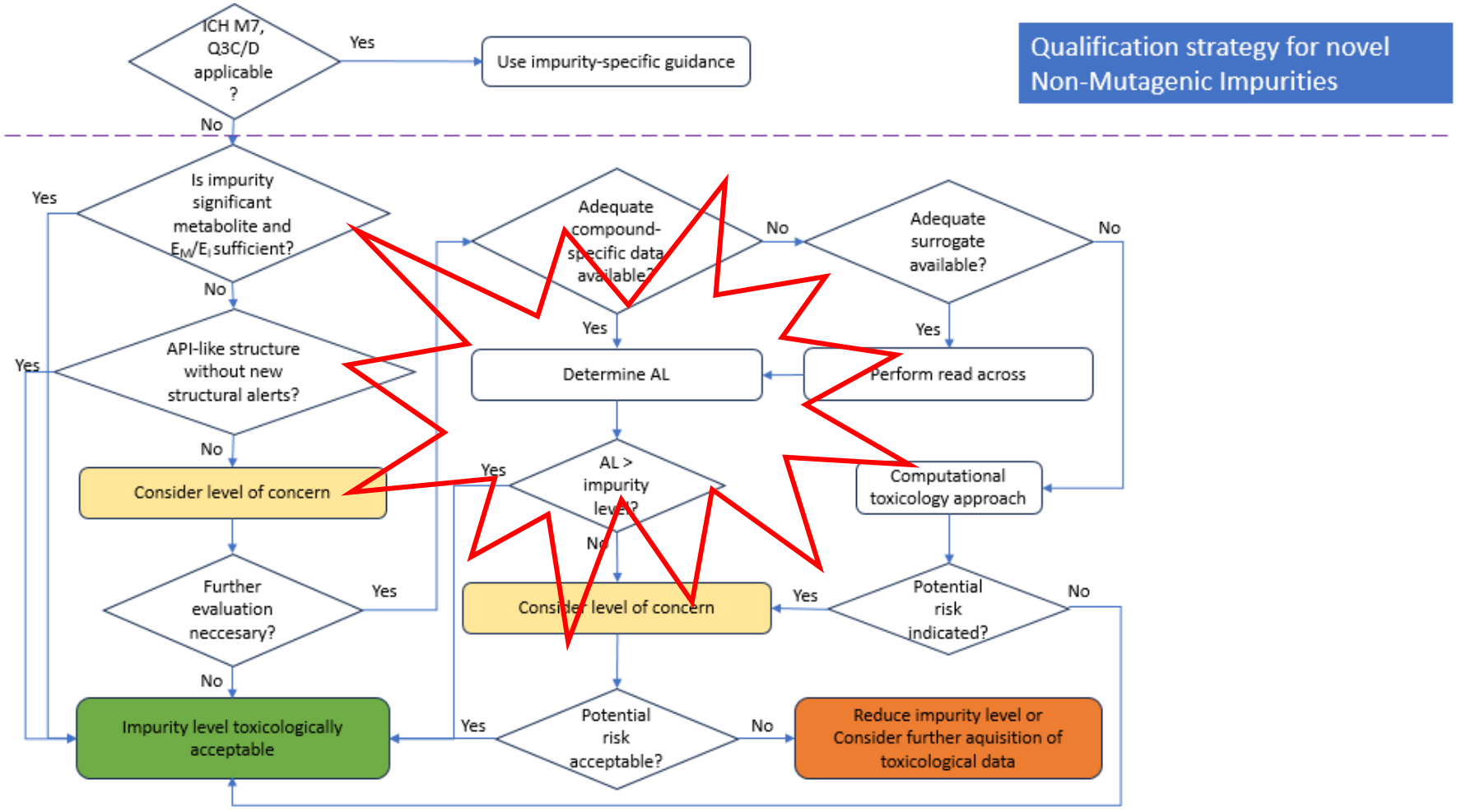


Key considerations: Level of concern considerations - Threshold of Toxicological Concern (TTC)

Route of administration	Class	DST[1]	TTC[2]
Oral	Cramer class 1		1500
	Cramer class 2		450
	Cramer class 3		75
	organophosphates or carbamates		15
Orally inhaled or nasal			4
Dermal	Non-reactive[3]	710	
	Reactive (non-HPC)[3]	73	
	HPC[3]	1	
			Parenteral TTC/absorption[4]
Parenteral			5

1 Dermal sensitisation threshold (µg/cm2), relevant only for sensitisation as an endpoint.[2] Threshold of Toxicological Concern for non-mutagenic endpoint (µg/day calculated for a 50 kg person).[3] Classification according to Roberts *et al*. (2015). HPC = High Potency Category[4] for other non-mutagenic endpoints.

Key considerations: Acceptable Level calculation



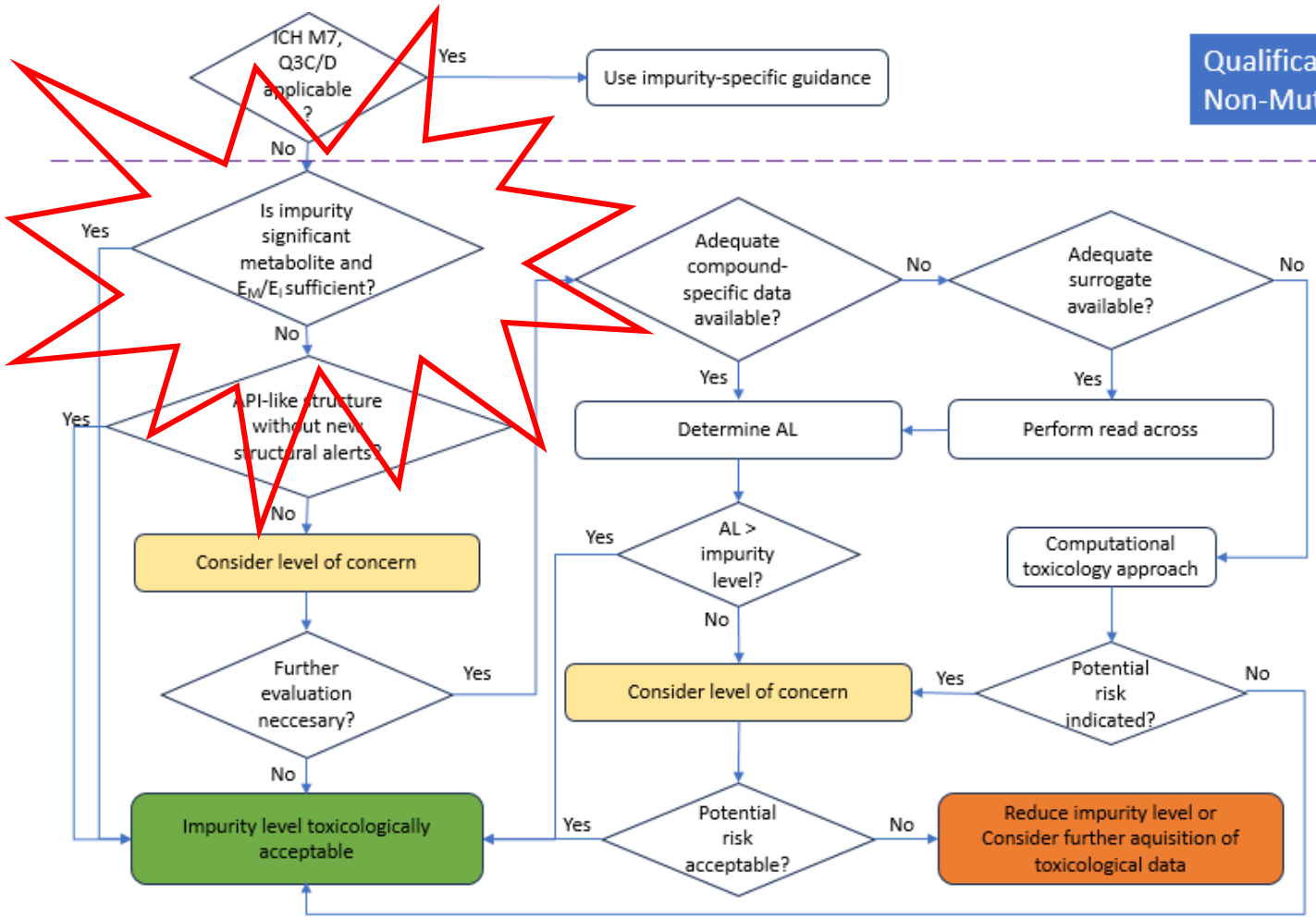
Key considerations: Acceptable Level calculation

- Similar to PDE calculation
- Assessment factors may deviate from standard modification factors based on product-specific level of concern considerations, e.g. duration or treatment.
- Includes AF6 for bioavailability correction
- Includes AF7 to account for uncertainty due to use of surrogate

$$AL\ (\frac{\mu g}{d}) = \frac{\text{PoD}\ \left(\frac{mg}{kg}/d\right) \text{ x } 50\ \text{kg x } 1000}{\text{AF1 x AF2 x AF3 x AF4 x AF5 x AF6 x AF7}}$$

- BenchMark Dosing Limit preferred Point of Departure
- Further reflections on applying assessment factors in Appendix

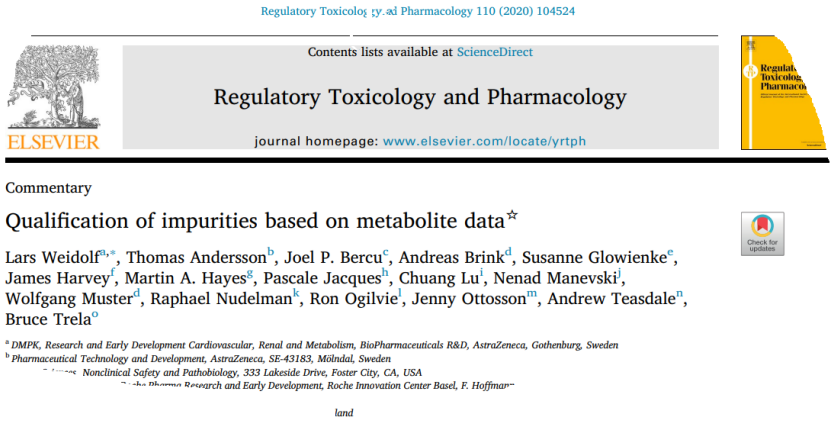
Key considerations: Metabolites



Qualification strategy for novel Non-Mutagenic Impurities

The RP only considers acceptability from safety perspective, not from a quality perspective

Key considerations: Metabolites



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Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Commentary

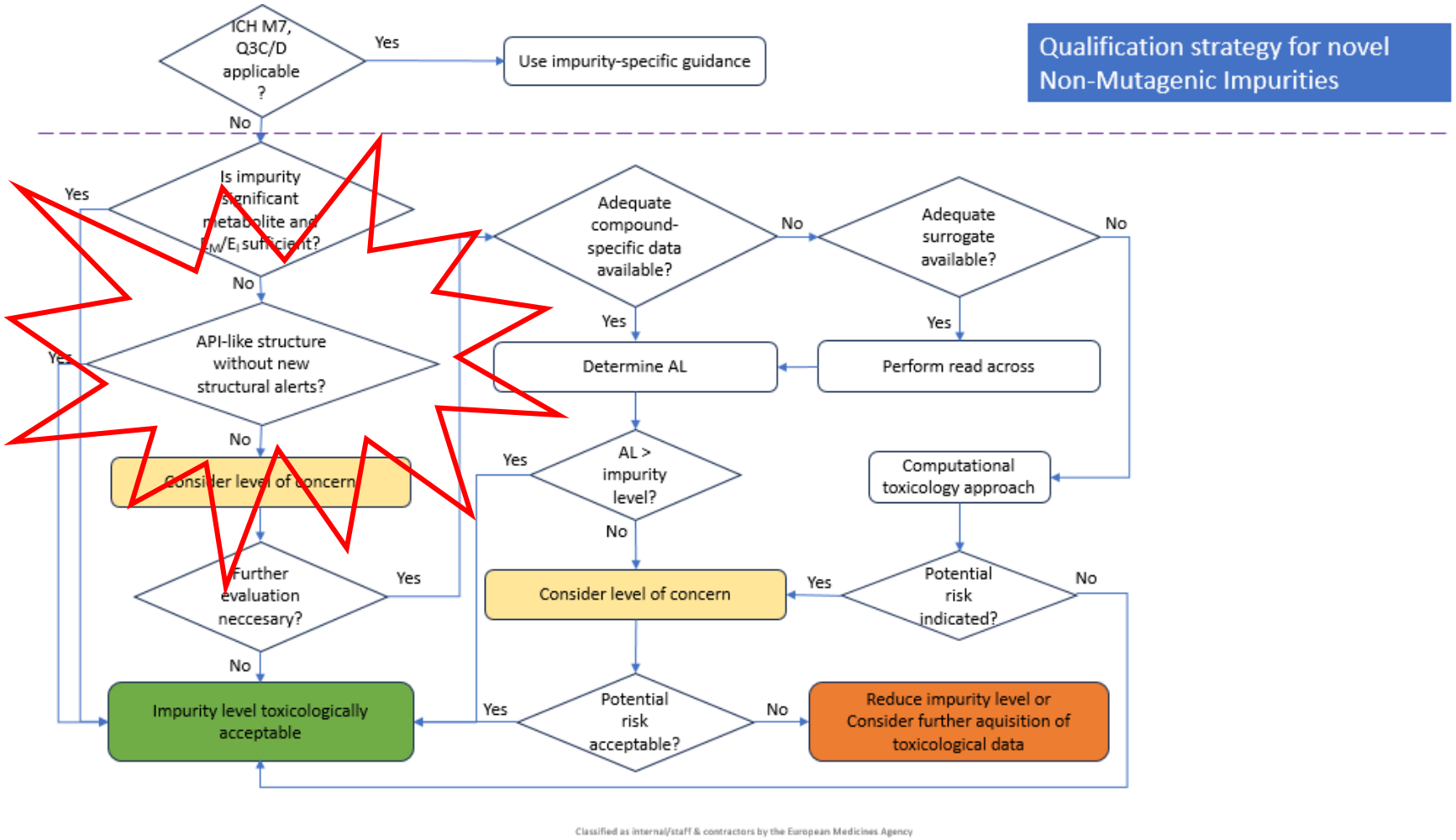
Qualification of impurities based on metabolite data☆

Lars Weidolf[a,*], Thomas Andersson[b], Joel P. Bercu[c], Andreas Brink[d], Susanne Glowienke[e], James Harvey[f], Martin A. Hayes[g], Pascale Jacques[h], Chuang Lu[i], Nenad Manevski[j], Wolfgang Muster[d], Raphael Nudelman[k], Ron Ogilvie[l], Jenny Ottosson[m], Andrew Teasdale[n], Bruce Trela[o]

[a] DMPK, Research and Early Development Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden
[b] Pharmaceutical Technology and Development, AstraZeneca, SE-43183, Mölndal, Sweden
Nonclinical Safety and Pathobiology, 333 Lakeside Drive, Foster City, CA, USA
Research and Early Development, Roche Innovation Center Basel, F. Hoffman-
land

- Q3A/B: Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified
- Significant ≠ >10% (as in ICH M3)
- E_M/E_I ratio sufficient: $E_M \geq E_I$ (low concern compounds) or $E_M > E_I$ (high concern compounds)
- For E_M use average observed plasma C_{MAX}
- For E_I derive the Maximal Theoretical Concentration (MTC):
  - Use the daily exposure of the impurity (µg/day) based on Maximum Daily Intake (MDD)
  - Divide by Extracellular fluid as volume of distribution (rat: 80.4 mL; human: 14 L)

Key considerations: API-like versus non-API-like



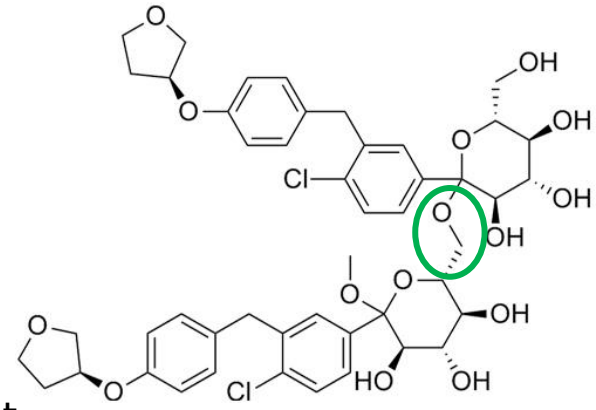
Key considerations: API-like versus non-API-like

- API-like: Impurity structurally similar to API with no new toxicophores while retaining functional groups.
- Insignificant changes to overall structure, size, physicochemical (PC), and pharmacokinetic (PK) characteristics compared to API.
- Use computational toxicology and read across (RaX) tools to assess similarity concerning structure (new toxicophores), PC and PK characteristics.
- Dimer/trimer considered API-like if dimerization bridge does not introduce new toxicophore and it systemically degrades to parent.
- Exceptions: Some enantiomers (e.g. S-thalidomide) and minor reaction products (lactone form of statins) may display higher toxicities

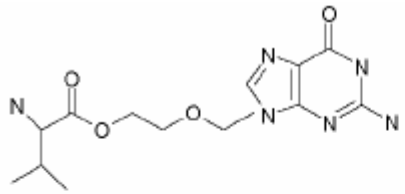
Key considerations: API-like versus non-API-like

Examples of API dimerization

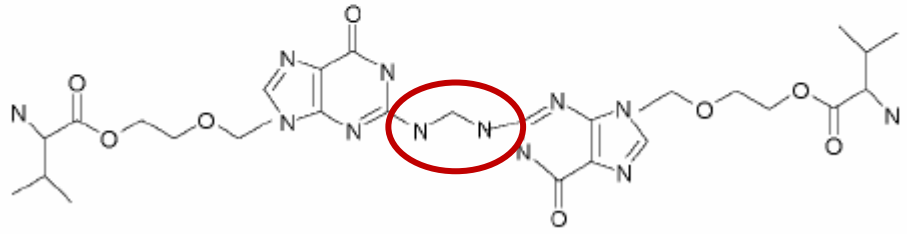
- Example 1: Empagliflozin sugar dimer
  - API-like: No new toxicophore is introduced and the dimer will degrade to the parent API systemically. The dimer is not considered more toxic than the parent, thus no further data is warranted.



- Example 2: Bis-valaciclovir
  - Non-API-like: NH-CH2-NH dimerization bridge may be a formalehyde releaser, which can be predicted using a QSAR tool.
  - Using formaldehyde as a surrogate for toxicity the PDE in ICH M7 Addendum 2 of 10 mg/day can be taken forward for risk assessment of the dimer impurity

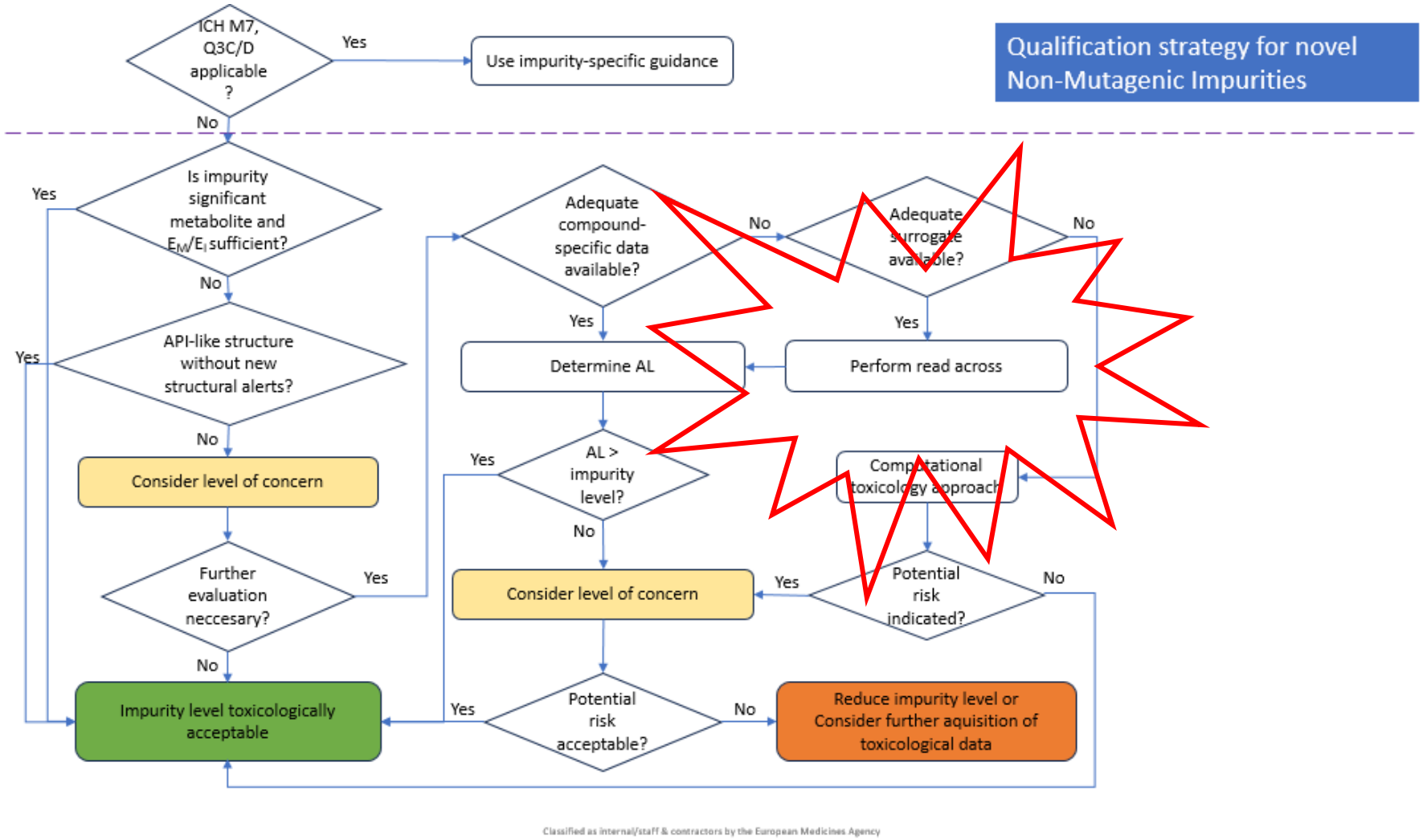


Valaciclovir



Bis-valaciclovir (BVACV)

Key considerations: New approach methodologies/ Read-across



Key considerations: New approach methodologies/ Read-across

Two read-across approaches are proposed

- Single surrogate approach
  - Identifying a robust surrogate for deriving an AL or for de-risking the target compound
- Grouping approach
  - Identifying several similar compounds containing the same toxicophores and functional groups for deriving a group AL or de-risking the group of compounds

Similarity assessment

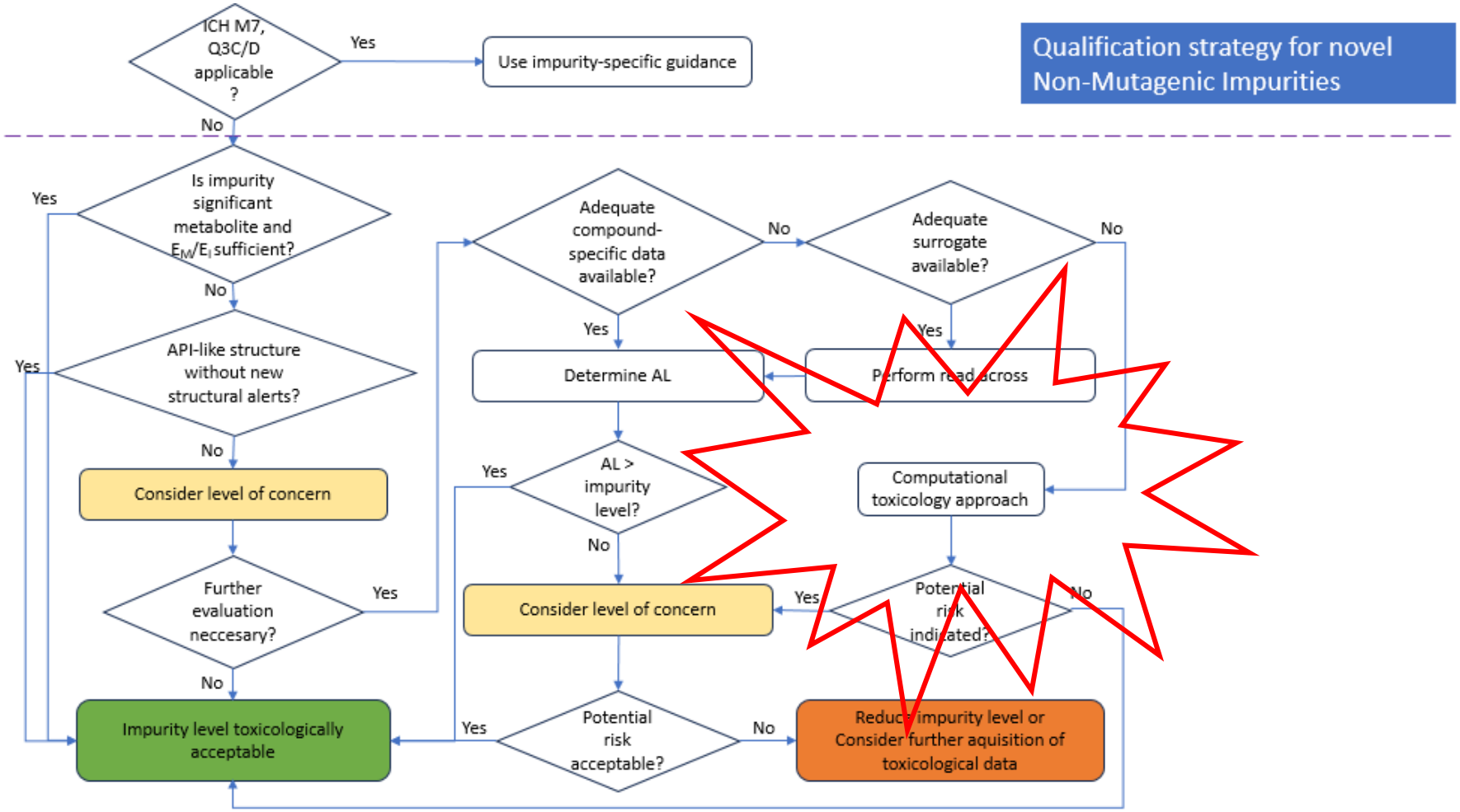
- Chemical-structural properties: toxicophores, global similarity
- PC properties: polarity, solubility, lipophilicity, ionizability, and molecular weight
- PK properties: bioavailability, distribution, metabolism and excretion
- Chemical assessment can be combined with prediction of PC and PK properties to increase the reliability of the surrogate.

Key considerations: New approach methodologies/ Read-across

Principles of the read-across approach

- Determine chemical-structural (including toxicophores), phys-chem and pharmacokinetic properties of target compound using databases or predictions from computational tools.
- Identify suitable surrogate compounds with robust data based on similarities in terms of chemical-structural, phys-chem and pharmacokinetic properties
- For identifying toxicophores using (Q)SAR tools relevant endpoints including chronic toxicity for major organs (liver, kidney, CVS, GIT, CNS, RS) as well as non-mutagenic carcinogenicity and reproductive toxicity should be considered
- The choice of adequate surrogate(s) should be justified based on the similarity and uncertainties with the RAX method and the reliability of the outcome of the assessment should be provided
- AL derived for surrogate(s) can be used for target compound
    - Assessment factor for uncertainty in read across (F7): 1 – 5.

Key considerations: New approach methodologies/ Computational toxicology



Key considerations: New approach methodologies / Computational toxicology

- Computational toxicology tools uses in silico methods to predict toxicity without animal testing
  - (Quantitative) structure activity relationships ((Q)SAR)
  - Read-Across (RAX)
  - Adverse Outcome Pathways (AOPs)
- Data sources and methodology
  - Broad databases with in vitro and in/ex vivo tested compounds
  - Machine Learning and Artificial Intelligence (ML/AI)
- Selection of the tool should be based on scientific validity
- The use of complementary methods is recommended to enhance confidence in the prediction

Key considerations: New approach methodologies/ Computational toxicology

Databases and Supporting Tools

- Commercial and free predictive tools available
- Databases for historical toxicological and pharmacological data
- Integration of multiple data sources enhances prediction accuracy
- Continuous updates to databases improve reliability of assessments

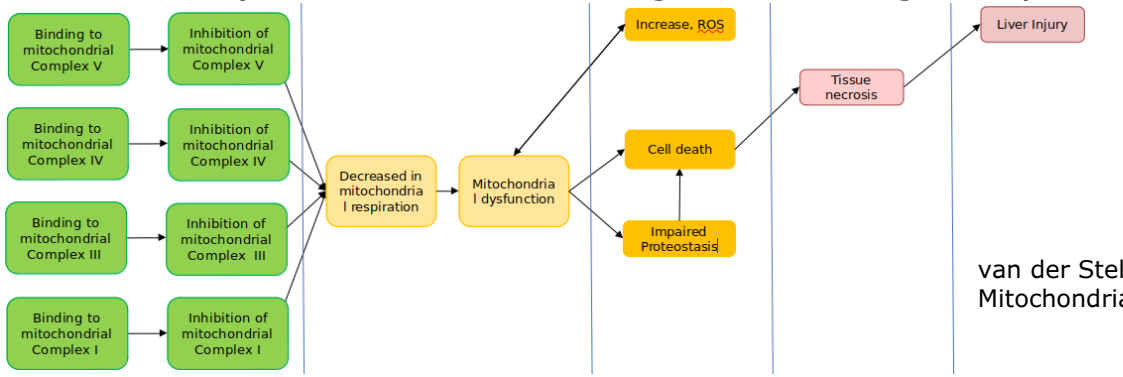
Associations developing computational toxicology tools:

- ASPIS (RISK-HUNT3R, ONTOX and PrecisionTox)
- AOP Knowledge Base – OECD framework for organizing data at the chemical and biological levels
- EPAA (European Partnership for Alternative Approaches) – e.g. QIVIVE and PBK modelling

Key considerations: New approach methodologies/ Computational toxicology

Examples of computational tools

- Adverse Outcome Pathways (AOPs)
  - AOP KB and AOP-wiki
  - Conceptual framework for organizing and presenting specialized scientific knowledge regarding the linkage between perturbation of a specific biological target (Molecular initiating event (MIE) or Key event (KE)) and a consequent adverse outcome (AO).
  - Assembly of individual AOPs into AOP networks provides the ability to capture the greater complexity of biological responses in an organized and systematic way.
  - AOPs can be used for addressing uncertainties or data gaps for major organs (liver, kidney, CVS, GIT, CNS, RS) as well as non-mutagenic carcinogenicity and reproductive toxicity



van der Stel, W., AOP-wiki: 273, Mitochondrial complex inhibition leading to liver injury

Key considerations: New approach methodologies/ Computational toxicology

Examples of computational tools

- Machine Learning and Artificial Intelligence (ML/AI) can be used to develop or validate new computational tools
  - PrecisionTox: applying metabolomics and transcriptomics to comparative toxicology samples to trace adverse outcomes via the molecular key events preceding them
    - Investigates biomolecular toxicity pathways through simultaneous high-throughput testing across five biomedical model species and human cell lines, using multi-omics and ML/AI to identify molecular key events that initiate disease progression.
  - MolCompass: multi-tool for the navigation in chemical space and visual validation of QSAR/QSPR models (Sosnin 2024)
    - The parametric t-SNE method employs an artificial neural network as its core mechanism, projecting chemical structures onto a 2D plane. The model is parameterized by the neural network weights, and it is trained to group structurally similar compounds together

Key considerations: New approach methodologies – Method validation

Method validation and regulatory acceptance

- Transparency in reporting methodologies:
  - OECD QSAR assessment framework for regulators (2024) and OECD Scientific Review of AOPs (2021)
  - Defined endpoint within a defined domain of applicability using an unambigious algorithm
  - Appropriate measures of goodness-of-fit, robustness and predictivity
- Justification that the selected *in silico* tool is fit-for-purpose
  - Consideration of performance metrics
  - Evaluation of the tool's reliability through peer-reviewed validation studies
  - Innovation Task Force and Scientific Advice Procedure for Regulatory acceptance and Qualification Advice/Opinion for NAMs, including computational toxicology tools

Key considerations: New approach methodologies/ Computational toxicology

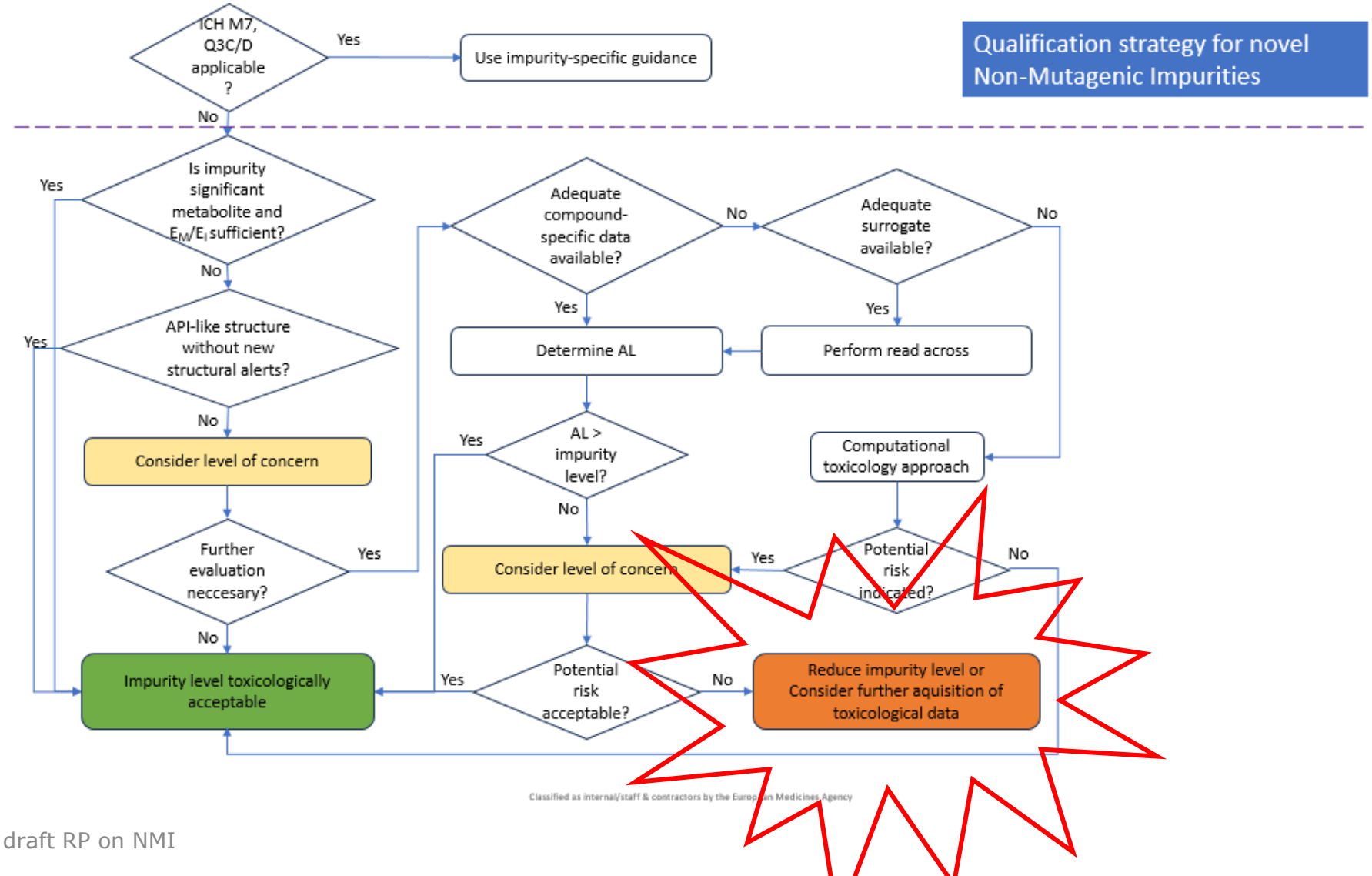
Expert judgment required to interpret results and assess reliability

- Out of applicability domain predictions require additional data and expert judgment
- Use of alternative tools with more suitable training datasets and complementary methods for consensus

- Documentation of assumptions, data gaps, and model limitations*
- Toxicity alerts should be further investigated using literature or complementary methods
- Combining multiple in silico tools with in vitro studies to address knowledge gaps

*the latest updated model version should be used, while earlier versions needs justification (e.g., the tool has not undergone significant changes that affect prediction performance)

Key considerations: New approach methodologies/ Others



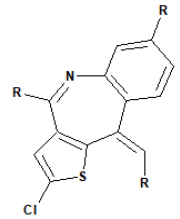
Key considerations: New approach methodologies/ Others

in vitro:

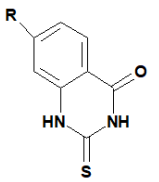
- Cell models 2D, 3D, microphysiological systems, biomarkers
  - e.g. GuardSkin, 3D human skin models, kidney, liver, gastrointestinal systems on Chip, cell painting models
- Extrapolation *in vitro* to *in vivo* (qIVIVE)

in chemico:

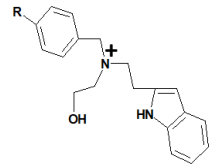
- Reactivity of compound
- Multiple tools (including *in silico*)→ integrate data → WoE



Thiophen



Thiourea



Protonated nitrogen

Data needed to support validity of approach taken

- Qualitative → hazard characterisation → absence of hazard = derisking
- Quantitative → potency data needed → no risk anticipated at proposed specification level

New Approach Methodologies

- NAM qualification guideline from EMA
  - Qualification of novel methodologies for drug development: guidance to applicants (EMEA/CHMP/SAWP/72894/2008 Rev. 5)
  - Essential considerations for successful qualification of novel methodologies (EMA/750178/2017)
  - Future-proofing Qualification of Novel Methodologies (QoNM) - Action plan
  - Draft reflection paper on the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3Rs - Revision 1
  - Concept paper on the revision of the guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches
- Hazard characterization versus quantitative risk estimation for NAMs
  - Usually, *in vitro* models are used for hazard characterization
  - Quantitative *in vitro* to *in vivo* extrapolation is needed for quantitative risk estimation
- Multiple international projects on developing and implementing NAMs in regulatory toxicology are ongoing
  - ASPIS-cluster (ONTOX, RISK-HUNT3R & PrecisionTox), TOX21, and many more.

Last exit:
Toxicological qualification with *in vivo* studies

- Should only be considered in exceptional circumstances
  - *In silico* qualification does not provide relevant data
  - *In vitro* qualification provides critical findings with need of in vivo follow up testing
  - Read across not possible
  - Impossible to reduce and control NMI at TTC/DST levels as outlined in sec 4.4.1
  - Availability of the neat impurity, amount sufficient to conduct a two – four week tox study

In vivo qualification studies

Key considerations for conduct of *in vivo* studies

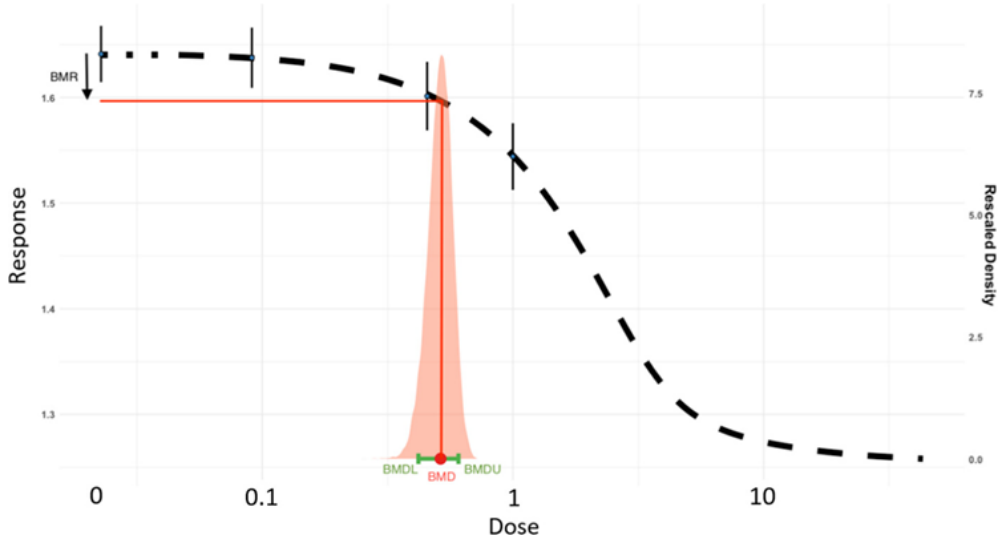
Parameter	Description
Test substance	Neat (isolated impurity without API), purity > 95%.
Study design	GLP compliant and adhere to principles of OECD guideline 407
Duration of study/administration route	28-days (14-days for short term administration) and no recovery period. Administered via clinical route of administration.
Species/sex	Rats, unless otherwise justified. Both sexes should be included unless the clinical use of the medicinal product is only in 1.
Animals per group/number of groups	3 rats/sex/group. 4 dose groups. The highest dose level should be established with a suitable exposure margin compared to the proposed specification level, with the second highest dose group projected at the anticipated specification level, multiplied by the relevant AL-related assessment factors.
Control groups	Vehicle control group
TK analysis	3 M/F should be included for TK analysis. The analysis can be integrated in the main study as part of the high dose group.

Deviations from OECD TG 407

- Dose group size: 3/sex/dose
- Number of dose groups: 4 plus vehicle control
- If possible integration of TK analysis into the high dose group
- Rational:
  - The study design should enable benchmark dosing (BMD) analysis
  - BMD modelling provides more reliable, robust and accurate dose response curve compared to NOEL.
  - Number of dose groups is more important for reliable BMD analysis than dose group size
  - Compromise to have 4 instead of three dose groups but less animals (3 instead of 5)
- For dose selection – EFSA BMD guidance on dose selection (EFSA 2022, https://doi.org/10.2903/j.efsa.2022.7584)
- Recommended to choose the most human relevant endpoint for determining the Reference Point for AL calculation, usually the endpoint with the lowest BMDL

Advantage of BMD vs NOEL

- NOAEL is the highest dose tested in a study without evidence of an adverse effect
- NOAEL is affected by the dose range selection and by the (statistical) power of the study
- BMD (benchmark dose) is a dose level estimated from the fitted dose–response curve
- BMD is associated with a specified change in response (benchmark response e.g. 10%)) relative to the control group
- BMD makes use of all the dose–response data to estimate the shape of the overall dose
    - More accurate provides CI, measure for data/study quality
- Bayesian model averaging recommended
- BMDL usually used as PoD for limit calculations



Principle for AL calculation

- Approach similar to PDE calculation
- Two additional assessment factors
  - AF6 for bioavailability correction
  - AF7 to account for uncertainty due to use of surrogate (not relevant in case of *in vivo* study with NMI)

$$AL\ (\frac{\mu g}{d}) = \frac{\text{PoD}\ \left(\frac{mg}{kg}/d\right) \text{ x } 50\ \text{kg x } 1000}{\text{AF1 x AF2 x AF3 x AF4 x AF5 x AF6 x AF7}}$$

- BMDL preferred Point of Departure
- Appendix provides additional detail and considerations on assessment factors

Key considerations: Oncology products

- Qualification of impurities in line with ICH S9
- Impurities may have safety profile similar to cytotoxic API
- Risk/benefit considerations
- Usually no need to control impurities at levels where no toxicity is anticipated

- *In vivo* qualification of impurities would generally be considered obsolete

Key considerations: Products under clinical development

- In general evaluation of impurities of IMPs in clinical development → ICH M3(R2)
- Studies with impurities are generally not required before phase III
- Consider level of concern for impurities to guide need for additional information
  - Special consideration/priority should be given to impurities of high concern
- If impurities of high concern are identified and data needed for qualification
  - apply principles as described in RP

Coffee/tea break

The session will start again in 10 minutes

Question and Answers

EMA

Questions – Scope

1. Would request to define in more detail about weight of evidence approach if can be applied for products in Market for more than 10 years or have been filed in EU by Well Established use?

Questions – Level of concern analysis

1. The proposed framework is highly complex and many aspects are open to interpretation. For example, to determine the level of concern for an impurity, there are seven aspects or risk factors to consider. Further, it is stated that each risk factor needs to be considered in the context of all other risk factors. Can EMA outline their vision for the successful implementation of the framework and comment on the likelihood of consistency within EMA's assessors?
2. We would like to understand how acute, subchronic and chronic treatments are classified in humans. In the case of chronic exposures, do these treatments include intermittent exposures and in these cases, must the exposure be greater than one year or is there some other requirement besides the duration of exposure for a product to be classified as chronic use? We suggest that a discussion of this issue be included in the final version of the document.

Questions – TTC (1/2)

1. Regarding the proposed use of TTCs, has there been an impurity safety issue (besides cohort of concern mutagens) that is driving the recommendation to assess impurities below 1 mg/day to determine if a safety investigation is needed? Based on our experience, current guidance (ICH M7, Q3C, Q3D) and industry practice (E&L assessments), already ensures control of the most potent impurities and Hasselgren et al (2024) have evaluated toxicity data for non-mutagens and identified compound classes that could require consideration below 1 mg/day.
2. EMA has proposed use of TTCs to identify new impurities that may require a safety assessment even when below the qualification threshold. Has the agency considered the recent publication by Hasselgren et al 2024 as an alternate way to identify impurities that may be unusually potent, and therefore warranting further safety evaluation?
3. It is unclear if this guideline expects lower ID and qualification thresholds than ICH Q3A/3B and thus diverges. Can EMA clarify how this guideline relates to the ID and Qual thresholds in these guidelines (do they take precedence for example)?

Questions – TTC (2/2)

1. Use of TTC is dramatically below current ICH guidance of 1 mg. Given that 1 mg/day has been in practice for 3 decades, what was the driver to moving towards the TTC for drug impurities and has there been an assessment on whether the use of TTC is achievable?
2. "Could you clarify that point regarding TTC? ""If the exposure level is below the relevant TTC, there is no need for further action. As TTC levels represent threshold levels for which there is no safety concern for most, but not all, chemicals, the level of concern still needs to be considered in the context of all other aspects as shown in Figure 2, even when the exposure to the NMI is below the TTC level."" Does it mean, that depending on the type of product, even when the level of impurity is below the defined TTC (e.g. 5 ug/day for a parenteral drug) we may need to further assess the impurity? (e.g. a parenteral drug indicated for lifelong for non life threatening diseases in pediatrics?) but when the type of product is of ""low concern"" according to figure 2, levels below TTC are deemed enough and no further action is deemed necessary?"

Questions – AL vs PDE and AF

1. Since there are now 7 adjustment factors, to set an acceptable level - the total will be maximum adjustment could be up to 10 million or more. Has there been an assessment on whether these impurity limits can be practically met?

Questions – Read-across

1. Is read-across necessary to determine whether the metabolite is structurally similar to the API?
2. What are the structural similarity requirements? Are there any reference guidelines?
3. If the read-across includes multiple analogs, what correction factor should be considered? Is it different from having only one analog?

Questions – API-likeness

1. Defining structural similarity can be subjective. For API-like impurities, which seem to be out of scope for qualification, how do we ensure company approaches to structural similarity will be accepted by EMA?
2. What is considered similar in terms of PK, physchem ang global similarity measures to define an impurity as API-like?

Questions – NAMs

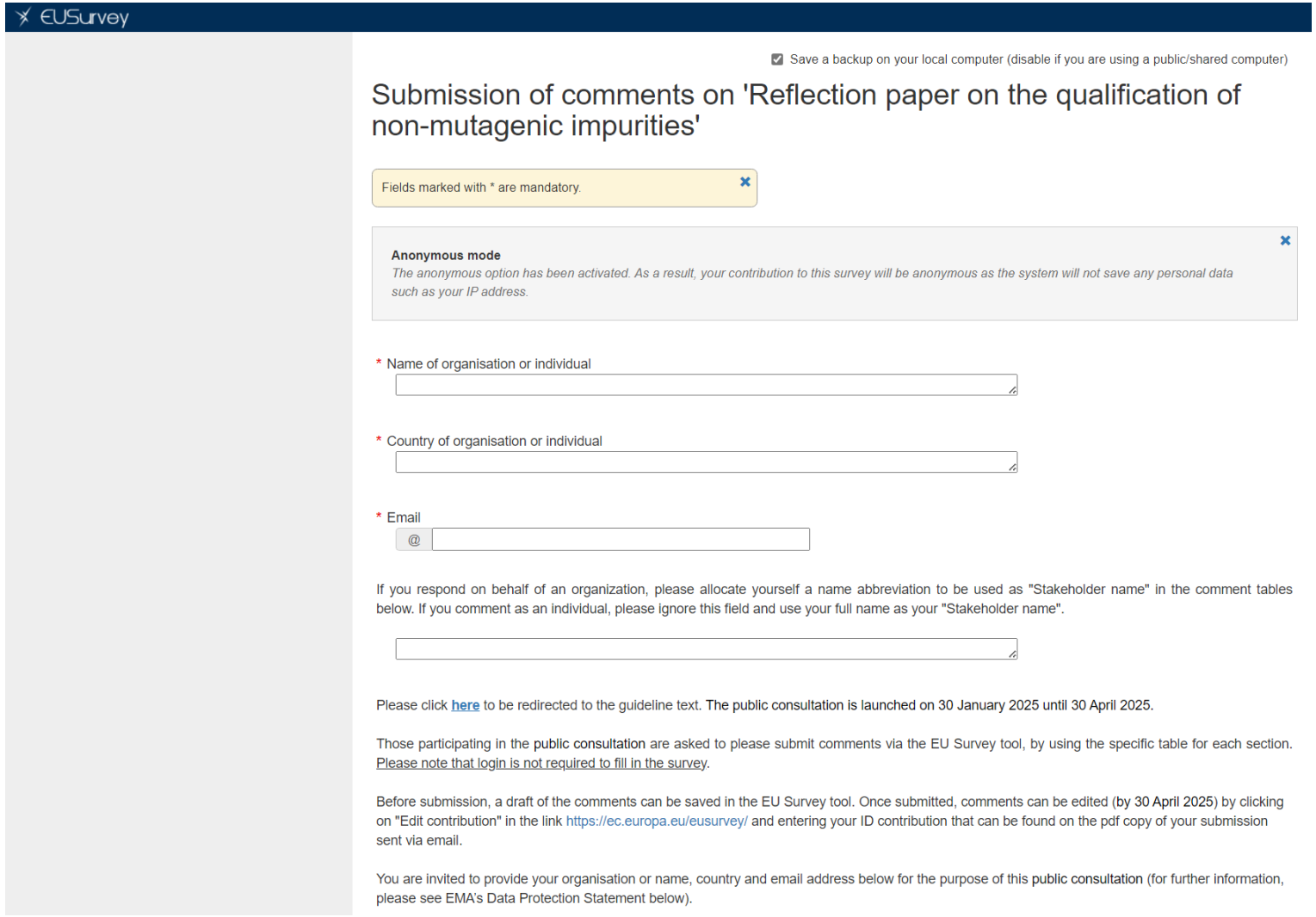
1. How in practice can NAM technologies be used to qualify impurities (what specific NAM tests, extrapolating in vitro to in vivo) - can examples be shown?
2. Would a case study where an impurity is assessed using NAM tools be introduced? I feel an example would help further to understand what is expected and how to summarize this kind of approach.
3. How can AOPs be used to qualify impurities?
4. What are the ML and AI strategies that can be applied to the impurity qualification?

Questions – In vivo testing

1. With the requirement to test neat isolated impurities in vivo, would that significantly increase the amount of animal testing as we typically qualify over 10 impurities per compound?
2. Typical dedicated impurity qualification studies, which test impurities spiked into DS, often test multiple impurities to reduce animal use. Has the EMA considered that the proposed in vivo test strategy using neat impurities to derive a BMDL is likely to increase animal use since each impurity will require a dedicated study?
3. Will the request to test neat impurities lead to increase the number of in vivo studies as every impurity will be tested in a dedicated study?

Wrap up and closure

Public consultation



EUSurvey

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Submission of comments on 'Reflection paper on the qualification of non-mutagenic impurities'

Fields marked with * are mandatory.

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The anonymous option has been activated. As a result, your contribution to this survey will be anonymous as the system will not save any personal data such as your IP address.

* Name of organisation or individual

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If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

Please click here to be redirected to the guideline text. The public consultation is launched on 30 January 2025 until 30 April 2025.

Those participating in the public consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section. Please note that login is not required to fill in the survey.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 30 April 2025) by clicking on "Edit contribution" in the link https://ec.europa.eu/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

You are invited to provide your organisation or name, country and email address below for the purpose of this public consultation (for further information, please see EMA's Data Protection Statement below).

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Thank you for attending the webinar

https://www.ema.europa.eu/en/qualification-non-mutagenic-impurities-scientific-guideline

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