Webinar com a GGMED e GGFIS discute o draft do Guia ICH Q3E for Extractables and Leachables e Consulta Regional Edital nº 13/2025

Realização:

Agência Nacional de Vigilância Sanitária

Coordenação de Gestão da Transparência e Acesso à Informação - CGTAI
Gerência-Geral de Conhecimento, Inovação e Pesquisa - GGCIP

Gerência-Geral de Medicamentos – GGMED
Gerência-Geral de Inspeção e Fiscalização Sanitária - GGFIS

Letícia Oyamada Sizukusa (Topic Leader)- GGFIS
Dandara Santana (Alternate Expert) - GGMED

ICH Q3E: Guideline for Extractables and Leachables

Step 3 Document – open for comments

Legal Notice

- This presentation is protected by copyright and may, with the exception of the ICH logo, be used, reproduced, incorporated into other works, adapted, modified, translated or distributed under a public license provided that ICH's copyright in the presentation is acknowledged at all times. **In case of any adaption, modification or translation of the presentation, reasonable steps must be taken to clearly label, demarcate or otherwise identify that changes were made to or based on the original presentation.** Any impression that the adaption, modification or translation of the original presentation is endorsed or sponsored by the ICH must be avoided.
- The presentation is provided "as is" without warranty of any kind. In no event shall the ICH or the authors of the original presentation be liable for any claim, damages or other liability arising from the use of the presentation.
- The above-mentioned permissions do not apply to content supplied by third parties. Therefore, for documents where the copyright vests in a third party, permission for reproduction must be obtained from this copyright holder.

Agenda

- Overview of ICH process
- History of ICH Q3E
- Background
- Key Principles
- High Level Overview of Guideline including Quality and Safety Sections

Overview of ICH process

ICH Overview

- Unique harmonisation project, involving the Regulators and research-based Industries across the globe
- Started in 1990
- Well-defined objectives:
  - **To improve efficiency of new drug development and registration process**
  - **To promote public health, prevent duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness**
- Accomplished through the development and implementation of harmonised Guidelines and standards

ICH members

- **23 ICH members:**

➢ **Founding Regulatory Members:**

  ➢ EC, Europe; MHLW/PMDA, Japan; FDA, United States

➢ **Founding Industry Members:**

  - EFPIA; JPMA; PhRMA

➢ **Standing Regulatory Members:**

  - Swissmedic, Switzerland; Health Canada, Canada

➢ **Regulatory Members:**

  - ANMAT, Argentina; ANVISA, Brazil; COFEPRIS, Mexico; EDA, Egypt; HSA, Singapore; JFDA, Jordan; MFDS, Republic of Korea; MHRA, UK; NMPA, China; SFDA, Saudi Arabia; TFDA, Chinese Taipei; TITCK, Turkey

➢ **Industry members:**

  - BIO; Global Self-Care Federation; IGBA

ICH Products

- **77 Guidelines on technical requirements on:**

Quality - 26 Guidelines

Safety - 16 Guidelines

Efficacy - 23 Guidelines

Multidisciplinary – 9 Guidelines

Electronic Standards for the Transfer of Regulatory Information (ESTRI)

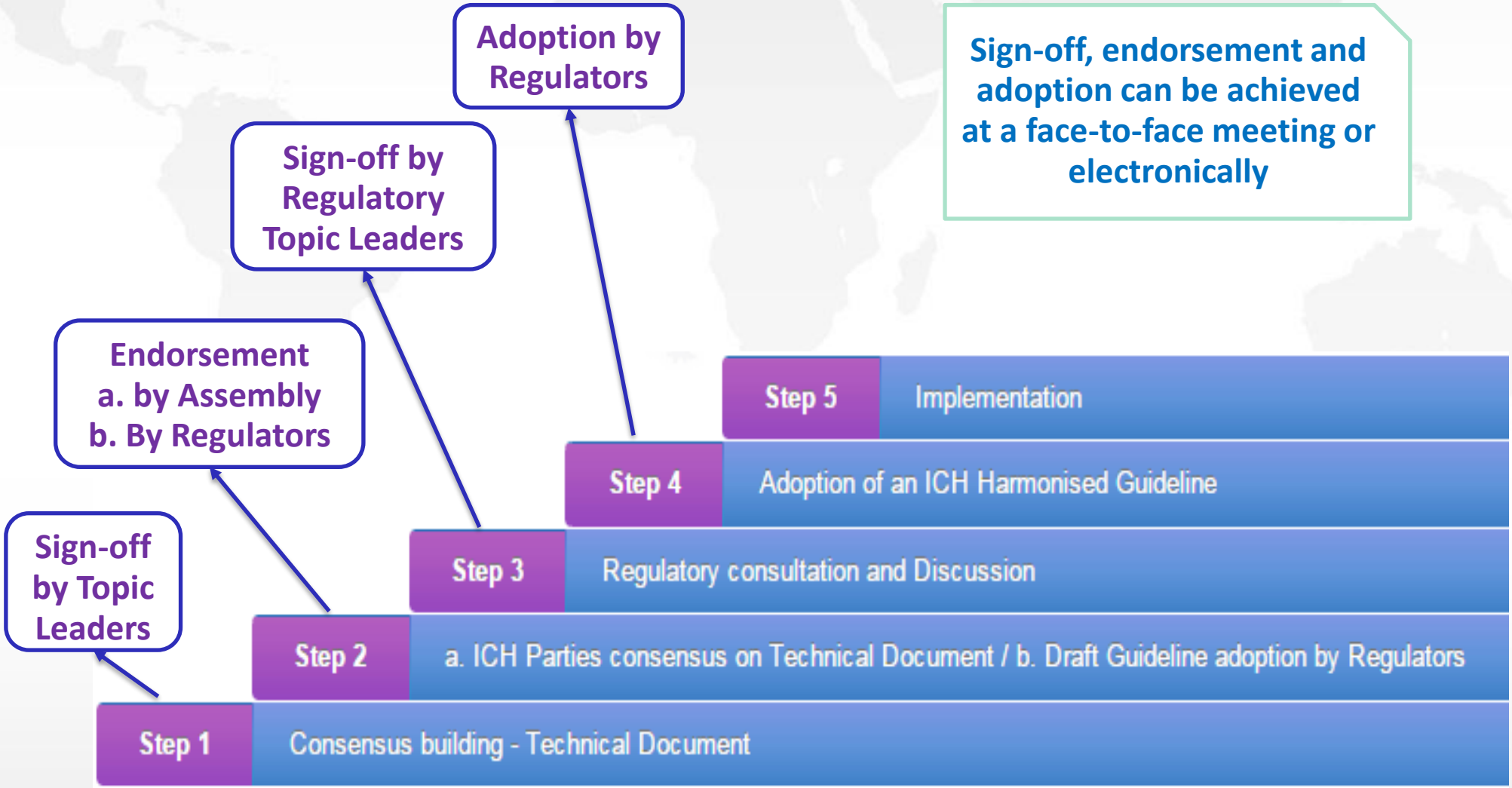
CTD/eCTD

MedDRA (standardised medical terminology)

ICH Process of Harmonisation

New topic for harmonisation of ICH?	Formal ICH Procedure	Concept Paper & Business Plan required
Clarification needed for an existing ICH Guideline?	Q&A Procedure	Concept Paper required (Business Plan may be required in certain cases)
Content of an existing ICH Guideline out of date or no longer valid?	Revision Procedure	Concept Paper required
New information to be added to an existing ICH Guideline?		
Change to be made to either a Guideline with a maintenance procedure or M2 Recommendations?	Maintenance Procedure	Concept Paper required for maintenance of Guidelines. No Concept Paper required for M2 Recommendations maintenance

Steps in the ICH Process

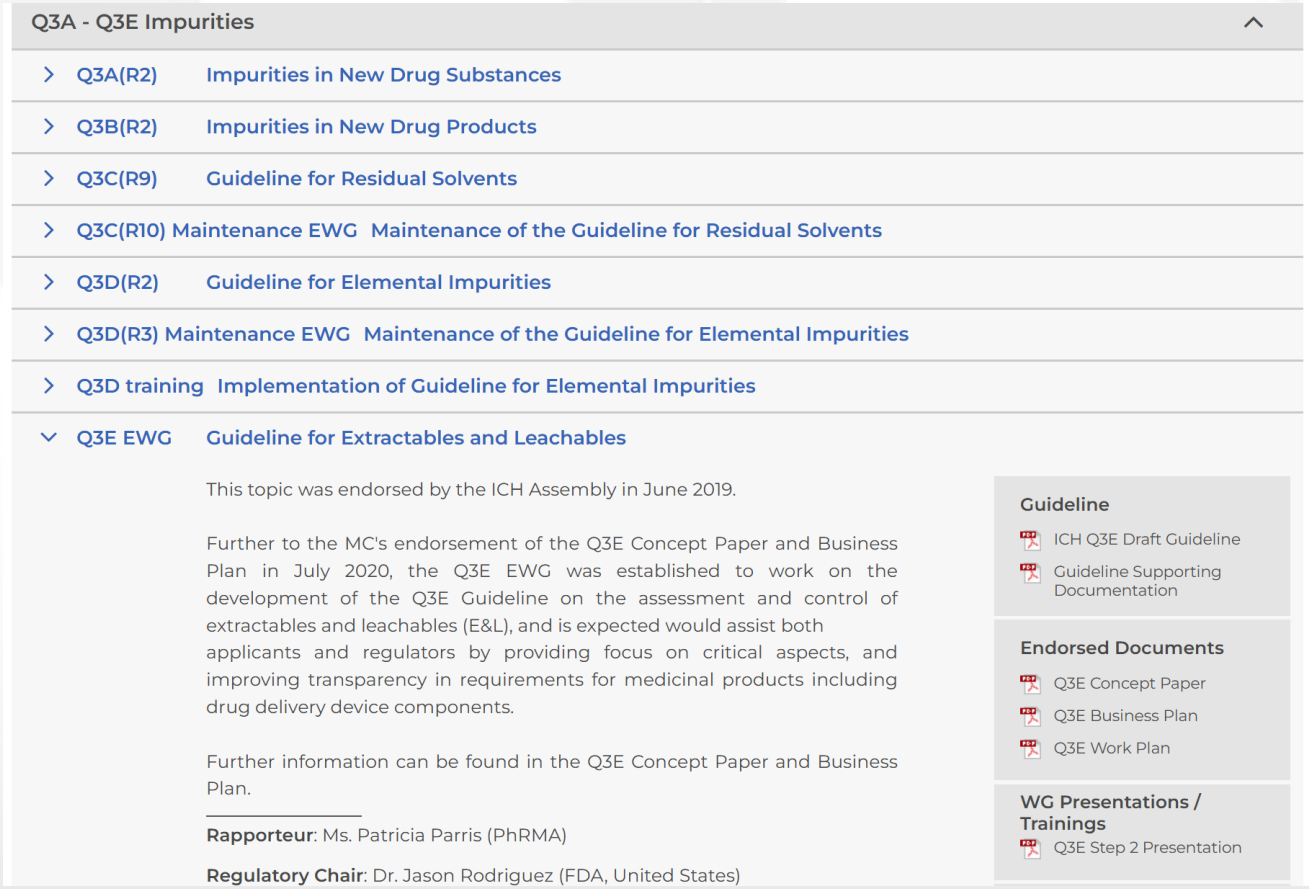


https://www.ich.org/page/formal-ich-procedure

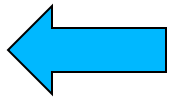
History of ICH Q3E

History

- This document was developed based on a Concept Paper (10 July 2020) and a Business Plan (10 July 2020)



History

- This document has been signed off as a Step 2 document (01 August 2025) to be issued by the ICH Regulatory Members for public consultation
- **Step 3: Regulatory Consultation and Discussion**
  - **i) regional consultation** 
  - ii) discussion of regional comments
  - iii) Step 3 Experts Sign-Off by the regulatory experts.
- **Step 4: Adoption of ICH Harmonised Guideline (June 2027)**

Q3E Guideline for Extractables and Leachables

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GUIDELINE FOR EXTRACTABLES AND LEACHABLES Q3E

Draft version

Endorsed on 01 August 2025

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

ICH Q3E: GUIDELINE FOR EXTRACTABLES AND LEACHABLES

SUPPORTING DOCUMENTATION: CLASS 3 LEACHABLE MONOGRAPHS

Draft version

Endorsed on 01 August 2025

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

ICH Q3E - Regional Consultation (Brazil)

COPIAR LINK CRIAR TAGS IMPRIMIR PDF VER NOTAS DE ALTERAÇÃO FECHAR NOTAS DE ALTERAÇÃO A+ | A-

VIGENTE E ABERTO À CONTRIBUIÇÃO **Edital de Chamamento n° 13, de 08/09/2025**

Edital de Chamamento n° 13, de 08/09/2025

ACESSE A INTEGRA DO ATO

Data Publicação DOU: 10/09/2025

Status: Vigente e Aberto á Contribuição

Prazo de Contribuição: 10/09/2025 a 10/11/2025

Assunto: Coleta contribuições para a minuta do ICH Q3E - Guia para Extraíveis e Lixiviáveis (Guideline for Extractables and Leachables).

Origem: International Council of Harmonization (ICH)

Edital de Chamamento n° 13, de 08/09/2025

ICH Q3E - Regional Consultation (Brazil)

- **Link for comments (english):**

http://pesquisa.anvisa.gov.br/index.php/592291?lang=pt-BR

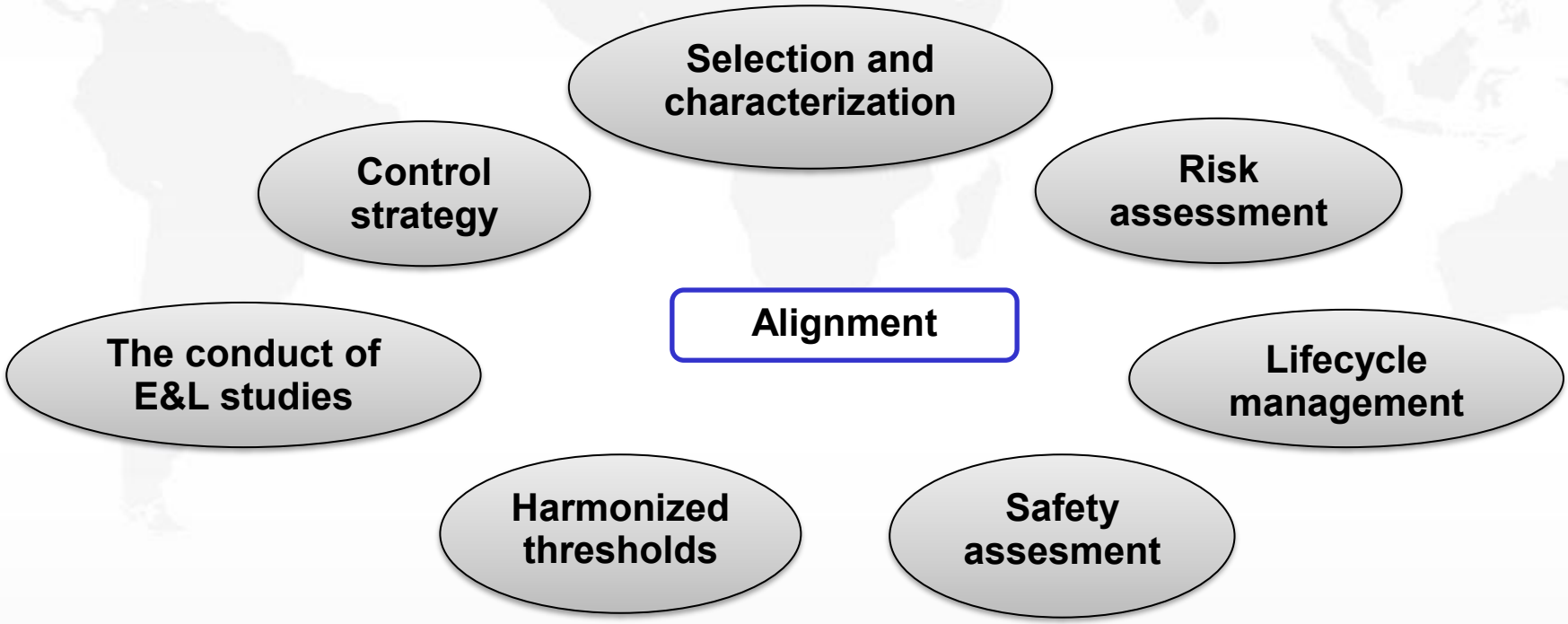
- **Documents available for Regional Consultation:**
  - GUIDELINE FOR EXTRACTABLES AND LEACHABLES - Q3E (https://database.ich.org/sites/default/files/ICH_Q3E_EWG_Step2_DraftGuideline_2025_0704.pdf)
  - SUPPORTING DOCUMENTATION: CLASS 3 LEACHABLE MONOGRAPHS (https://database.ich.org/sites/default/files/ICH_Q3E_Step2_SupportingDocumentation_Class3_LeachableMonographs_2025_0704.pdf)

Background

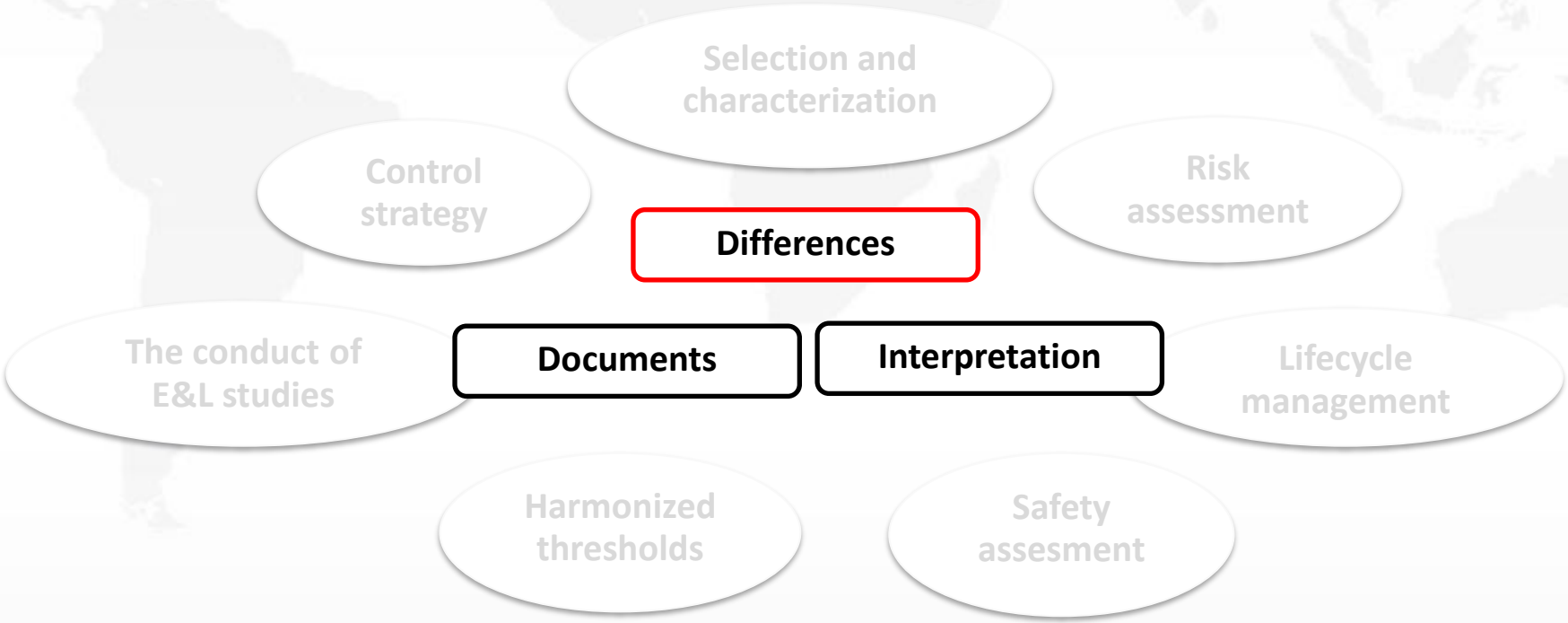
Background

- The new ICH Quality Guideline, Q3E, is intended to:
    1. Minimize uncertainty to meet (global) regulatory expectations.
    2. Encourage design of holistic science and risk-based extractable and leachable (E&L) control strategy based on quality by design principles.
    3. Focus on critical aspects of E&L assessment and control to improve transparency in requirements for pharmaceutical products, including drug delivery device components.
    4. Incorporate a standardized safety assessment based on multiple qualification thresholds in the context of route of administration, drug indication and patient exposure with an emphasis on science- and risk-based approaches.
    5. Compliment and be consistent with existing ICH impurities guidelines (Q3A-D, M7) and align diverse, regional pharmacopoeias.

Background


Selection and characterization
Control strategy
Risk assessment
Alignment
The conduct of E&L studies
Lifecycle management
Harmonized thresholds
Safety assesment

Background


Selection and characterization
Control strategy
Risk assessment
Differences
The conduct of E&L studies
Documents
Interpretation
Lifecycle management
Harmonized thresholds
Safety assesment

Key Principles

Key Principles

Risk-Based Approach

- Risk management described in ICH Q9.
  - Fundamental framework
  - Scientifically justified E&L risk assessment
- Primary purpose
  - Protect patient safety and product quality through assessment and control of leachables in drug product
  - Requires materials characterization and process understanding

Key Principles

Definitions

- **Extractables** are chemical entities that are intentionally extracted from manufacturing components/systems, packaging or delivery device components under specified laboratory test conditions and are potential leachables.
- **Leachables** are chemical entities that migrate from manufacturing components/systems, packaging or delivery device components into a drug product under the established manufacturing and labelled storage conditions.

Key Principles

Safety Concern Threshold (SCT)

- The **SCT** is the threshold below which a leachable* would have an exposure so low as to present negligible mutagenic and non-mutagenic toxicity effects.
  - * Except for Class 1 (high concern) leachables
- SCT is determined by whichever of the following is lower for the drug product:
  - ICH M7 Threshold of Toxicological concern (TTC) for mutagenicity
  - ICH Q3E Qualification Threshold (QT) for nonmutagenic systemic toxicity endpoints
    - Varies by route of exposure

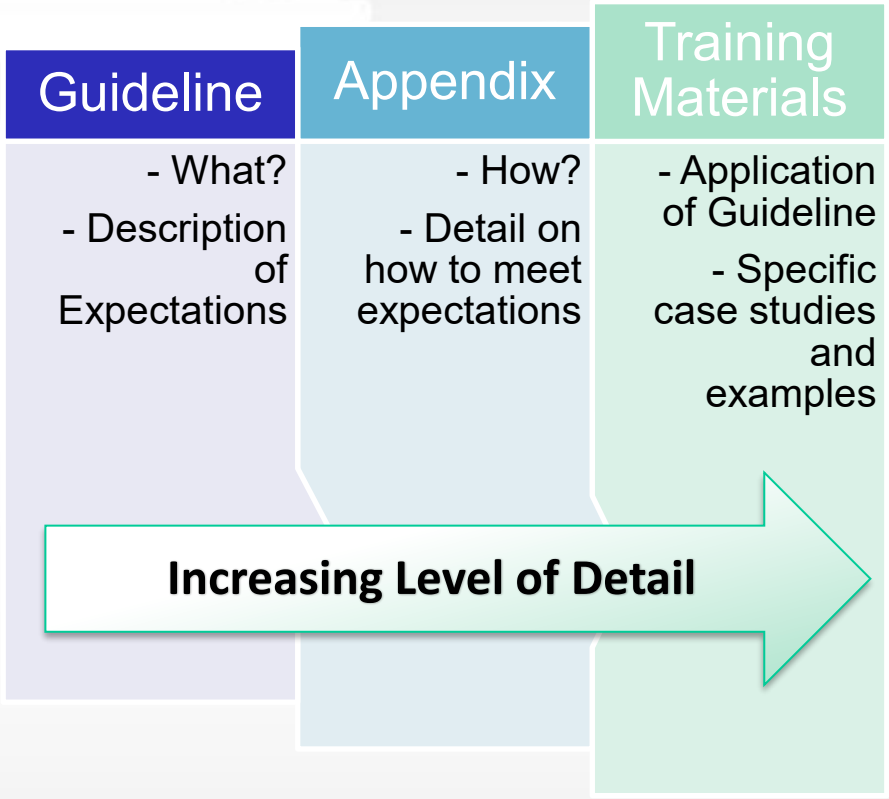
Key Principles

Analytical Evaluation Threshold (AET)

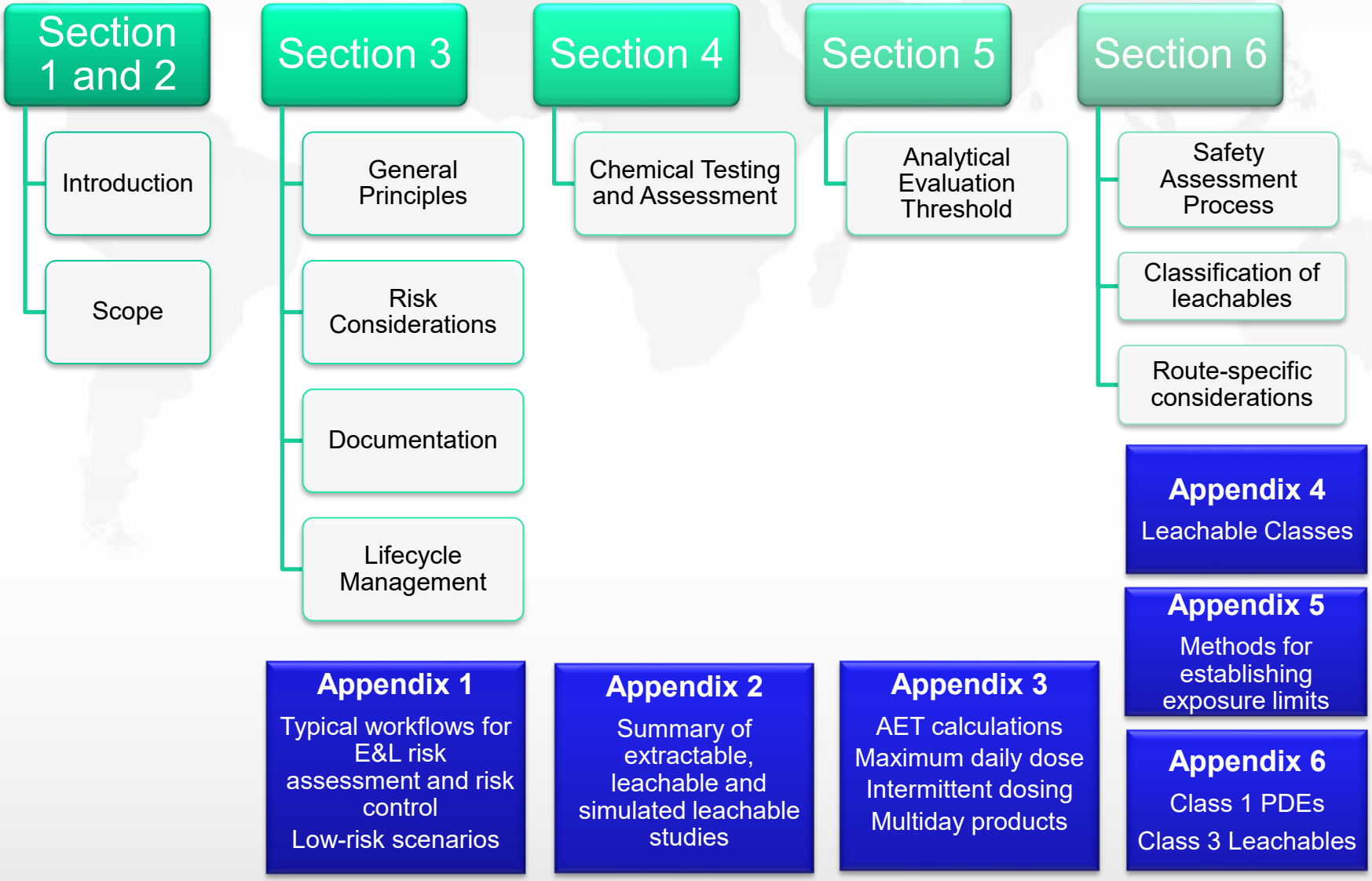
- The **AET** *is not a control threshold*, but a threshold corresponding to a concentration above which E or L should be identified (chemical structure elucidation), quantitated and reported to the toxicologist(s) for safety assessment
- The **AET** Forms the basis of the risk assessment and control strategy and thus proper determination is critical tothe risk management process for E&Ls
- ICH Q3E recommends the establishment of a study-specific **AET** based on maximum daily dosing and the appropriate **SCT**.

High Level Overview of Guideline

Level of Detail



General Outline



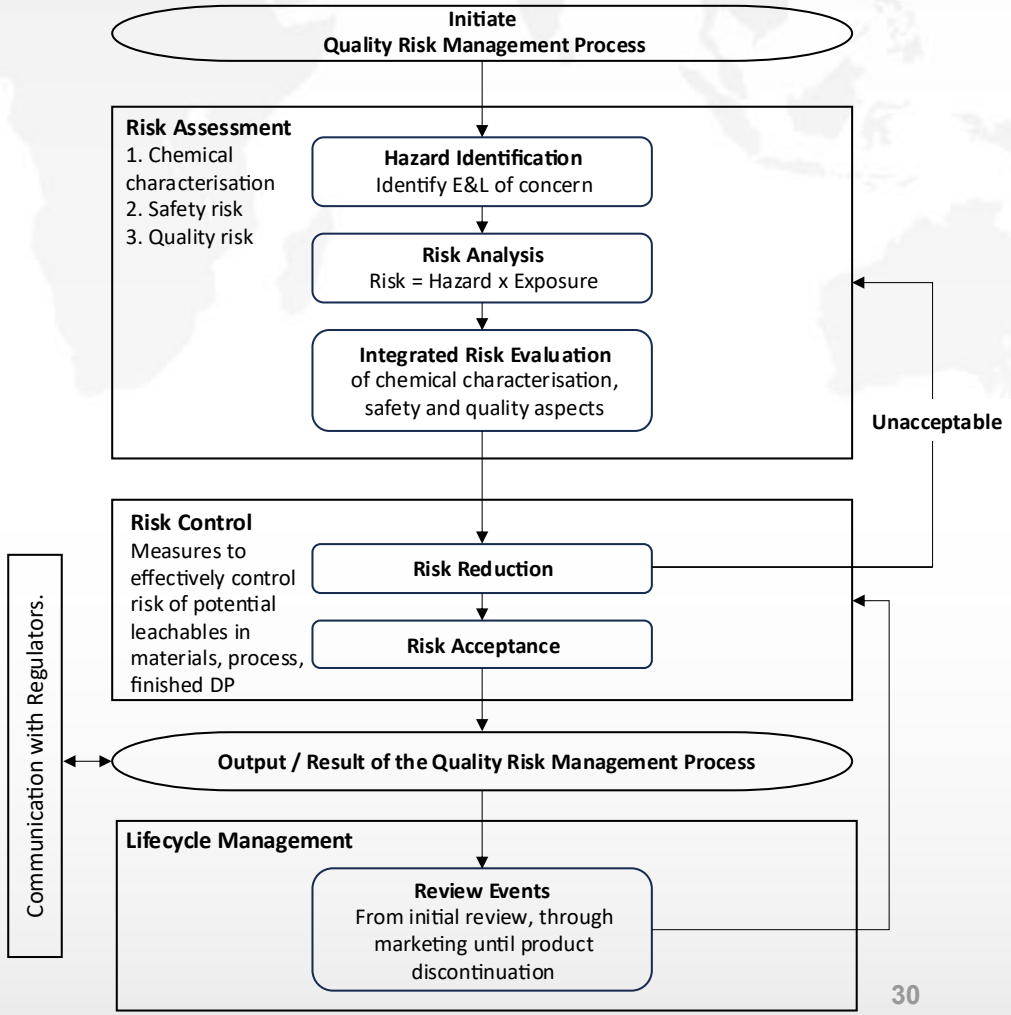
Scope: Organic* Leachables in New Drug Products (DPs)

Intended	Not Intended
New DPs, including cell and gene therapy products	To be applied retrospectively to approved products
Drug-device combination products that require marketing authorization and meet the definition of pharmaceutical or biological products	Extrinsic, extraneous or foreign substances resulting from product contamination or adulteration
Life cycle management changes relating to formulation, manufacturing, dosing, container closure system etc.	Herbal medicinal products and crude non-processed products of animal or plant origin
Storage of a liquid or semi-solid drug substance.	Clinical development products
	Excipients
	Radiopharmaceuticals (unless cause for concern)

*Most principles applicable to inorganic leachables, but safety assessment per Q3D

Overview of Risk Management Process

- Aligned with principles of risk management defined in ICH Q9
- Quality Risk Management Process should be initiated with every product, each with its own Risk Assessment, Risk Control and Lifecycle Management process
- Risk assessment composed of 3 steps:
  1. Hazard Identification
  2. Risk Analysis
  3. Integrated Risk Evaluation

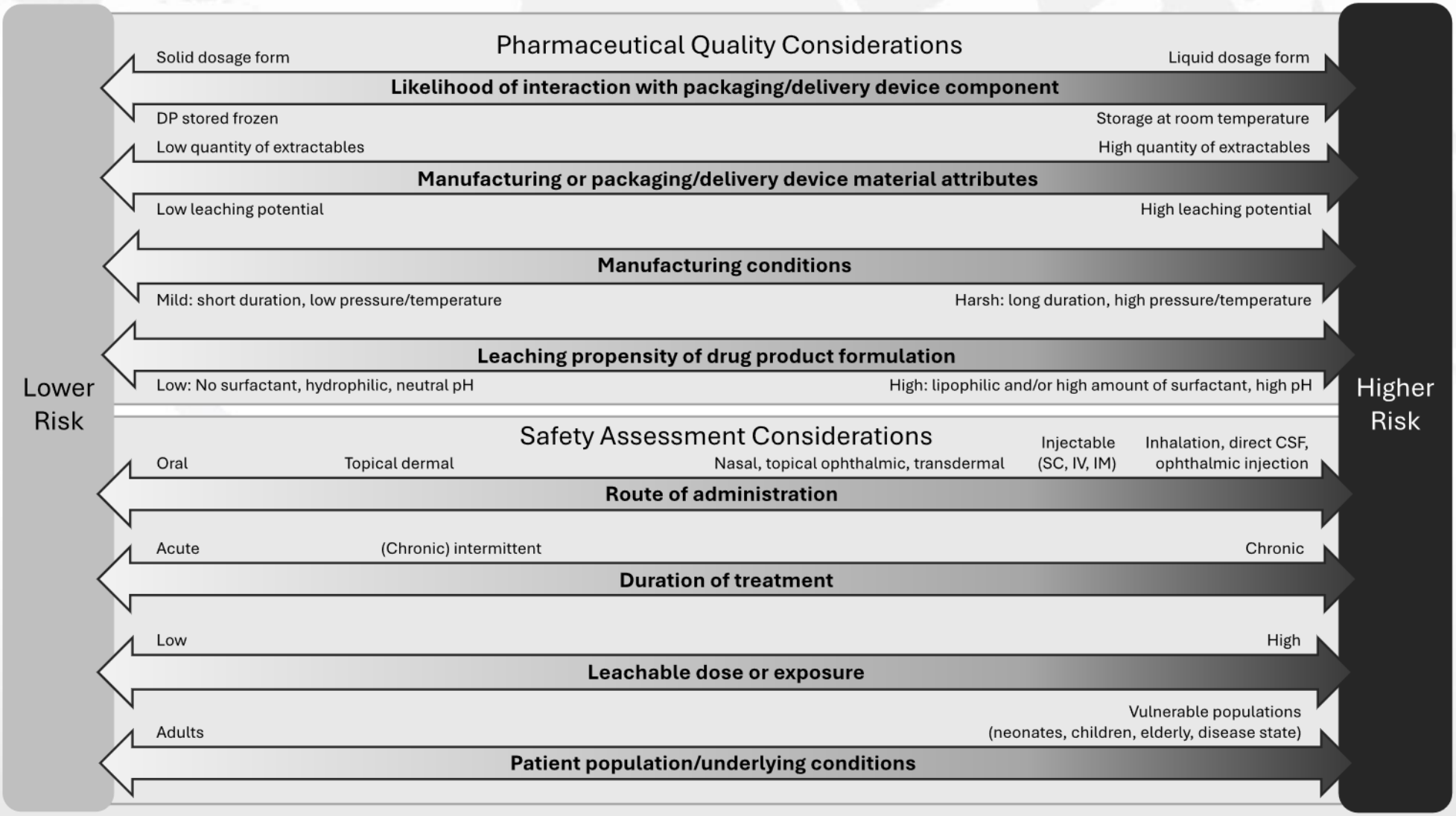


E&L Quality Risk Management

Prior knowledge and thorough understanding of desirable and critical attributes for the manufacturing/packaging components and drug product, as well as manufacturing and storage conditions

Close collaboration between analytical chemist(s) and safety expert(s) essential for knowledge sharing and development of the E&L quality risk management process

Risk Matrix – Multifactorial Aspects



Risk Matrix - Multifactorial

- The risk matrix and factors described highlight the complexity of the risks associated with a leachables assessment. Understanding the respective risk level of the corresponding factors is part of the risk assessment process and may inform manufacturing and packaging components selection as well as the development of the overall assessment/control strategy

E&L Strategy Should be Risk Proportionate and Justified

Depending on anticipated risk and leveraging prior knowledge, various approaches can be adopted.

From compliance with relevant food-contact safety or pharmacopeial standards/regulations up to more extensive E&L characterization and assessment.

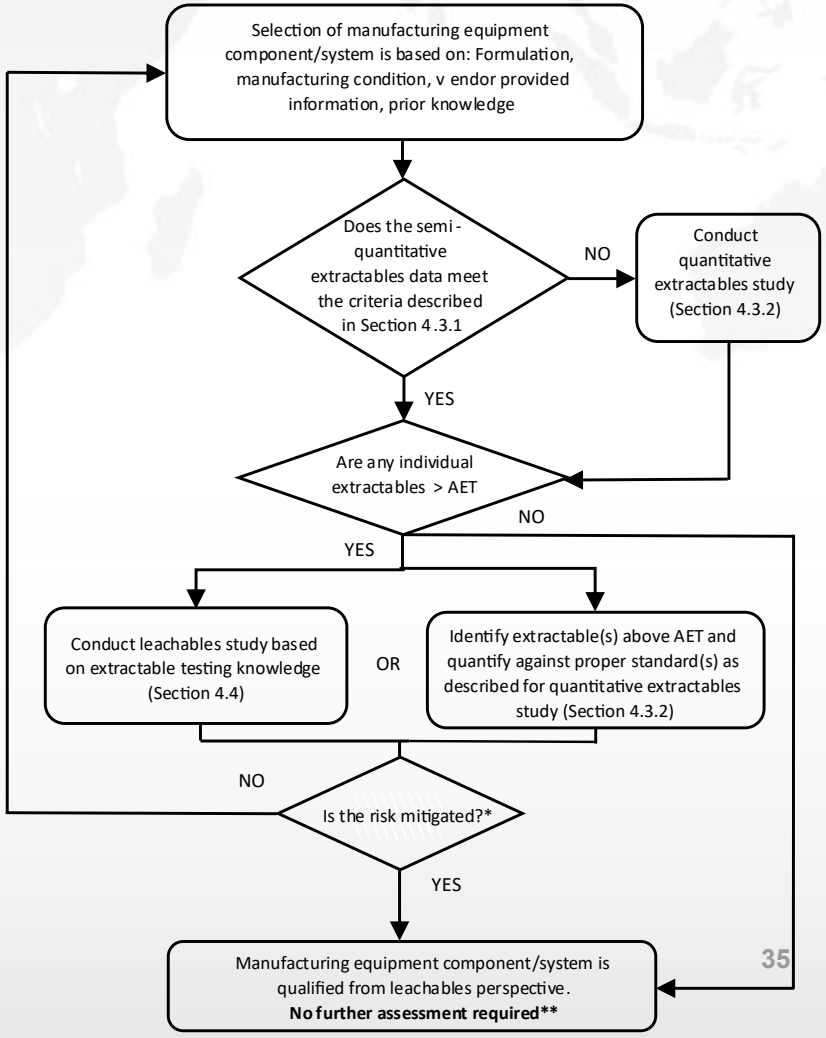
Under certain low risk circumstances, alternative approaches with an abbreviate data package can be proposed with proper justifications.

Typical Workflow for E&L Assessment of Manufacturing Components/Systems

- Overall lower risk due to:
  - Short contact duration
  - Larger volume:surface
  - Few extractables predicted above AET

* Amount of E or Ls below the applicable safety threshold for each compound.

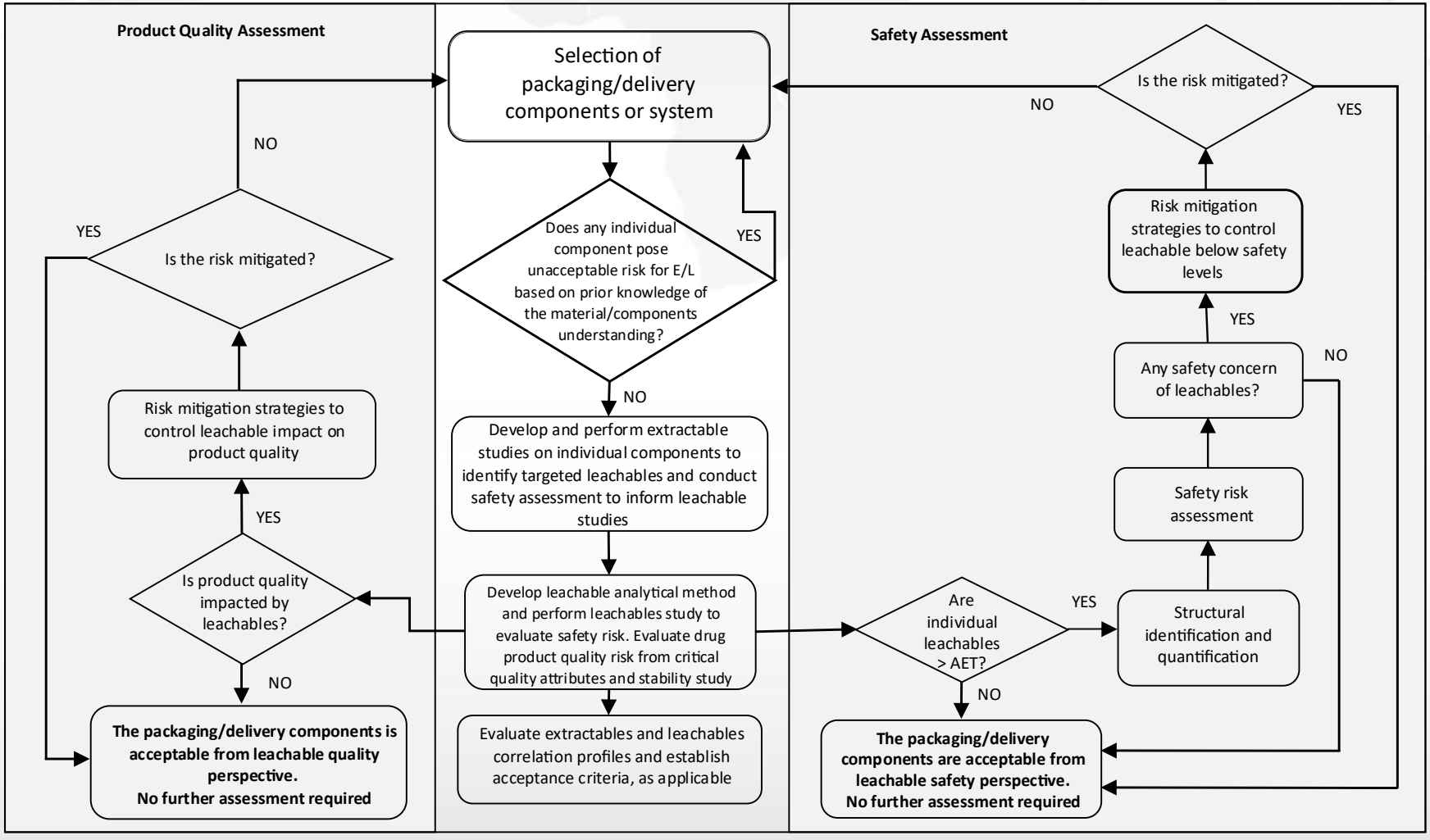
** For manufacturing process employing multiple components constructed with the same or similar material cumulative leachables risk should be assessed for the final DP



Manufacturing Equipment Components/Systems Low Risk Scenarios

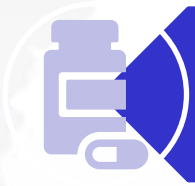
Risk Scenario	Potential Outcome
Scenario 1: Solid oral drug product manufactured using equipment components compliant with relevant regional food and/or pharmaceutical grade requirements.	Components considered qualified without additional extractables or leachables testing.
Scenario 2: Liquid oral drug product using polymeric manufacturing equipment/systems compliant with relevant regional food-contact safety regulations, use of these materials is consistent with the relevant regulations, and the leaching propensity of the drug product is not greater than identified in the relevant regulation.	
Scenario 3: No manufacturing components/systems extractables above the applicable AET in a semi-quantitative extractables study.	
Scenario 4: All manufacturing equipment extractables detected, identified, and quantified in the quantitative extractable study above the applicable AET are below their applicable safety threshold (TTC/QT or compound-specific AI/PDE).	

Typical Workflow for E&L Assessment of Packaging Components/Systems



Examples For Abbreviated Data Package for Packaging Components/Systems

- **Generally, comprehensive E&L data should be provided for all packaging components/systems.**
- However, for overall low-risk scenarios an abbreviated data package may be adequate with justification.



Container closure system components for oral drug products compliant with regional food contact regulations including composition, fabrication, specification, testing results, and in-use limitations specified therein.

Frozen, non-lyophilized drug product stored in well-characterized packaging system (i.e., prior knowledge provided by the applicant). DP thawed and administered within a short time-period and the duration between initiation of filling and freezing is also short (e.g., < 24 hours).

Delivery device components with very short/transient contact with oral drug products (e.g., oral syringes, oral dosing cups) are compliant with regional food contact regulations.

Documentation and Compliance

E&L studies conducted	Rationales, methods, analytical performance and results
Safety assessment of E* or L above AET * If leachables studies not perfomed	
Risk control strategy	Adequacy of proposed mitigation measures
Leachables to extractables correlation when unexpected leachables are observed	Correlation may support lifecycle management changes

Lifecycle Management

- Robust change management system in compliance with GMP requirements and principles of Quality Risk Management (Q9) and Pharmaceutical Quality Systems (Q10)
- Changes which may trigger further E or L evaluation:
  - New information that may impact patient exposure or benefit:risk
  - DP formulation
  - Packaging component/system
  - Manufacturing process
  - Manufacturing components/systems that contact DS and/or DP

Chemical Testing and Assessment

Prior knowledge	• Leverage existing supplier information relevant and drug products or processes
Component selection	• Company responsibility to demonstrate acceptable selection based on multifactorial risk assessment
Extractable study	• Semi-quantitative • Quantitative
Leachable study	• For DP registration representing actual manufacturing conditions and intended storage conditions throughout proposed shelf-life and in-use period
Simulated leachable study	• Augment or replace a leachables study when not technically feasible to conduct
E&L Correlation	• Understand the source of leachables and implement mitigation measures, if necessary

Analytical Evaluation Threshold (AET)

Corresponds to a concentration above which extractables or leachables should be identified, quantified and reported for safety assessment

For semi-quantitative analytical methods, an appropriate uncertainty factor (UF) should be applied to account for potential underestimation of analyte concentrations

The determination of the appropriate UF depends on:

- Prior knowledge
- Materials of construction
- Chemical structure of compound(s)
- Availability of reference standards covering the range of response factors
- Limitations of the analytical methods

Safety Assessment

- Leachables below SCT* considered to have no appreciable patient safety risk
  - *Except Class 1 leachable: if potential presence determined during risk assessment, should be controlled by leachable testing to <PDE (appropriate to DP)
- SCT is product-specific and is defined by
  - Toxicological endpoint
  - Route of administration
  - Duration of administration

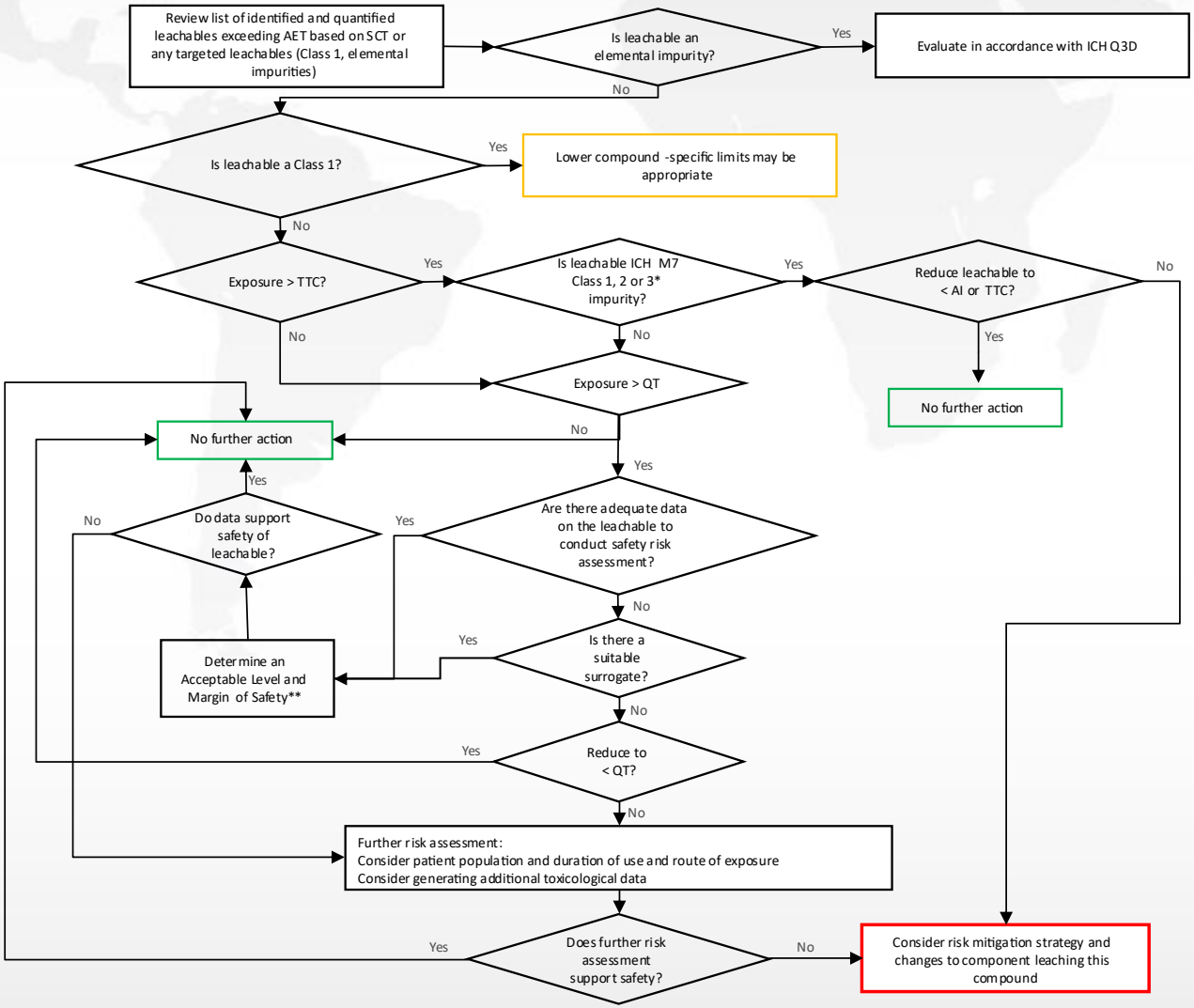
Systemic and Local Toxicity Thresholds

Systemic Toxicity Thresholds				
Exposure Duration	**Oral**		**Parenteral, Dermal/Transdermal, Inhalation**	
	TTC	**QT**	**TTC**	**QT**
> 10 years	1.5 µg/day	48 µg/day	1.5 µg/day	12 µg/day
> 1 to 10 Years	10 µg/day		10 µg/day	
> 1 Month to 1 Year	20 µg/day		20 µg/day	
≤ 1 Month	120 µg/day	136 µg/day	120 µg/day	26 µg/day

Local Toxicity Thresholds				
Topical Ophthalmic	**Subcutaneous and Intradermal**	**Dermal and Transdermal**	**Intracerebral, Intrathecal, Epidural and Intraocular**	**Inhalation**
20 ppm	50 ppm	500 ppm	Compound-specific evaluation	5 µg/day

- *QT values for inhalation and dermal/transdermal routes have been temporarily established based upon parenteral QT. To be updated in subsequent revision.

Safety Assessment Workflow



* As described in ICH M7.

** If daily exposure to leachable is >1 mg/day, genotoxicity studies should be considered, as recommended in ICH Q3A and ICH Q3B (e.g., bacterial mutagenicity study and *in vitro* chromosomal aberration assay).

Safety Assessment

- Conducted for:
  - All observed Class 1 leachables
  - Class 2 leachables detected at levels above the relevant SCT
  - Class 3 leachables when present at levels above 1.0 mg/day.
- Should demonstrate acceptability of anticipated patient exposure levels considering the following endpoints as appropriate for the route of administration:
  - Mutagenic properties
  - Non-mutagenic properties
  - General/systemic effects
  - Local toxicity effects

Potency Classes for Leachables: Appendix 4

Class 1	• ICH M7 Class 1 with an Acceptable Intake (AI) <1.5 µg/day and Cohort of Concern as defined in ICH M7. • Should be avoided or a compound-specific acceptable exposure level should be established. • Currently includes Benzo(a)pyrene (carbon black) and Bisphenol A (polycarbonate, epoxy resin).
Class 2	• Default classification for leachables where mutagenicity (TTC) and systemic toxicity (QT) are considered to be sufficiently patient protective. • ICH M7 Class 1 with AI ≥ 1.5 µg/day or ICH M7 Class 2 or 3 impurities. • Non-mutagenic leachables that do not qualify as ICH Q3E Class 1 or Class 3.
Class 3	• Leachables considered to have relatively low potency for systemic toxicity (i.e., chronic parenteral PDE ≥ 1 mg/day using the methodology described in ICH Q3E). • Considered qualified up to daily exposure levels of 1 mg/day (independent of route and duration) or the compound specific PDE. • Currently includes BHT, Erucamide, 4-Tert Amylphenol, C8-C22 Fatty acids, Rubber Oligomer $C_{21}H_{40}$ and 3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propanoic acid.

Toxicological Risk Assessment Principles: Appendix 5

- Toxicological evaluation may comprise defining compound-specific PDE or Acceptable Exposure Level, or demonstrating large dose ratio between well defined and justified NOAEL and daily patient exposure (e.g. sufficient safety margin)
- If necessary, scientific justification via available in silico analyses and through read across to similar compounds (i.e., surrogate compound[s]) is encouraged to establish acceptable exposure levels.
- Alternative approaches should be considered prior to conducting in vitro and/or in vivo studies.

ICH
harmonisation for better health

Thank you!