

# ICH Q3E: Guideline for Extractables and Leachables

Step 2

**Step 2 Draft guideline – Released for comments**

**Date Aug, 2025**

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## History

- This document has been signed off as a *Step 2* draft guideline (Aug 2025) to be issued by the ICH Regulatory Members for public consultation
- This draft guideline was developed based on the MC-approved Concept Paper (10 July 2020) and a Business Plan (10 July 2020)
- Anticipating finalisation as a *Step 4* final guideline to be implemented in the local regional regulatory system: Jun 2027

## Outline

- **Background**
- **Key Principles**
- **High-Level Overview**
- **Scope**
- **Summary of Guideline Sections/Principles**

# 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 (ICH Q3A-D, ICH M7) and align diverse, regional pharmacopoeias.

# Key Principles

## Risk-Based Approach

- Risk management described in ICH Q9.
  - Fundamental framework to be used
  - 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 for E&Ls

- **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)

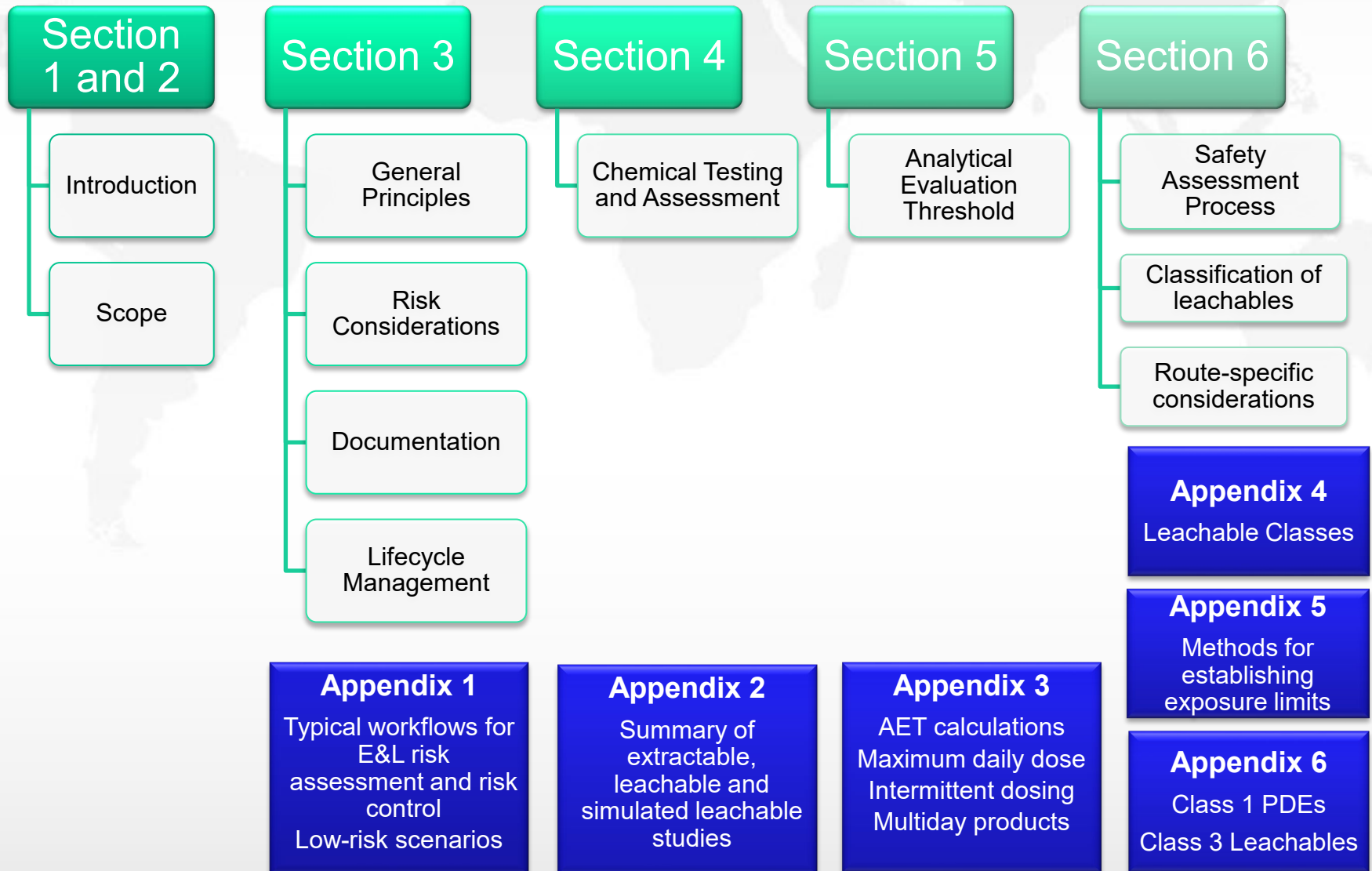
- The **SCT** is the threshold below which a leachable\* would have an exposure so low as to present negligible mutagenic and non-mutagenic toxicity effects
  - \*Except for Class 1 (high concern) leachables
- SCT is determined by whichever of the following is lower for the drug product:
  - ICH M7 Threshold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



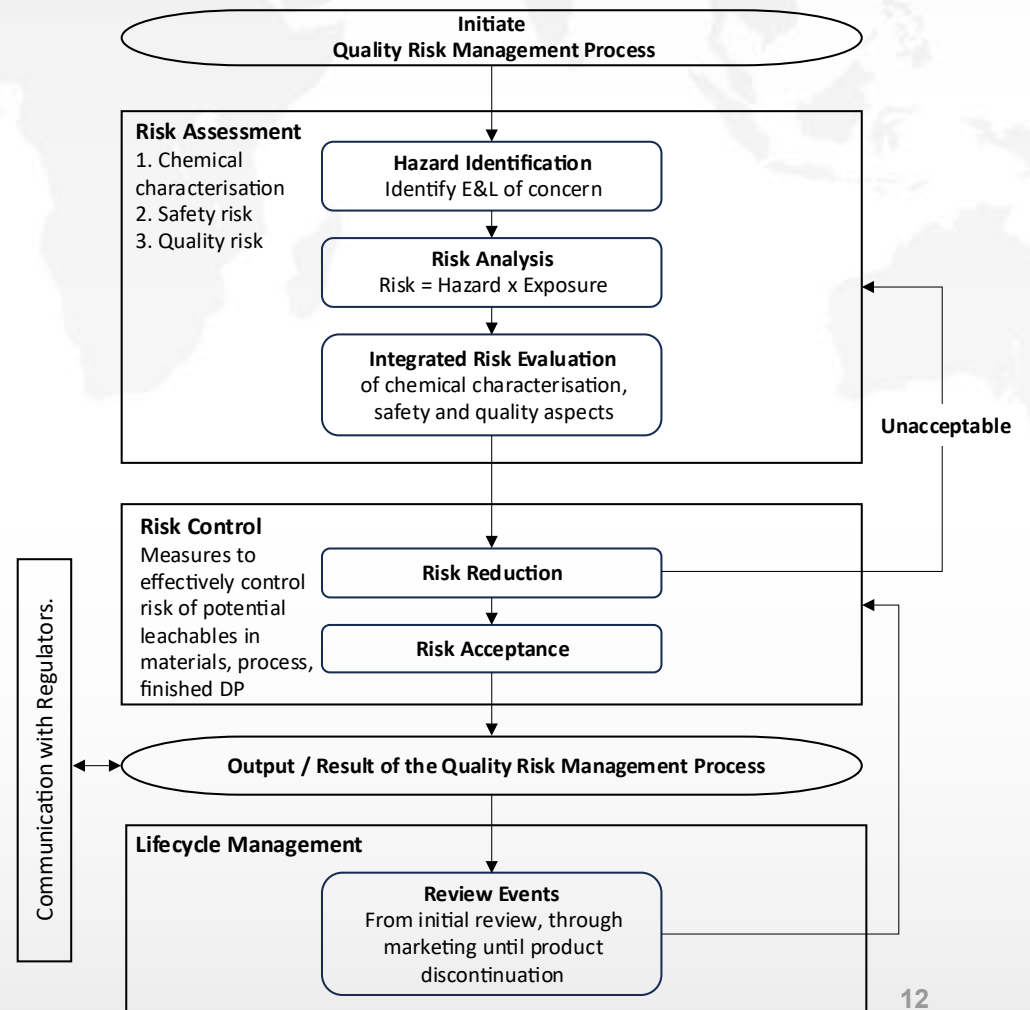
## Scope: Organic\* Leachables in New Drug Products (DPs)

Intended	Not Intended
<ul style="list-style-type: none"><li>• New DPs, including cell and gene therapy products</li><li>• Drug-device combination products that require marketing authorization and meet the definition of pharmaceutical or biological products</li><li>• Life cycle management changes relating to formulation, manufacturing, dosing, container closure system etc.</li><li>• Storage of a liquid or semi-solid drug substance.</li></ul>	<ul style="list-style-type: none"><li>• To be applied retrospectively to approved products</li><li>• Extrinsic, extraneous or foreign substances resulting from product contamination or adulteration</li><li>• Herbal medicinal products and crude non-processed products of animal or plant origin</li><li>• Clinical development products</li><li>• Excipients</li><li>• Radiopharmaceuticals (unless cause for concern)</li></ul>

\*Most principles applicable to inorganic leachables, but safety assessment per Q3D<sub>1</sub>

# 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

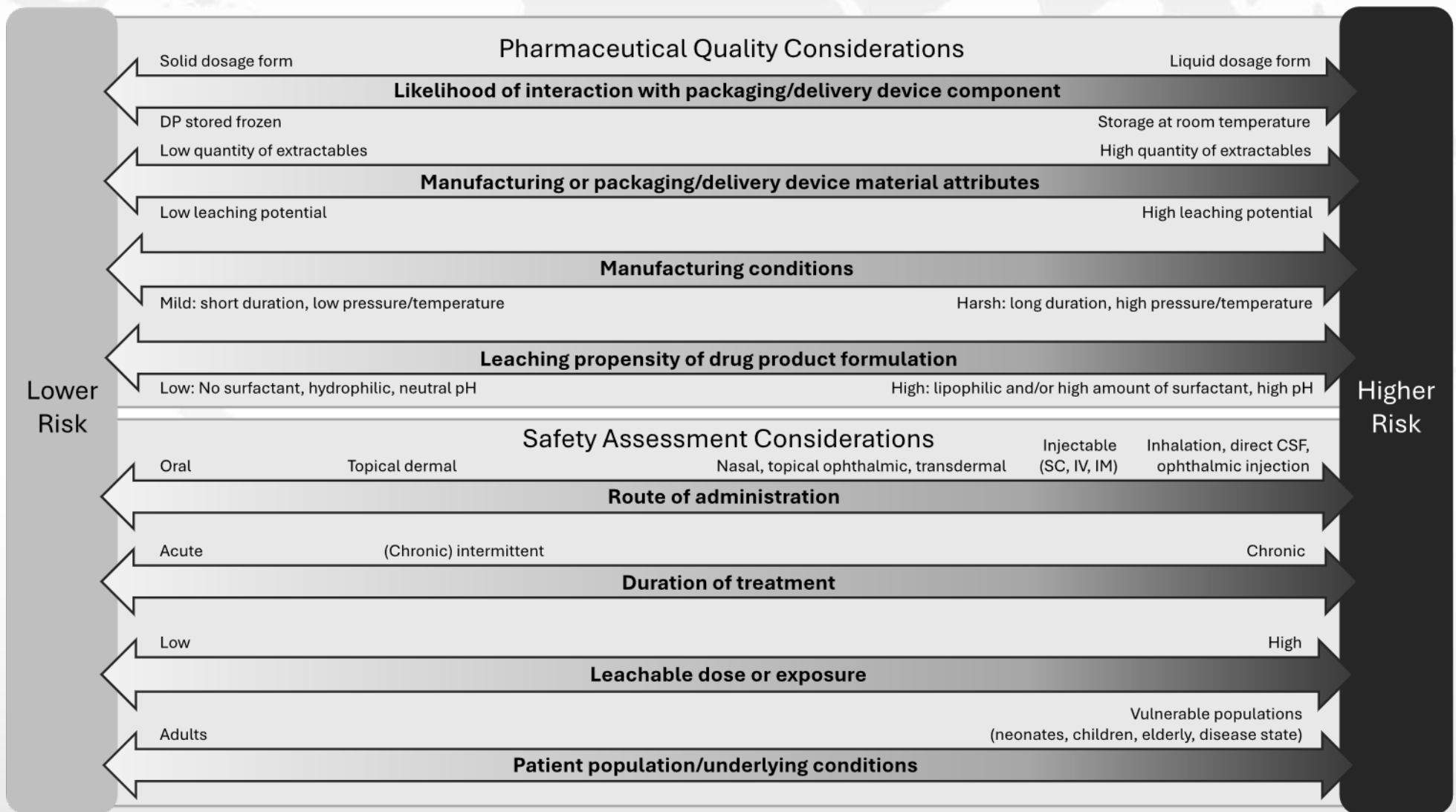
Prior knowledge and thorough understanding of desirable and critical attributes for the manufacturing/packaging components and drug product, as well as manufacturing and storage conditions

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

- **Pharmaceutical Quality Critical Dimensions:**
  - Potential for interaction between manufacturing equipment and/or CCS and the DP
  - Physico-chemical properties of equipment/CCS components, including any pre-treatment of components prior to use
  - Manufacturing and storage conditions (e.g., SA:V ratio, temperature, duration of contact, etc.)
  - Leaching propensity of the formulation (e.g., API, pH, organic co-solvents, surfactant/chelating agents, etc.)
- **Safety Assessment Dimensions:**
  - Potential safety impacts posed by leachables, inclusive of exposure-related factors such as the risk impact of the route(s) of administration, pertinent patient population(s), maximal dosing, dosing frequency and/or intervals, and maximum potential treatment duration in a lifetime.

# Risk Matrix – Multifactorial Aspects to Consider



## 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.

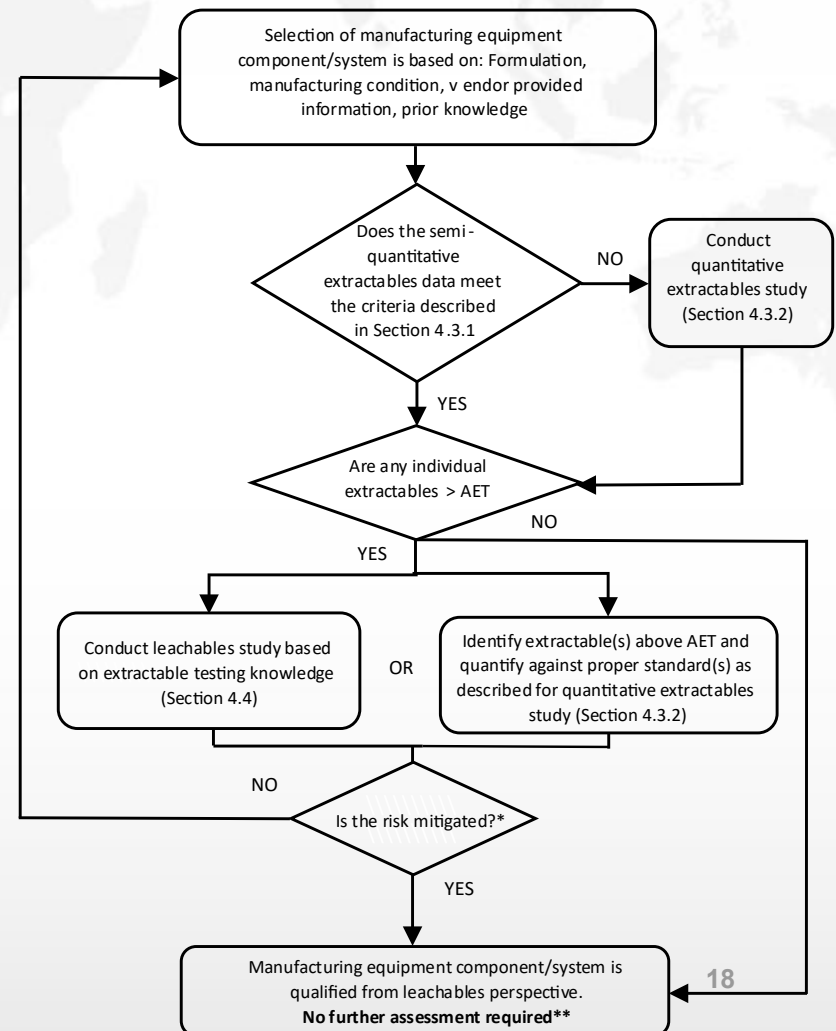
Under certain low risk circumstances, alternative approaches with an abbreviate data package can be proposed with proper justifications.

# Typical Workflow: 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.

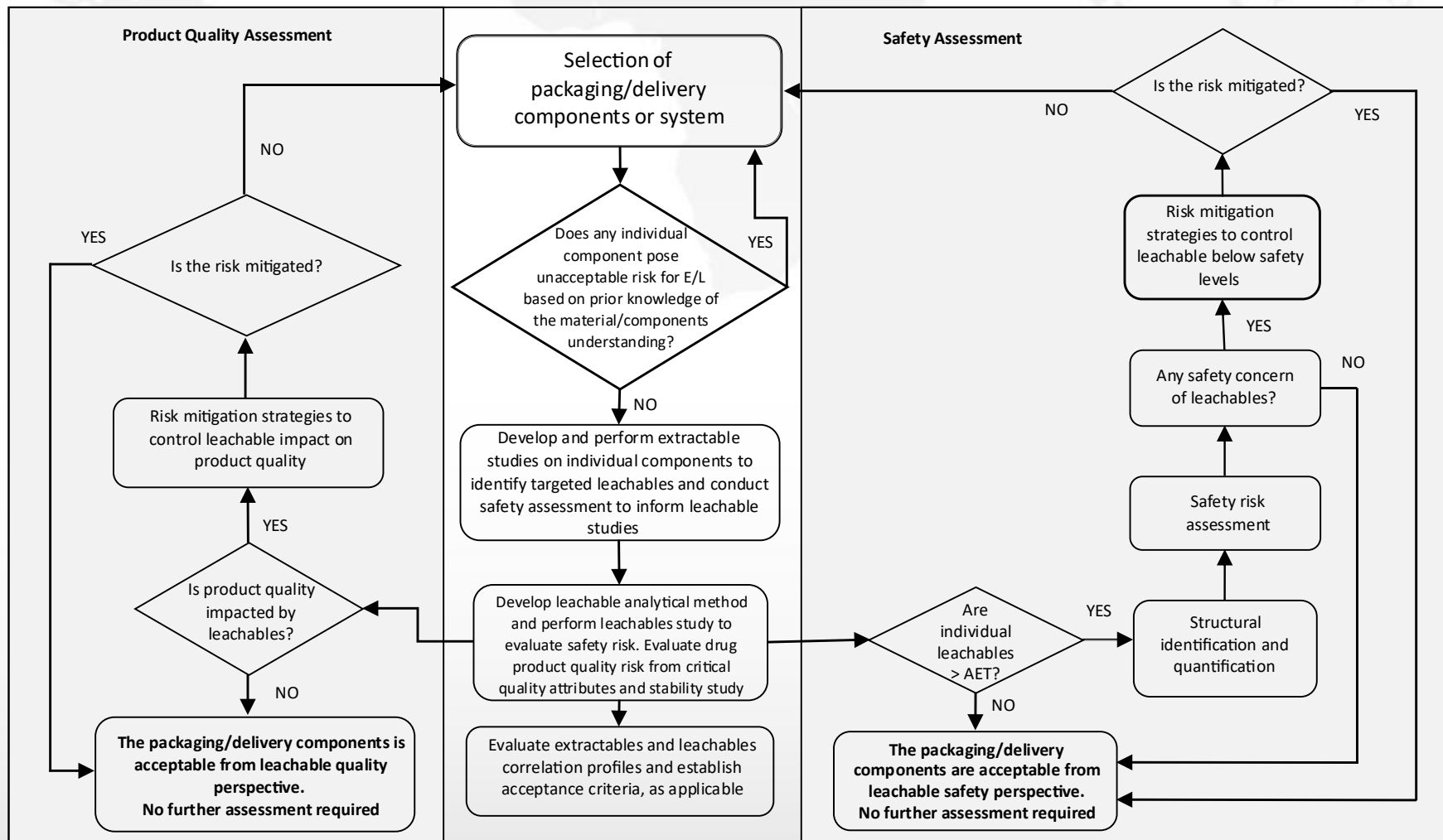
\*\* For manufacturing process employing multiple components constructed with the same or similar material cumulative leachables risk should be assessed for the final DP



## Manufacturing Equipment Components/Systems Low Risk Scenarios

Risk Scenario	Potential Outcome
<p><b>Scenario 1:</b> Solid oral drug product manufactured using equipment components compliant with relevant regional food and/or pharmaceutical grade requirements.</p>	<p>Components considered qualified without additional extractables or leachables testing.</p>
<p><b>Scenario 2:</b> 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.</p>	
<p><b>Scenario 3:</b> No manufacturing components/systems extractables above the applicable AET in a semi-quantitative extractables study.</p>	
<p><b>Scenario 4:</b> 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).</p>	

# Typical Workflow: 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 proper 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 performed



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 (ICH Q9) and Pharmaceutical Quality Systems (ICH 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

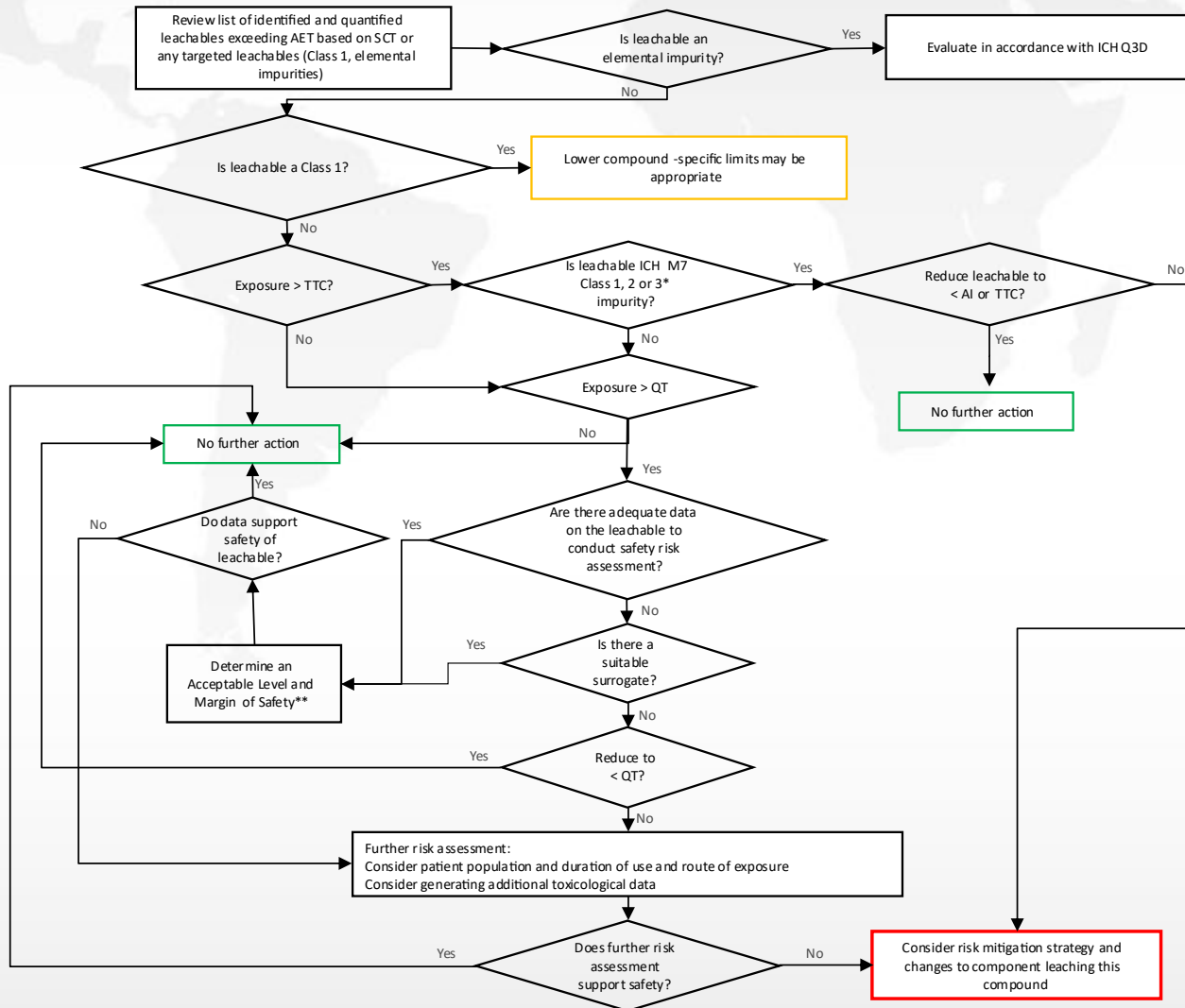
- Leachables below SCT\* considered to have no appreciable patient safety risk
  - \*Except Class 1 leachable: if potential presence determined during risk assessment, should be controlled by leachable testing to <PDE (appropriate to DP)
- SCT is product-specific and is defined by
  - Toxicological endpoint
  - 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)  $<1.5 \mu\text{g}/\text{day}$  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  $\geq 1.5 \mu\text{g}/\text{day}$  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  $\geq 1 \text{ mg}/\text{day}$  using the methodology described in ICH Q3E).
- Considered qualified up to daily exposure levels of  $1 \text{ mg}/\text{day}$  (independent of route and duration) or the compound specific PDE.
- Currently includes BHT, Erucamide, 4-Tert Amylphenol, C8-C22 Fatty acids, Rubber Oligomer  $\text{C}_{21}\text{H}_{40}$  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.

## Timeline

- **Q3E draft Guideline currently under public consultation**
  - EMA comment period ends Mid-December
- **March 2026: Meeting to finalize Threshold Project**
- **June 2027: Step 3 sign-off and Step 4 adoption of final Guideline**

# Acknowledgements – Q3E EWG



**THANK YOU!** 😊