Introduction: Concepts in LEACHABLES RISK MANAGEMENT

OVERVIEW

The ELSIE consortium has developed this set of white papers to describe how extractables and leachables evaluation related to drug product (including drug-device combination products) and manufacturing systems can be approached within a risk management framework, based on the comprehensive risk management framework described in ICH Q9 Quality Risk Management, and illustrated in Figure 1.

These papers describe conceptually how each of the main elements of risk management noted in the figure – screening and materials selection, risk assessment, risk control and risk review -- could be applied to overall leachables management. These are considered "living" pages and will be updated from time to time with new insights and information

We also note and recognize several standards, industry publications, and regulatory guidelines that provide invaluable information on how to consider extractables and leachables testing and aspects of risk associated with leachables. Some of these have served as foundational documents for ways to think about leachables risk and control (e.g., PQRI recommendations for orally inhaled and nasal drug products; FDA packaging guidance; EMA plastic packaging guideline).

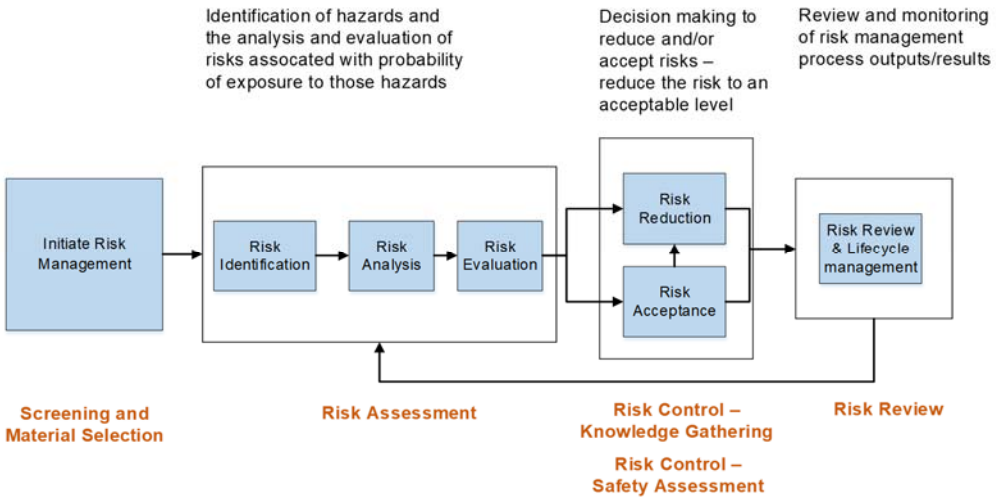

Figure 1. Risk management framework for extractables and leachables, based on ICH Q9

GAPS IN CURRENT GUIDANCE

Important gaps exist in the current global regulatory guidance on extractables and leachables. A key general gap is the lack of an articulation of leachables management that is grounded in an overall risk management framework, and which provides risk-based context within which existing standards, industry practice documents, and regulatory concepts can be prioritized and applied.

In addition to this overall gap, we have identified some specific gaps, including:

- Lack of a shared glossary of terms which can be applied in all scenarios in which there is a risk of leachables (manufacturing, small and large molecules, delivery devices, etc.)
- No agreed requirement for material selection criteria, in alignment with quality by design.
    - No broadly agreed definition of “pharmaceutical grade material”
    - No minimum standards or selection rules or concepts based on risk from materials
    - No agreed weighting of relative importance of different information sets available to define a material’s suitability with respect to leachable risk.
    - Lack of alignment on role of supply chain quality in maintaining quality assurance through product lifecycle
- No clear risk management requirement for each dose form type (requirement most clear for high risk dose forms only)
- No coherent, and consistently described process for risk management of leachables in any guidance which is applicable to all sources of leachables (including manufacturing, packaging, and administration) covering all modalities.
    - No agreed definitions for risk factors (Severity, Probability) to allow risk analysis and scoring
    - No guidance on an appropriate risk evaluation matrix for transformation of risk analysis into risk control decisions
- Lack of clarity and consistency in regulatory expectations for risk control at each stage of drug development and through the lifecycle
    - No agreed study design requirements for each study type (extractables and leachables)
    - No holistic, unified guidelines that consistently apply the threshold concepts of reporting, identifying and qualifying impurities.
    - No agreed safety risk assessment limits for all toxicological end-points
- Lack of defined process for study of lifecycle changes and risk review
    - No definition of Major and Minor changes which might affect leachables
    - No alignment to requirement for prior approval or post notification change

These papers refer to some of these gaps within the context of the proposed comprehensive risk management approach, and its specific elements.

CONTACT US

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