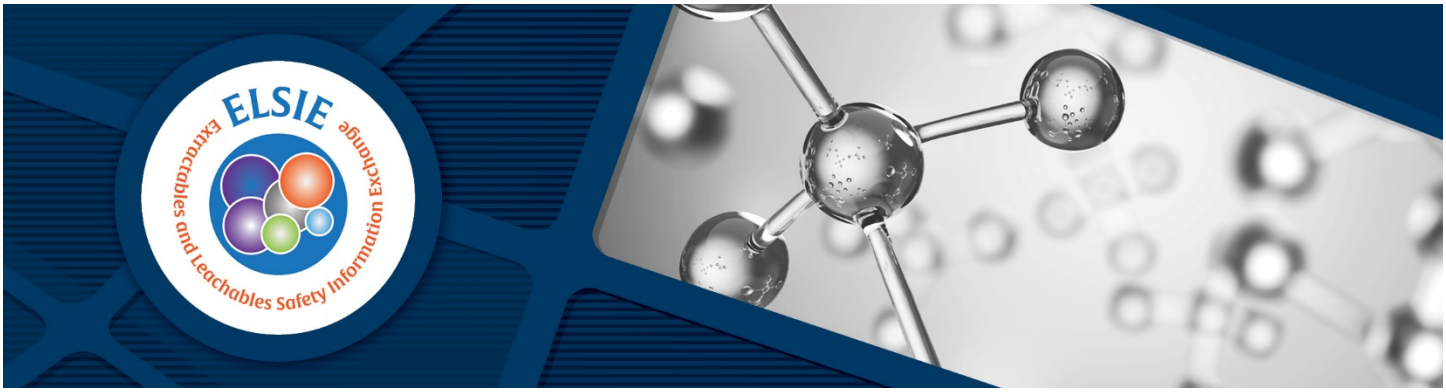

RISK ASSESSMENT FOR LEACHABLES

in Drug Product and Drug Product Manufacturing Systems

INTRODUCTION

This white paper presents a risk assessment process applicable to extractables and leachables (E&L) in systems for packaging, drug delivery, and drug product manufacturing, based on the general principles outlined in ICH Q9, *Quality Risk Management*. It seeks to demonstrate that the ICH Q9 risk management framework can be applied to the management of leachables, regardless of source, in the drug product lifecycle, with respect to both quality and safety.

Risk assessment constitutes a part of the risk management process and is defined as “the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.” Risk assessment includes the activities of risk identification, risk analysis and risk evaluation and feeds into the risk control process (Figure 1).

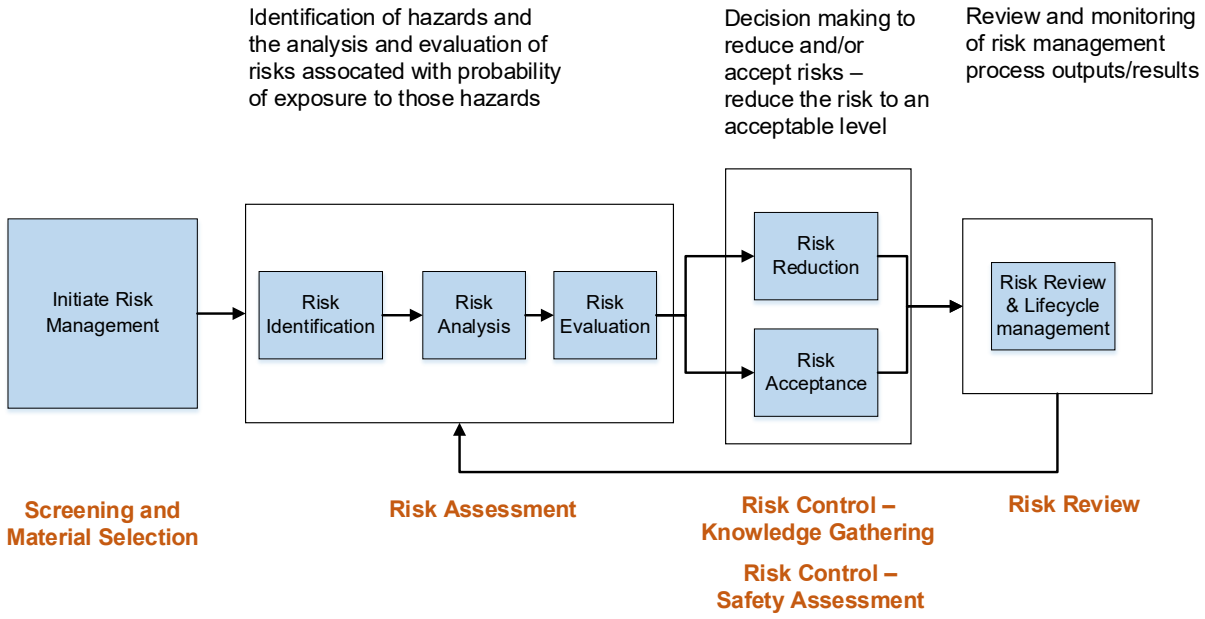

Figure 1. Risk assessment, within the ICH Q9 risk management framework.

According to ICH Q9, risk identification is a systematic use of information to identify hazards referring to the risk or problem; risk analysis is the estimation (scoring) of the risk associated with the identified hazards; and risk evaluation compares the identified and analyzed (scored) risk against a given risk criteria.

As leachables risk evaluation is an important aspect of managing drug product quality and safety, it is appropriate to consider leachables within a risk management framework, and thus how risk assessment can be applied to leachables. The need for leachables-related risk assessment is alluded to in some regulatory guidance, and described in other industry related documents.[1, 2, 3, 4, 5] Leachables risk assessment within the larger risk management framework, however, is not described in current regulatory documentation. In this paper, we will thus:

I. highlight current gaps in information and understanding related to this topic, particularly where such information could help advance harmonized regulatory approaches to leachables evaluation;

II. describe concepts and considerations relevant to risk assessment and its elements of risk identification, risk analysis, and risk evaluation pertaining to leachables; and

III. note existing resources that can assist in providing supporting information on leachables risk assessment.

The scope of our discussion includes drug product packaging, delivery systems, and manufacturing systems relevant to both clinical and commercial production, as well as any modality type, e.g., small molecules, antibodies, cell and gene therapies, oligonucleotides, antibody drug conjugates, and others. Further, although it is recognized that industry uses a variety of risk assessment approaches, and should have the flexibility to do so, we will frame this discussion using some concepts from Failure Mode, Effects and Analysis (FMEA). Using these concepts, the paper discusses a structured examination of how information related to leachables can be assessed with respect to probability, severity, and information hierarchy. Other tools are available for risk assessment as has been demonstrated in the draft chapter USP <1665> and BPOG publications, although these are focused specifically on manufacturing processes.[3, 5]

GAPS

The industry and regulators currently lack a general understanding and agreement on whether there is a regulatory expectation to apply risk management and risk assessment to managing leachables, and if so, how specifically product manufacturers might think about risk assessment as applied to leachables in order to assure product quality and safety. Risk assessment concepts related to leachables, in regulatory guidance, have been very general, as expressed in the FDA's 1999 packaging guidance risk table, which was later presented in modified form in the USP <1664> (Table 1), and the European Medicines Agency decision tree in its plastic immediate packaging materials guideline (Figure 2). [2, 6, 7]

Table 1. General risk considerations as per USP <1664>, based on FDA packaging guidance

Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	**Likelihood of Packaging Component-Dosage Form Interaction**		
	High	Medium	Low
Highest	Inhalation Aerosols and Sprays	Injections and Injectable Suspensions; Inhalation Solutions	Sterile Powders and Powders for Injection; Inhalation Powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and Suspensions: Nasal Aerosols and Sprays	-
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	-	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders

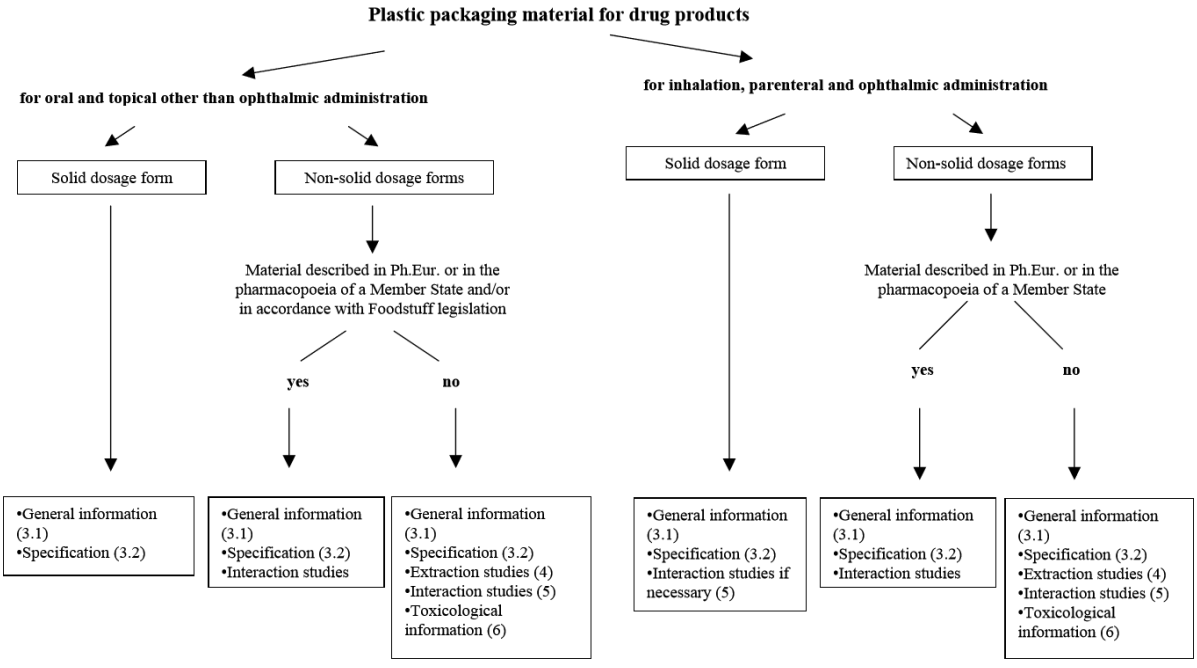

Figure 2. Decision tree on presentation of documentation for drug product plastic packaging material, from the EMA Guideline on Plastic Immediate Packaging Materials.

Further considerations for risk assessment within a larger risk management approach, for leachables are not provided. Specifically, important gaps in information and understanding related to leachables risk assessment within a risk management framework are:

- Currently no agreement on shared glossary of risk terms to apply to extractables and leachables risk assessment (such as found in, e.g., ICH Q9)
- No clear risk management guidance for each dose form type (e.g., guidance most clear for high risk dose forms only)
- No clear and consistently described process for risk management and, specifically, risk assessment of leachables in any regulatory 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

In the following sections, we identify and describe some concepts and principles that could provide a basis for further discussion and creation of a framework for leachables risk assessment, and ultimately a solid basis for guidance on leachables risk management.

RISK IDENTIFICATION

As per Figure 1, the first step of the assessment is risk identification. Risk identification is a systematic understanding of the system under study, and in this paper refers to the risk that leachables following interaction with the materials would have an effect on patient safety and/or product quality.

Conceptually, interaction commonly involves the following processes: (i) leaching of small molecule constituents from a material and into the pharmaceutical preparation; and (ii) sorption/penetration of small (volatile) molecules (solvents) from the pharmaceutical preparation into a plastic material potentially causing swelling and thereby co-extraction from the material. This interaction with the materials can affect the equilibrium levels of leachables and potentially accelerate leaching or result in a negative impact on quality, safety and efficacy of a drug.

For materials used in container closure systems, including delivery systems, leachables could result from interactions with the materials during shelf life storage, transportation and in-use period. For materials used in manufacturing systems, leachables could result from interactions with the materials during production and final formulation. Specific failure mode statements describing the risk can be developed during risk identification, and some examples are these are noted in the Risk Review - Lifecycle Management section.

Risk identification may also incorporate findings from an initial hazard appraisal process (HAP) (see Screening paper) and other studies. As an example, the initial hazard assessment - based on knowledge of the drug product – can be used to identify the main leachables related risks and may lead to a decision that no further risk assessment and E&L testing is needed, as long as the materials of construction and/or components meet certain minimum requirements. This may be the case for low risk dosage forms (Table 1) where the product contact materials or components comply to local pharmacopoeial standards, food standards, and other standards, and drug product formulation compatibility can be shown. Such an assessment is, in effect, a “gap analysis,” which can be done prior to any further detailed risk analysis and evaluation in areas where a “gap” in needed information, exists.

RISK ANALYSIS

The second step of risk assessment is risk analysis (Figure 1), which includes (i) establishing the factors required to analyze the risk and (ii) developing a scoring system with a description and further advice, in alignment with ICH Q9. Risks identified in step one are scored prior to evaluation, based upon the available knowledge and understanding of severity and probability.

As per ICH Q9, risk is considered to consist of two dimensions severity (hazard) and probability, where,

- *Severity* refers to knowledge and understanding of the material and/or the substances present in it. ICH Q9 defines severity as "a measure of the possible consequences of a hazard." This hazard is directly related to the safety and quality of the materials and components that are used to manufacture, contain and deliver pharmaceutical products,;
- *Probability* is an estimate of the likelihood that the identified risk will occur. Based on factors which relate to knowledge and understanding of the processes that give rise to producing leachables in the drug product or process streams. Various aspects should be taken into consideration when assessing the probability of a risk to occur. The probability of the risk defines the likelihood of the risk event occurring to an extent that it would result in an adverse toxicological or product quality event. The probability of substances leaching during the manufacture, storage and/or administration of a drug product is complex and may including processes which are additive or indeed reductive of leachables (such as clearance steps in a manufacturing process or losses during storage), and is best understood by evaluation of leachables data (or simulation studies).

Scoring can be qualitative or quantitative but should be based on well-defined principles which are science-led and easy to understand and implement (e.g., knowledge of the formulation of a contact material is desirable but not always easy to establish and so makes a poor choice as a principal factor to include in a risk assessment scoring system).

Severity and Probability Information

Examples of types of knowledge that might be gathered by the drug substance and drug product manufacturer to address severity and probability scoring are summarized in Tables 2 and 3. In these tables, note that

- The hierarchy of available knowledge for severity and probability is listed in decreasing impact order; and
- An exhaustive extractable study may typically be conducted with the intent to gain a qualitatively complete understanding of what substances are present in a given material. As such, this type of extractable study is aligned to severity associated with a material and its component substances

Table 2. Examples of knowledge impacting severity scoring

	Knowledge impacting severity scoring
Knowledge Types: Studies	Extractable studies data, e.g., qualitative understanding of substances present from instrumental analysis or total amount of substances present via non-volatile residue (NVR) and/or total organic carbon (TOC)
Knowledge Types: Material Compliance (Direct Relevance)	Toxicological study data including biocompatibility assessments e.g. ISO10993-1 compliance[8] USP <87>, USP <88> [9, 10]
	Material compliance statements with direct relevance to severity term, e.g., USP <660>,[11] USP <661>,[12] USP <661.1>,[13] USP <661.2>,[14] USP <381>,[15] USP <232>[16] Ph.Eur. 3.1 and Ph.Eur. 3.2[17, 18]
Knowledge Types: Material Compliance (In-Direct Relevance)	Material compliance statements with in-direct relevance to severity term, e.g., Food compliance (USA), food compliance (EU) REACH declarations
Knowledge Types: Product Knowledge	Compositional information, supplier information (non-study or compliance) such as absence statements

Table 3. Examples of knowledge impacting probability scoring

	Knowledge impacting probability scoring
Knowledge Types: Studies	Leachable studies (or simulation study) data Extractable studies data
Knowledge Types: Product Knowledge	Manufacture and/or processing steps with ability to affect material or leaching (e.g., sterilization, coating, dilution or purge points) Knowledge on limiting solubility and understanding of partitioning behavior between material and formulation (Direction and extent of migration) • Solubilization strength of pharmaceutical preparation (composition/polarity, surfactants / co-solvents (solubilizers)) • Differential solubility / solubilization of leachables in material versus drug solution Kinetics of leaching (i.e., time to equilibrium): • Diffusion behavior • Structure and morphology of material • Temperature • Contact time • Contact surface area to material volume ratio (SA/V_{mat})

Further description of information affecting severity or probability can be found in Appendix 1. A set of physicochemical factors inherent to the system determine both the partitioning and diffusion behavior of a chemical with a potential to leach. These factors are addressed in more detail in Appendix 2. The accumulation of leachables in the drug solution as a result of partitioning, solubility limits and diffusivity can be either experimentally determined or calculated based on science-based and validated models for partitioning and diffusion. Some key principles of this type of mathematical modeling (mass transport modeling) approach are discussed in Appendix 3.

Scoring Severity

A scoring system for severity can be developed on the basis of the available information. Below is an example of a four-level scoring system for severity giving a basic definition and example of how the definition might be met when scoring. The numerical scoring approach on a scale from 1-10 is illustrative only, and other scores can be used for a mathematical risk level determination (Table 4). Additionally, different approaches such as a categorization ladder can be applied, e.g., very low, low, medium, high; low, medium, high, severe, if the risk level discrimination mechanism is based on a risk map.

Table 4. Example of Severity Scoring

Severity Score (category)	Definition
10 (High)	Demonstrated to be a hazard affecting safety (or quality) to an unacceptable degree: Material information details or analytical data which indicates substances hazardous to patients
7 (Medium)	Limited or no information related to safety (or quality): Materials without knowledge from experimental studies or compliance statements
4 (Low)	Some information, but not sufficient to establish for this application there maybe something which affects safety (or quality): Materials which have compliance statements but incomplete experimental studies and associated safety assessment
1 (Very Low)	Demonstrated to have no discernible effect on safety (or quality): Complete experimental studies showing no risk or very low hazard materials (Appendix 3)

Scoring Probability

As with severity, a scoring system for probability can be developed. This can be done based on knowledge of factors contributing to unacceptable levels of leachables in the drug product. The levels and types of leachables can be estimated based on one or more of the following approaches:

I. experimental studies (simulation studies, extractables studies, and/or leachables studies

II. (qualitative consideration of physicochemical factors determining leaching as delineated in Appendix 2, or

III. mathematical modeling (mass transport modeling) as discussed in Appendix 3.

Note that items (ii) and (iii) represent tools to check or to complement experimental data, in particular when severity is low or experimental analysis is challenging.

Table 5 presents an example for probability scoring based on four levels with a definition for each level and an example of how the definition might be met. This scoring approach is illustrative only, and other scores can be used as noted above.

Table 5. Example of Probability Scoring

Probability Score (category)	Definition
10 (High)	Information or experimental studies indicating an inevitable probability of leachables will be dosed to patients: Combination of probability factors indicate leaching is probable, data from an appropriate study indicates that substance will exceed a specific allowable limit[2]
7 (Medium)	No knowledge, or likely probability of leachables will be dosed to patients: Combination of probability factors indicate leaching is likely. It is uncertain if experimental show if allowable limit[2] will be exceeded or generic safety thresholds are exceeded
4 (Low)	Information or experimental studies indicating low probability of leachables being dosed to patients: Combination of Probability Factors indicate leaching is low probability. Experimental data is >10% but <30% of allowable limit[2]
1 (Very Low)	Information or experimental studies indicating very low probability of leachables being dosed to patients: Combination of Probability Factors indicate leaching is low probability. Non-selective methods indicate all substances don't exceed generic thresholds or <10% of allowable limit[1]

[1] Allowable limit for each identified substance in study. See safety assessment paper for discussion on approaches to allowable and generic threshold limits

The probability terms share many of the same characteristics of the terms described in the draft USP <1665> and the BPOG leachables best practices document. It is important to make use of all available data and knowledge that exists at the time of risk assessment and to weight it accordingly when scoring is done.

The example scoring given in this section leads to a 4 x 4 matrix. Other approaches can be used to derive different matrices (e.g, 3 x 4, 2 x 3, etc.). All would share the common goal of establishing risk by combining severity and probability to derive an overall risk score that can be used for a risk evaluation.

RISK EVALUATION

Risk evaluation is closely coupled to risk analysis and is the final step in risk assessment. The matrix developed for risk analysis is used during risk evaluation. Risk evaluation is the process step in which the calculated risk score is evaluated against criteria.

On the basis of the four-level scoring schemes for probability and severity outlined in above, a risk priority number (RPN) can be calculated (the product of severity and probability) and used to create a pre-agreed risk evaluation criterion. The numerical scores and RPN are illustrated in Figure 3 below.

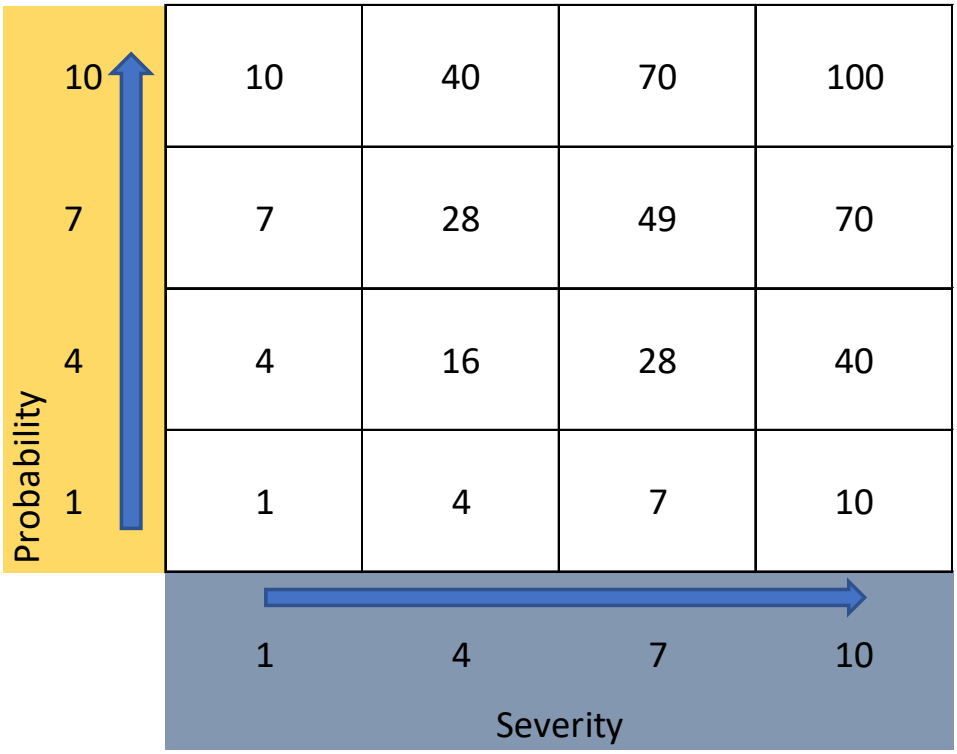

Figure 3. Example RPN matrix for use in risk evaluation

Risk evaluation criteria can be created to reflect a variety of approaches. For example, a criterion for evaluation might be, *risk reduction is required for all RPN greater or equal to a RPN of 28*. However, this does not account for scenarios where probably or severity has scores of 10 (a score of 10 representing either almost certain leaching or an unacceptably high hazard). Thus, it may be prudent to modify the

criterion to read, *RPN scores greater or equal to 28 or individual scores of probability or severity equal to 10 require action*. The nature of the action can be tailored to a choice of risk reduction or lead to risk acceptance for low risks.

- If the alternative (non-numeric) descriptions of severity or probability are to be used, the process is the same. A clear statement of risk evaluation must be written leading to clear outcomes to pass to risk control.
- Regardless of whether numeric or non-numeric scoring is used, it is suggested risk evaluation has the following characteristics:
- Scenarios that are low risk have been sufficiently assessed not to require further risk reduction (risk acceptance).
- Events that are highly probable or severe consequences require some form of risk reduction. Events which have both high probably and high severity also require risk reduction.
- The borderline scenarios (e.g., low likelihood of leaching for a toxic compound) in which an event might be improbable, but have severe consequences, or highly likely, but with little impact, might also require risk reduction, though the outcome is more subjective. The subjectivity of these borderline scenarios are the ones which benefit most from a clear risk evaluation criterion.

As such, a 2-level outcome (Figure 4) or a 3-level outcome (Figure 5) can be generated, depending on the risk evaluation approach taken.

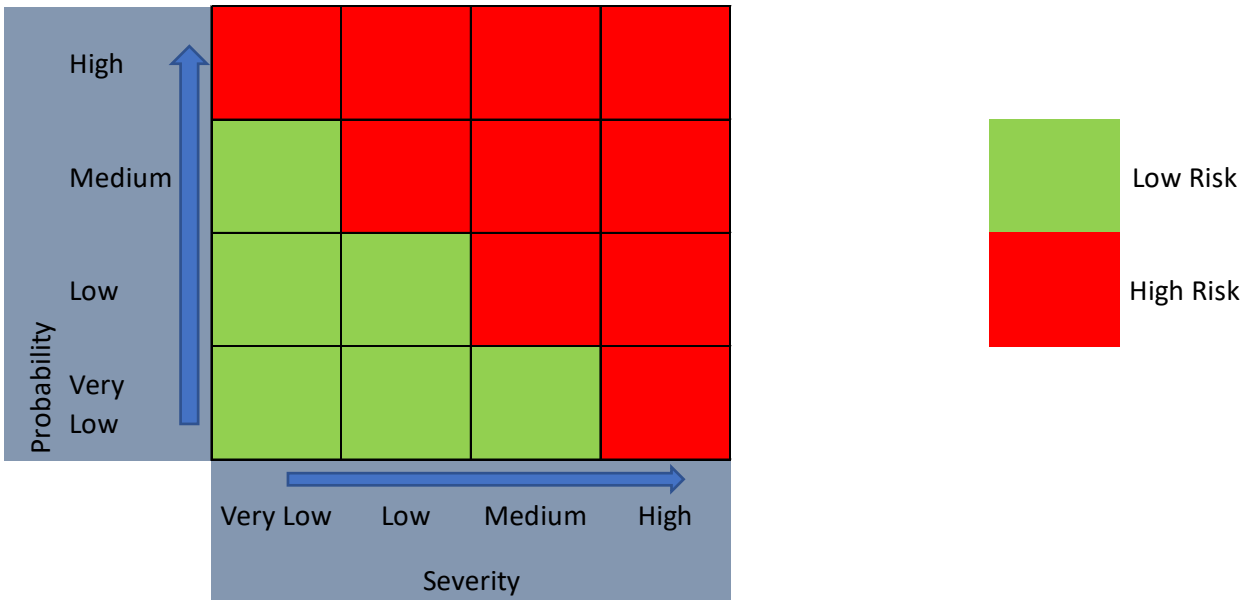

Figure 4. 2-level risk categorization approach using a 4 x 4 risk matrix

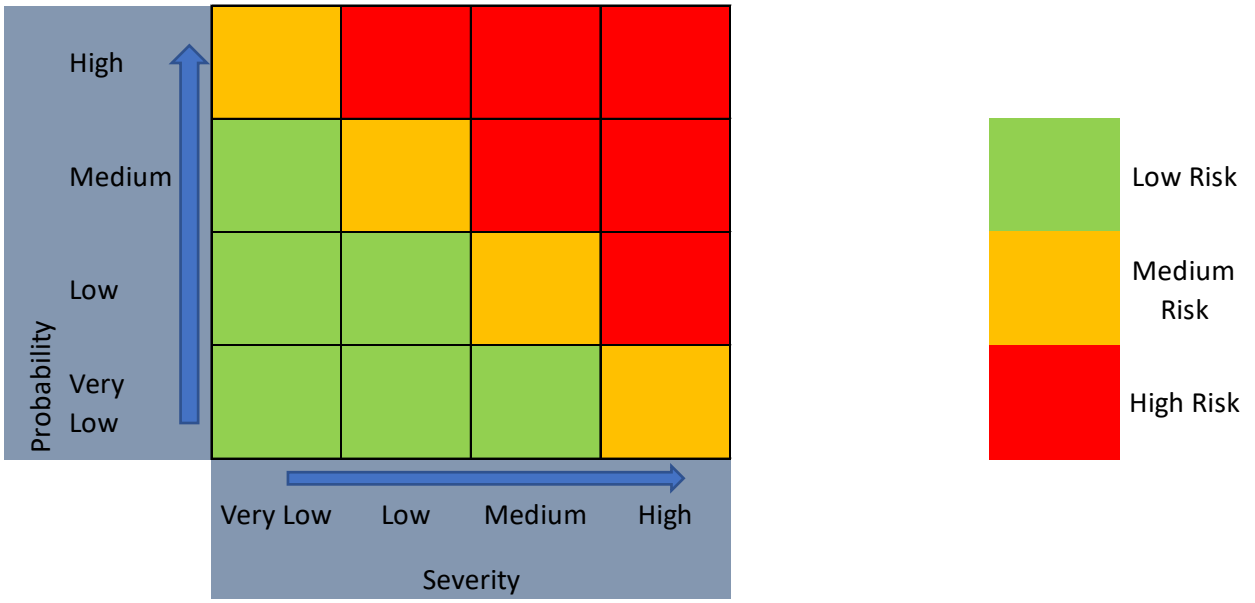

Figure 5. 3-level risk categorization approach using a 4 x 4 risk matrix

Other risk assessment models might have different scoring definitions, or indeed a different number of outcome levels. But the basic requirements are the same: (1) a method to score risk and (2) a method to evaluate the risk. However, it is recommended that risk evaluation should lead to a clear outcome with regard to risk control. It should be simple to understand and lead to simple risk control choices with clear links to risk acceptance or risk reduction. The concepts of risk acceptance and risk reduction are discussed in more detail in the risk control sections.

After risk assessment is completed the process moves to risk control where the assessed risks are further considered. Lifecycle management may include a return to risk assessment as part of a risk review. The section on lifecycle management gives further details on this.

CONTACT US

For more information, please contact us at ELSIE.REPLY@faegredrinker.com

APPENDIX 1.

Additional information on knowledge impacting severity and probability scoring

This section provides a more detailed discussion of types of information on the materials a system is made of including their constituents with a potential to leach. This information is allocated to either the dimension of severity of harm or probability of occurrence. Information types are listed in descending order with respect to their significance in the risk assessment process.

A1.1 Severity of harm (severity)

Extractables data information

An extractable study is typically conducted with the intent to gain a complete understanding of what substances are present within a material and provide chemical characterization. Extraction solvents, as well as time, temperature and methodologies are chosen in such a way that materials of construction are subjected to more aggressive conditions in comparison to the environment in which the material is exposed to during manufacture, storage or delivery. These aggressive conditions ensure a broad range of chemical classes are extracted from the material at levels as close to the amount in the material as possible. Extractable data are toxicologically assessed and if no concerns in terms of patient safety are identified, the risk severity is anticipated to be decreased.

Biocompatibility information

Materials intended for use within a medical or pharmaceutical application should not exhibit biological reactivity, and as a minimum should comply with the requirements of USP<87>. More extensive in vivo biocompatibility testing (i.e., USP<88> and ISO10993) provides a greater degree of understanding of a material's biocompatibility. Compliance with relevant tests in USP<88> (e.g., systematic injection and intracutaneous tests) and ISO10993 (e.g., parts 3, 5, 10 and 11) standards provide further reassurance that the material is appropriate for its application since an extract of it has not elicited a biological response in vivo. Where a material elicits an adverse biological response, material characterization would be necessary to identify the substance (and its source) that is causing this response in the animal. The extraction conditions and solvent systems employed in these studies are less aggressive than those applied during an extraction study. While it could be considered a more representative test for ascertaining the toxicological risk associated with leachables originating from container closure systems and manufacturing materials or components exposed to aqueous or lipid-based biopharmaceuticals, it is unable to characterize material(s), informing the amounts and identity of each substance within a material. Nevertheless, biocompatibility information related to a specific material or component can be used, if available, during the severity risk analysis as materials that have fulfilled compendial testing criteria (e.g., USP <87>, USP <88>, USP <661.2>) are deemed less severe in terms of risk.

Note: One can review the extraction conditions used for the biocompatibility test(s) to ascertain if they are applicable and relevant to the specific material and drug product being assessed. For example, biocompatibility data on a plastic that contacts an aqueous based (pH7) drug product formulation for short periods of time during manufacture could be used to understand the toxicological risk to the patient. However, it would be inappropriate to use biocompatibility data on its own to inform the toxicological risk associated with materials that are subjected to a highly organic environment for extended periods of time (e.g., MDIs).

Compendial compliance

Regulatory standards for plastic materials that are intended for use in pharmaceutical applications should be applied whenever possible. At a minimum, materials used within a pharmaceutical environment should meet these requirements and documentation to that effect should be available from the raw material

manufacturer. Suppliers that modify the raw material into a component/product should be aware of these regulatory expectations and have gone through due diligence with their raw material supply chain, if the intent is to market the material for use in pharmaceutical and biopharmaceutical applications.

Medical grade plastics as defined by VDI (VDI 2017:2019-07, Medical Grade Plastics)[19] that have been demonstrated to be compliant with relevant monographs and regulations have a lower risk severity than materials not designated for the same purpose. Examples of compendial compliance include, but are not limited to, USP <661.1>, USP <661.2>, USP <381>, USP <660>, USP <381>. Ph.Eur. 3.1., Ph.Eur. 3.2.

Note: additional testing by the end user might be required to complete the testing requirements. Consider the value and relevance of any missing data or information in light of the overall risk control strategy.

Non-compendial compliance
Information pertaining to elemental impurities levels can be used to evaluate the severity of the risk based on limits defined in ICH Q3D.

Information concerning food contact materials can also be leveraged to assess risk severity based on COMMISION REGULATION (EU) No 10/2011 of 14th January 2011 on plastic materials and articles intended to come into contact with food and the Code of Federal Regulations (CFR): 21CFR Parts 172 – 179, among others. At a minimum, materials used within a pharmaceutical environment should meet requirements described in these regulations for materials that are intended for use in food packaging applications. Whenever possible and applicable, compliance statements from the supplier should be procured. Suppliers that modify the raw material into a product should be aware of these regulations and should perform this due diligence if intent is to market material as suited to pharmaceutical and biopharmaceutical applications. Suppliers should also have systems in place to manage changes and communicate them to end users.

Compositional information
A detailed description of the monomers, additives package (e.g., antioxidants, nucleating agents, cure system, UV inhibitors, colorants, and etc.) and any processing aids (e.g., mold release agents) used to formulate and manufacture the material should be gathered whenever possible.

This information can be used to consider if chemicals used to manufacture the material present negligible risk to patient safety and have been used at the level previously endorsed by the regulatory agencies and are not on the Substances of Very High Concern (SVHCs) list within the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation within the EU.

Note: substances included in REACH annexes are not to be considered a comprehensive list of extractables as degradation products and non-intentionally added substances are included. This list informs on what chemical entities are added to the material at the raw material supplier level.

Supplier information
Absence declarations for substances with high toxicological concern as natural latex, phthalates, nitrosamines, 2-mercaptobenzothiazole, and etc., should be procured, whenever available as it provides a means to decrease the severity associated with the identified risk.

A1.2 Likelihood of occurrence (probability)

Various aspects should be taken into consideration when assessing the probability of a risk to occur. The probability of the risk defines the likelihood of the risk event occurring to an extent that it would result in an adverse toxicological or product quality event. The probability of substances leaching during the manufacture, storage and/or administration of a pharmaceutical product is complex and is best understood by evaluation of leachables data.

Leachables information

An analytical study that uses a variety of analytical methodologies which identify and demonstrate the absence of a broad range of chemical substances that have migrated into a commercially representative drug product formulation (subjected to storage at its normal or accelerated temperature and humidity environments over its shelf life) from materials used to manufacture, package and/or deliver the drug product, provides the most accurate representation of patient exposure to leachables by confirming the amount of a substance that has migrated into the drug product. Leachable studies, if designed appropriately, discharge the risk of all failure modes. Nonetheless, leachable studies can reveal high concentrations of organic and inorganic compounds due to unexpected introduction of extraneous chemical species during the manufacturing process and this aspect should be factored in due the probability risk estimation.

Nevertheless, in the absence of leachable data, physicochemical factors relating to the material itself (e.g. porosity, structure, types of extractable species, and etc.), its environment during use (e.g. temperature, type and duration of contact, and etc.) and its extractable profile can be considered to qualitatively assess risk probability (see also Appendix 2). For a more quantitative treatment, mathematical (mass transport) modeling can represent an expedient means to estimate leachables levels (see also Appendix 3). Note that both qualitative or quantitative projection of the impact of physicochemical factors on the accumulation of leachables can complement and/or support experimental data, in particular with respect to the correlation of extractables and leachables.

Extractables data information

An extractable study aims to predict the potential leachable burden from one specific material, components or container closure system. It relies on selecting a solvent system that 1) brackets the different products/formulations that interact with the material, 2) is representative of the commercial drug product, and 3) uses extraction conditions that model manufacture and storage of the product. While the choice of extraction solvents should be guided by best mimicking the propensities of a contacting pharmaceutical fluid matrix, this study is best suited to drug product formulations that are simplistic and easily represented as an extraction solvent, or for materials that will encounter a variety of drug product formulations, e.g., empty pre-filled syringes, IV bags, administration sets. While these studies might be fairly straightforward for sterile Water for Injection (WFI) products, they might be more challenging for complex biopharmaceutical formulations. In these cases, appropriate mixtures of organic and aqueous solvents might be required. These studies are a reliable alternative to leachable studies providing the study design is representative of the environment the material is used in for the commercial product.

APPENDIX 2.

Physicochemical factors impacting the levels and types of leachables in a pharmaceutical preparation (drug solution)

The accumulation of leachables in a pharmaceutical preparation and similarly the sorption of compounds to a plastic material are driven by (i) thermodynamic (i.e., partitioning, solubility) and (ii) kinetic constraints (i.e., diffusion, material diffusivities). A number of physicochemical factors imposed by the system and its constituents with a potential to migrate between the system phases impact both partitioning and diffusion behaviour and are specified below.

A2.1 Thermodynamic factors: partitioning and solubility limit

Partitioning of a compound between a (plastic) material and a contacting pharmaceutical preparation representing two homogeneous phases relates to its differential solubilities in both phases. A compound's partition coefficient is a key determinant dictating its maximum level of accumulation in the pharmaceutical

preparation. This is discussed further in Appendix 3 on Mathematical Modeling (Mass Transport Modeling), eq. (1) and (2).

Limiting solubilities constrain the maximum accumulation of leachables to their level of saturation in the contacting solution (liquid drug product or process stream). They are thereby important physical determinants impacting probability of occurrence (see also Figure A3.1).

A2.2 Solubilization strength of the pharmaceutical preparation (drug solution)

The solubility of an extractable compound in the pharmaceutical preparation depends on its composition. While polar (hydrophilic) compound show good solubility or even miscibility in purely aqueous solutions the solubility of more hydrophobic compounds strongly increases in the presence of organic solubilizers (for example, surface-active agents (polysorbate 80) or co-solvents (e.g., ethanol)) thus increasing the propensity of the preparation to extract/accumulate constituents from the contacting material. Some materials (e.g., polyamide) are known to swell upon solvent contact and this should be taken into consideration when assessing the probability of the risk.

A2.3 Clearance and fate of leachables

During manufacturing of biopharmaceuticals, there is potential to reduce the likelihood of the risk by clearance of leachables during steps including ultrafiltration, diafiltration, chromatography or others. Such processes can effectively dilute or even reduce (purging, fate of leachables) leachables levels thus potentially reducing the probability of a failure mode occurring.

A2.4 Factors affecting migration kinetics (time-to-equilibrium)

Material structure and morphology
The physical characteristics imposed by structure and morphology of materials of construction can play a role in analysing the probability of the risk as packaging materials display different porosities, water barrier properties, glass transition temperature, densities, etc. While these materials characteristics impose primarily compound diffusion but also partitioning, they can be considered when performing a risk analysis.

Sterilization technology
Sterilization of closure container systems can be done by steam, but other technologies are also employed for molded parts (e.g., ethylene oxide, gamma-irradiation). The effect of these different techniques can affect the probability of leachables to migrate into drug solution by alteration of the material's physical properties. Additionally, by introducing energy or reactive chemicals (e. g. ethylene oxide) into the material, sterilization processes might contribute to degradation-/reaction products altering the profile of compounds with a potential to leach.

Temperature
Diffusion / migration processes are distinctly accelerated as a result of a temperature increase. Therefore, when systems are exposed to elevated temperatures during processing, storage and distribution, this typically contributes to higher leachables levels after a certain time-period, shorter time-to-equilibrium and therefore a generally increased risk of leaching to occur, respectively.

Contact time
The probability of a leachable to cause harm increases with longer exposure times of the materials in contact with solution due to dependency of compound migration on time (see also eq. (3), Appendix 3). This is applicable, but not limited to:

- container closure/bag systems in contact with liquid and/or solid drug ingredients/formulations
- time of residence or contact in biopharmaceutical manufacturing systems (vessels, tubing, connectors, filters etc.)
- sterilization time

Contacting material surface area to volume ratio
The ratio of the material's contacting surface area towards the pharmaceutical preparation and the material's own volume (SA/V_{mat}) is decisive for the kinetics of migration as it represents the ratio of the cross section leachables need to pass in relation to the total pool of leachables in the material and thereby available for mass transport. A high surface area-to-volume ratio promotes the rate of mass transport (leaching) and shortens the time for equilibration of the system. This results in an overall greater likelihood for substances to migrate from the material.

This ratio should not be confused with the material's contacting surface area towards the pharmaceutical preparation and the volume of the pharmaceutical preparation itself (SA/V_{PhP}) as the latter is only deemed to indirectly affect partitioning.[20]

APPENDIX 3.
Mathematical modeling (mass transport modeling)

Knowledge of the nature and role of physical factors that affect leaching allows a qualitative analysis of risk arising from leachables compounds. Expanding on this (qualitative) knowledge, the predictive concept of mass transport modeling (MTM) connects relevant physical factors with (i) further physicochemical properties of materials, pharmaceutical preparations and potentially leaching compounds and (ii) with thermodynamic and kinetic (diffusion) models.

As a result, MTM presents a science-led and structured evaluation of the parametrization of factors relevant to leaching (and sorption as a similar process). Ultimately, this leads to numerical estimates for the evolution of leachables levels over time.

With a detailed treatment far beyond the scope of this document, Figure A3.1a and A3.1b below are meant to illustrate basic principles of MTM. Based on the schematics of a simplified two-phased system consisting of a polymer (P) and a contacting pharmaceutical preparation or medium (M), it is demonstrated how fundamental key factors controlling migration (leaching) can be leveraged for quantitative characterization of leachables.

Here, $K_{i,P/M}$, is the equilibrium partition coefficient for a solute/migrant i, which is typically equivalent to the differential liquid solubilities[2] of the solute in both phases:

$$K_{i,P/M} = \frac{C_{iP,\infty}}{C_{iM,\infty}} \approx \frac{S_{iP}}{S_{iM}} \quad (1)$$

with: $C_{iP,\infty}$ equilibrium concentration of solute in polymer, $C_{iM,\infty}$ equilibrium concentration of solute in medium, S_{iP}: solubility limit compound in polymer, S_{iM}: solubility limit of the compound in medium.

Of note, by knowing the partition coefficient, the systems phase ratio ß and the initial concentration in the polymer, $C_{iP,0}$, the maximum achievable level of a leachable, $C_{iM,\infty}$, in the pharmaceutical preparation can be derived:

$$C_{iM,\infty} = \frac{C_{iP,0}}{1/ß + K_{i,P/M}} \quad (2)$$

Thus, instead of conducting a "worst-case-calculation" by assuming total transfer of the migrant pool into the medium, a more realistic estimation based on eq.(2) is useful when a partition coefficient polymer/medium is available.

Further, as illustrated in Figure A3.1b, Eq.(2) is expressing the maximum level a leachable can attain which is dictated solely by its initial concentration in polymer (typically representing its total pool), the phase volume ratio of polymer and contacting medium, and, importantly, the partition coefficient between polymer and medium.

It is emphasized, that the situation of partition-controlled levels can only be realized, if the total pool of migrant, m_T, in the two-phased system is sufficiently low to allow the equilibrium concentration levels ranging at or below the migrant's solubility limits in both phases ($c_{M,\infty} \leq S_M$; $c_{P,\infty} \leq S_P$). This requirement is also reflected by Figure A3.1b, indicating that the diffusion controlled concentration profile can, at a maximum, reach the level dictated by the partition coefficient which in turn cannot exceed the solubility level of the migrant in the medium. Only worst-case calculations hypothesizing transfer of the total pool of migrants can lead to higher, although unrealistic levels for leaching.

[2] Note that the subcooled solubility, i. e. the solubility of a compound in the dissolved state at the given temperature has to be used for the calculation of partition coefficients

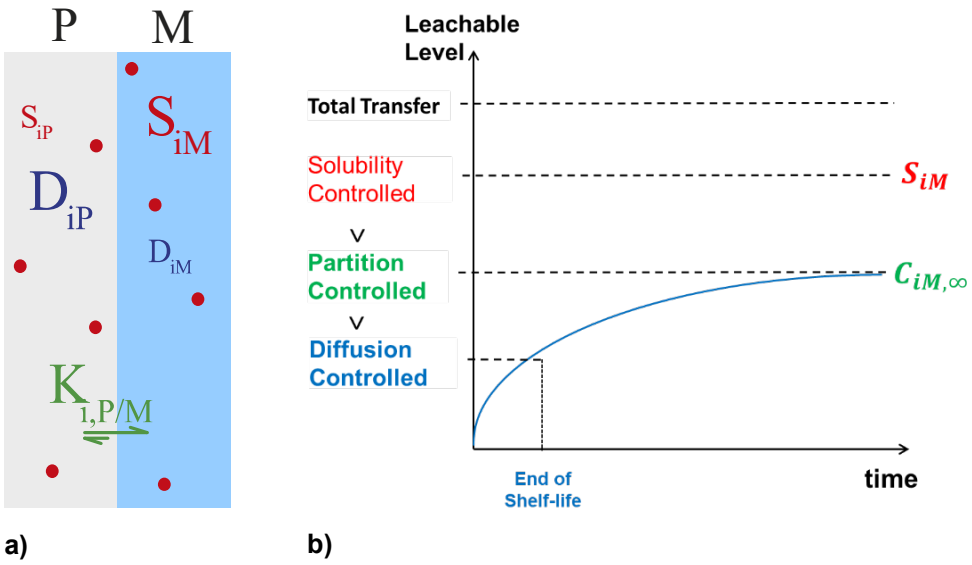

Figure A3.1. Idealized, two-phased contact situation polymer/medium with key parameters D_{iP}, (D_{iM}) $K_{i,P/M}$ and S_{iM} (S_{iP}) affecting leaching a) and their role in governing maximum levels leached through Fickian migration into the contactingmedium b). For symbols/equations see text.

With the diffusion coefficient for the solute i in the polymer, D_{iP}, typically much lower than in the medium, D_{iM}, the kinetics of migration (or mobility of the migrant) can then be derived based on Fick's second law.[21]

For a two-phased system with a migrant homogeneously distributed, the rate of mass transport ($m_{i,t}/A$) for a compound leaching into the pharmaceutical preparation per area of contact, A, ís then proportional to the square-root of time, t, according to:

$$\frac{m_{i,t}}{A} = 2C_{P,0}\rho_P\sqrt{\frac{D_{iP}t}{\pi}} \qquad (3)$$

with: $m_{i,t}$: migrated mass of i after time t through area, A; $C_{P,0}$: initial concentration of migrant in polymer ρ_P: polymer density.

Consequently, as indicated in Figure 1 b), a situation of **diffusion-controlled** migration/leaching would result if the time point-where equilibrium has been reached would reside after a specified time of interest, for example end-of-shelf life.

REFERENCES

[1] Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission. Section 6.1.3. European Medicines Agency. 2016

[2] Container Closure Systems for Packaging Human Drugs and Biologics, Guidance for Industry. U.S. Food and Drug Administration. May 1999.

[3] USP <1665> Characterization of Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products. United States Pharmacopoeia. 2019.

[4] ISO 10993-18:2020 Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process. International Standards Organization. 2020.

[5] Best Practices Guide for Evaluating Leachables Risk from Polymeric Single-Use Systems Used In Biopharmaceutical Manufacturing. Biophorum Operations Group (BPOG). https://www.biophorum.com/best-practices-guide-for-evaluating-leachables-risk-from-polymeric-single-use-systems-used-in-biopharmaceutical-manufacturing/ Accessed 24 March 2020.

[6] USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery systems

[7] European Medicines Agency. Guideline on Plastic Immediate Packaging Materials. 2005. https://www.ema.europa.eu/en/plastic-primary-packaging-materials

[8] ISO 10993-1:2018. Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process.

[9] USP <87>. Biological Reactivity Tests – In Vitro

[10] USP <88>. Biological Reactivity Tests – In Vivo

[11] USP <660> Containers -- Glass

[12] USP <661> Plastic Packaging Systems and Their Materials of Construction

[13] USP <661.1> Plastic Materials of Construction

[14] USP <661.2> Plastic Packaging Systems for Pharmaceutical Use

[15] USP <381> Elastomeric Closures for Injections

[16] USP <232> Elemental Impurities -- Limits

[17] Ph.Eur. 3.1 Materials Used for the Manufacture of Containers

[18] Ph. Eur. 3.2 Containers

[19] VDI 2017:2019-07. Medical Grade Plastics (MGP). https://www.beuth.de/en/technical-rule/vdi-2017/307527917

[20] Jenke, D. (2011). "A general assessment of the physicochemical factors that influence leachables accumulation in pharmaceutical drug products and related solutions." *PDA Journal of Pharmaceutical Science and Technology* **65**(2): 166-176.

[21] Piringer, O. G. B., Lawrence A. (2008). Plastic Packaging - Interaction with Food and Pharmaceuticals, Wiley VCH.