Technical Brief

Extractables and Leachables for Filters, Bags and Other Components
Used in Biopharmaceutical Manufacturing Processes

OBJECTIVE

This Technical Brief provides an overview on how to approach extractables and leachables evaluation for filters, bags and other components used in biopharmaceutical manufacturing processes including Single-Use applications. The Technical Brief is based on our best understanding of regulatory guidance as well as industry practice. It aims at assisting our world-wide customers in fulfilling their responsibilities with respect to extractables and leachables evaluation.

The Technical Brief contains the following:

- Background
- Regulatory and industry guidance
- Risk assessment
- Millipore's approach
- Frequently asked questions and answers
- References

BACKGROUND

Filters, bags and other components constructed of plastic and/or elastomeric materials are extensively used in the biopharmaceutical manufacturing processes. As a result of their contact with a drug product, they can potentially leach compounds into the drug product. The objective of the extractables and leachables evaluation is to demonstrate that these product-contact materials will not adversely affect the product's safety.

Extractables refers to compounds that can be extracted from plastic or elastomeric materials in solvents of different physicochemical properties under aggressive conditions; while leachables refers to compounds that leach from the plastic or elastomeric materials into actual drug product under normal use conditions. Because leachables are expected to be a subset of extractables, the extractables profile should be predetermined.

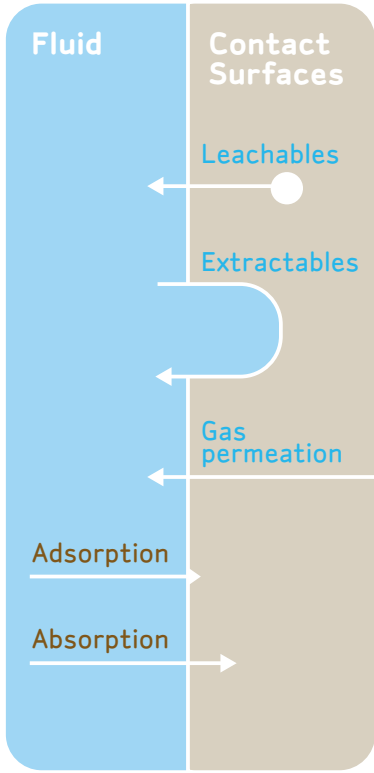

Figure 1. Possible interactions between fluid and its contact surfaces

REGULATORY AND INDUSTRY GUIDANCE

GMP guidelines around the world require that surfaces which contact drug products shall not be reactive, additive, or absorptive so as to alter the safety or efficacy of the drug product beyond the official or other established requirements (Ref. 1-3).

Specific to the filters, in the "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products", the US Food and Drug Administration (FDA) requires users to submit extractables information as part of an evaluation of the impact of the filter on the product (Ref. 4). European Union (EU), in GMP Annex 1, "Manufacture of Sterile Medicinal Products", states that the filter should not affect the product by removal of ingredients from it or release of substances into it (Ref. 5).

Parenteral Drug Association (PDA) Technical Report No. 26 provides details on how to approach the extractables and leachables validation for liquid sterilization filtration (Ref. 6). It outlines the scope of the extractables studies as quantitation of the total amount and identification of the extractables. Within the Technical Report No. 26, PDA recommends users not only obtaining the extractables information from filter suppliers, but also performing the leachables studies, whenever possible, especially if sterile filtration is the final step in the manufacturing process prior to the filling process.

Currently, there are no specific regulatory standards with respect to bags and other Single-Use assembly components. However, if bags are used for final drug product storage, the FDA guidance for container closure systems (Ref. 7) and the European Medicines Evaluation Agency (EMA) guideline on plastic immediate packaging materials (Ref. 8) can be used as references. Both guidelines recommend that an extractables study be followed by a leachables study, as well as accompanied by a toxicity evaluation and risk assessment. Please refer to Figure 2 Summary of EMA requirements for plastic immediate packaging materials. In addition, U.S. Pharmacopeia (USP) Chapter <661> "Containers" and European Pharmacopeia (EP) Chapter 3 "Materials and Containers" describe the compendia test methods for containers (Ref. 9-10).

To address the lack of regulatory guidance for the Single-Use applications, Bio-Process System Alliance (BPSA) has published its recommendations for extractables and leachables testing. BPSA also suggests users obtain the extractables information from suppliers, conduct the toxicity evaluation, as well as quantify and identify the leachables, as necessary. The BPSA recommendations focus on a risk assessment-based approach, where the degree of testing and analysis is determined by the relative risk that leachables from a Single-Use component pose to a final drug product. Please refer to Figure 3 Decision Tree for Disposable Manufacturing.

Finally, Product Quality Research Institute (PQRI) has recently established safety thresholds and "best practices" with respect to the extractables and leachables for orally inhaled and nasal drug products (Ref. 12). Based on a statistical analysis of a large number of compounds, the PQRI Leachables and Extractables Working Group sets the safety threshold at 0.15 µg per day, below which no further safety assessment is necessary. It should be noted that this level is considered valid only for high-risk applications such as orally inhaled and nasal spray drug products, and may not be applicable to other forms of drug products such as parenterals that are of significantly lower risks.

Figure 2. Summary of EMA requirements for plastic immediate packaging materials

Is this Plastic Material as described in European Pharmacopeia?	
YES	**NO**
General information(1) Specification(2) Leachables studies(3)	General information(1) Specification(2) Leachables studies(3) Extractables studies Toxicological documentation

(1) - Chemical name of the material, monomer, additives, etc.
(2) - Specification of plastic material. See Validation Guides.
(3) - Leachables studies can be omitted if, based on the outcome of the extractables studies, the calculated maximum amount of the individual leachables substance that may be present in the drug product leads to levels demonstrated to be toxicologically safe.

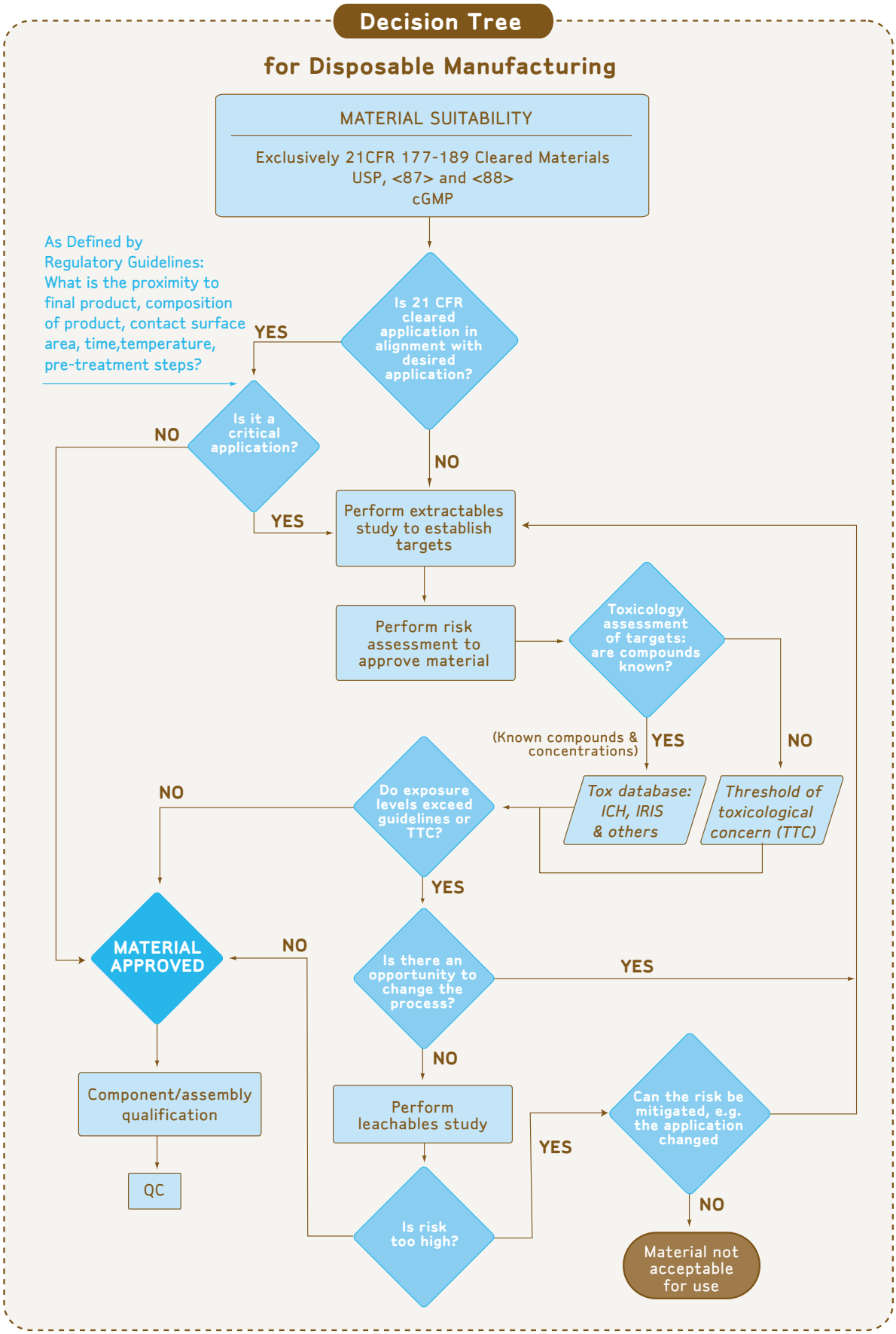

Figure 3. Decision Tree for Disposable Manufacturing

RISK ASSESSMENT

The first step in an extractables and leachables evaluation is to identify all product-contact materials based on process knowledge. The second step is to perform a risk assessment to determine critical materials that require further information on the extractables and leachables. Multiple factors should be taken into consideration, including but not limited to the following:

- Chemical compatibility between material and drug product
- Toxicity of the extractables
- Contact time
- Contact temperature
- Surface area-to-volume ratio (including batch vs. contiunous processing)
- Proximity of material to final product
- Dosage form
- Route of administration

A risk factor can be categorized into varying degrees of severity (see Table 1 below), as well as characterized based on the combination of severity and frequency. A numerical value can be assigned to reflect the relative ranking that a risk poses to a drug product (Ref. 13).

In applications where the risk is low, it is possible that the risk assessment combined with an evaluation of the extractables information will be sufficient and therefore no further action is required for leachables (Ref. 11). Millipore provides customer consultation in the area of risk assessment based on our extensive knowledge, but ultimately the decision of the type and level of testing rests with drug manufacturers based on their risk assessment analysis and regulatory experience.

Table 1. Risk factors and their various degrees of severity in different applications

APPLICATIONS	DEGREE OF SEVERITY		
	Low	Intermediate	High
Chemical compatibility	Compatible	Limited	Incompatible
Toxicity of extractables	Non-toxic	Toxic at high levels	Toxic at low levels
Contact time	Short	Moderate	Long
Contact temperature	Ambient or below	Elevated	High
Surface area-to-volume	Low	Medium	Large
Proximity	Upstream	Downstream	Final fill/Storage
Dosage form	Solid	Liquid	Vapour
Route of administration	Topical, Oral	Ophthalmic, Transdermal	Inhalation, Injections

MILLIPORE'S APPROACH

Given the complexity of the extractables and leachables, and the analytical challenges involved, multiple analytical techniques are often employed to yield the most comprehensive information. The intimate knowledge of our raw materials and manufacturing process, combined with our expertise in analytical instrumentation and methodology, allows us to develop and validate analytical methods most suitable for the extractables and leachables testing of our products.

To assist customers in fulfilling their validation requirements, Millipore has developed a model solvent, worst-case scenario approach to evaluating extractables. In this approach, a material of interest is extracted in solvent(s) representative of the drug product, under aggressive conditions such as time and temperature. The extractables are quantified for the total amount, identified and linked to the materials that have been shown to be non-toxic per USP Class VI (Ref. 14).

Recently, in response to increasing demand, Millipore has developed technical capabilities for evaluating leachables (patent pending). Depending on the test article and drug product formulation, the leachables testing can be developed in the drug product or modified drug product. Applications have been successfully developed on final filtration devices with a wide-range of drug products.

Our practice is consistent with regulatory expectations and industry standards, and our laboratory is compliant with quality requirements outlined under cGMP. Please refer to Figure 4 for a summary of the regulatory and industry documentation that is applicable to a Single-Use assembly. Raw materials used by Millipore for product contact meet USP Class VI safety requirements post sterilization (autoclave, steam-in-place and/or gamma irradiation), and the results are published in Validation Guides and Certificates of Quality for the respective product.

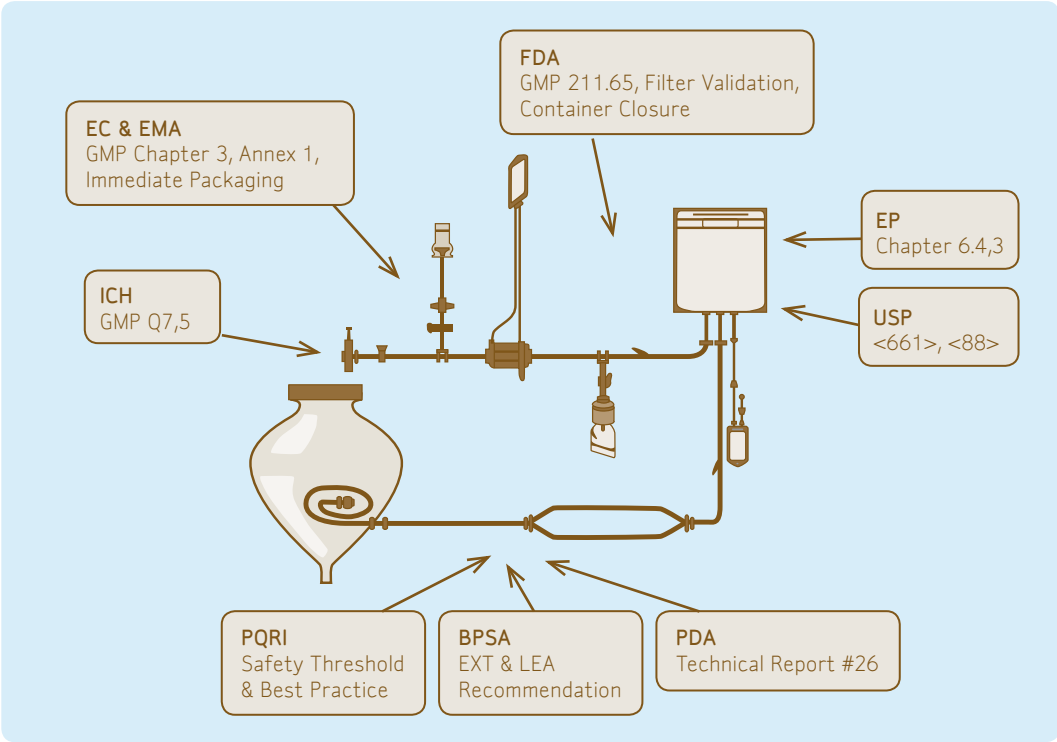

Figure 4. **Overview of regulatory and industry guidelines on Single-Use assembly**

REFERENCES

1. FDA, Code of Federal Regulations, Part 211, "Current Good Manufacturing Practice for Finished Pharmaceuticals", Part 211.65, "Equipment Construction", 2005
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FAQ'S

When do I need to consider extractables and leachables evaluation?

In Millipore's experience, extractables and leachables evaluation usually is performed at a late stage in drug product development and commercialization, when the formulation and process parameters are well established. However, during the early phases, such as pre-clinical trials, it would be prudent to select a material that is compatible with the drug product, and monitor the impact of the extractables and leachables throughout various product development testing.

How are model solvents selected to represent my drug product?

Model solvents are selected to exhibit similar physical and chemical characteristics to the drug ingredients. Common factors to simulate a drug product include pH, organic solvents and solutes if present at significant concentrations. Contrary to the organic solvents and solutes, inorganic solutes are not considered for modelling as they are known to increase the ionic strength of the solution and thus decrease the extraction capability.

Which process condition will affect extractables levels?

Extraction is a partition of an extractable compound between the solid phase (filter membrane, film, etc.) and the liquid phase (extraction solution). The extent and the rate of the partition are driven by multiple factors. For example, longer times and higher temperatures typically result in higher levels, and organic solvents yield more extractables than aqueous solutions. Additionally, any thermal, chemical and mechanical stress introduced by sterilization can produce more extractables. On the other hand, flushing prior to processing has been shown to be effective in removing the majority of the extractables.

Are there any acceptable levels of extractables and leachables established?

Users are expected to establish their own criteria based on the toxicological evaluation and process control. Currently, there are no official extractables and leachables levels established by any regulatory agency, as they are compound dependent.

Are leachables a subset of extractables?

Yes, they should be a subset of the extractables when the extractables study is well designed in terms of the model solvent(s) and worst-case extraction conditions used. Under such circumstances, the extractables study will reveal all potential leachables that might occur in the drug product, and the leachables study in return will verify the presence or absence of the extractables in the drug product.

I have requested an extractables study done in the past. Shall I consider a leachables study now?

It depends. Based on regulatory and industry guidance, users shall consider a leachables study if, upon risk assessment, a product-contact material may introduce leachables at levels that may alter the safety of the drug product. Specific examples that may require further leachables evaluation include final sterilization filtration, final container/closure system, high-risk applications such as inhalation and nasal spray products, etc.

Who is responsible for generating leachables information if deemed necessary?

You, as a user. It has been an industry practice for vendors like Millipore to provide extractables information, and users to conduct leachables testing as deemed necessary. For many years Millipore has been successful in generating the extractables information using the model solvent and worst-case scenario approach. Recently, we have also developed a leachables study capability.

What information will be generated during a leachables study?

While the extractables study offers information about the total quantity and identity of the extractables, the leachables study will confirm the presence/absence of those extractables in the (modified) drug product. Because the extractables study generates valuable information that is not attainable in the leachables study, and vice versa, one cannot replace the other.

How does Millipore compare to the other vendors in the industry in the area of extractables and leachables validation?

Our in-depth technical capabilities, combined with our extensive knowledge about customers' processes and regulatory expectations, allow us to develop the most suitable analytical methods for the extractables and leachables analysis. In addition, we have intimate knowledge of raw materials and manufacturing processes of our products that assists us in extractables and leachables identification, which can be analytically challenging to a third-party. Finally, our practice matches regulatory expectations and industry standards and our laboratory complies with quality requirements outlined under cGMP.