

A risk-based approach to extractable and leachable evaluations of in-process materials

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Introduction

The use of single-use systems to manufacture drugs and biopharmaceutical products has increased dramatically in the past decade. These disposable systems – which typically consist of items such as tubing, filters, o-rings/gaskets, storage bags and connectors as well as more complex components such as bioreactors – offer many advantages. They afford the user tremendous flexibility when setting up new processing lines. Additionally, while there are recurring expenses to purchase the disposable systems, these costs are usually more than offset by not having to perform cleaning and sterilization process validation.

However, there are also downsides to using disposable systems. Traditionally, most manufacturing components were stainless steel. In single-use systems, these stainless steel components are replaced by polymeric and elastomeric materials. While stainless steel is relatively inert, the likelihood of interaction between the polymeric/elastomeric materials and in-process materials and/or the drug product is greatly increased.

Just as container closure systems may release chemicals that can affect the safety, efficacy and quality of the pharmaceutical or biological drug product, so too can polymeric and elastomeric manufacturing components. In a laboratory setting, extractable compounds can migrate from the single-use system into an extraction solvent under exaggerated conditions of time and temperature. A subset of these compounds – termed leachables – can actually migrate into a drug product formulation under normal manufacturing conditions. Although the contact time of a drug product with the manufacturing components is typically low as compared to the product packaging, regulators still identify the need to evaluate single-use systems for extractable and leachable compounds.

According to the FDA Code of Federal Regulation 21CFR211.65:

Equipment shall be constructed so that

surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements [...]

Specifically for biopharmaceutical products, 21CFR600.11 states:

[...] All surfaces that come in contact with products shall be clean and free of surface solids, leachable contaminants, and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use [...]

In Europe the same requirements are addressed in EU Good Manufacturing Practice Guidelines, EudraLex Volume 4, Part 1, Chapter 3:

Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to such an extent that it will affect the quality of the product and thus present a hazard.

Although an industry standard still does not exist, a few organizations have published guidance documents to help vendors and end-users correctly address these requirements. The Bio-Process Systems Alliance (BPSA) published recommendations for extractable and leachable testing of single-use systems in 2010. In 2014, the BioPhorum Operations Group (BPOG) suggested a standardized approach for generating the extractables data, which they revised in April 2020. USP has also weighed in on the matter by drafting <665> and <1665>, although neither are effective as they have yet to be officially published in their final form.

These guidance documents generally recommend extraction conditions that bracket the most common manufacturing conditions and drug formulations. However, it is ultimately the end-user's responsibility to ensure that the extractables data is relevant by verifying that it brackets their manufacturing

conditions. Moreover it is advisable to begin evaluating extractables and leachables as early as possible during drug development in order to avoid additional requests from regulators that can delay clinical trials and postpone marketing authorizations. The need of managing a change to a more suitable material could also have huge impacts on the drug development cycle.

A strategic risk-based approach to extractables data

Performing analytical evaluations to detect extractables and leachables for all components that come in contact with the process stream can be expensive and time-consuming. As a result, a risk-based approach should be taken when determining what testing is necessary to support the selection of each manufacturing component. An effective strategy ensures that all the items belonging to a specific manufacturing process are evaluated for their regulatory compliance and potential to interact with the process stream.

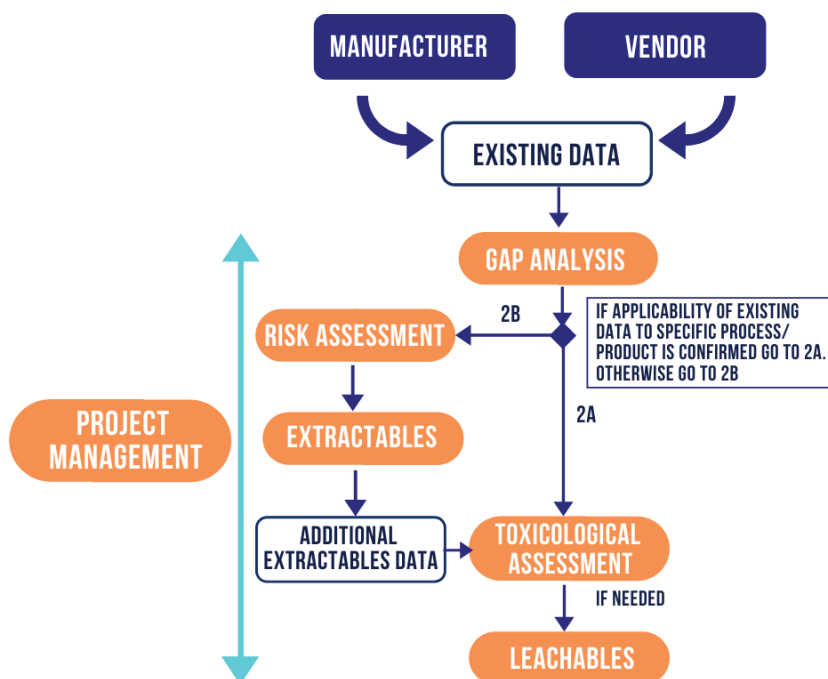
The flowchart describes the steps that should be taken to ensure that an effective risk assessment is performed.

Gap analysis

As a first step, existing data for each manufacturing item should be assessed against the actual process and product specifications. The suitability and applicability of this data, normally provided by the material suppliers or previously generated for other products or processes, is documented during a formal **gap analysis**.

For use in the pharmaceutical industry, basic material qualification data along with a certificate of conformity is expected. Although it was initially developed for container closure systems, USP <661.1> (which includes biological reactivity testing as per USP <87> and/or <88>) defines standard requirements for materials of construction.

Extractables data for the manufacturing components are often provided by the material suppliers as part



of a basic validation package. In addition, end users may have already performed extractables testing for a given component while assessing it for use with a similar product or process. In any case, all existing data should be evaluated, paying particular attention to the following factors: drug product formulation (e.g., organic content, surfactants, and pH) and physical-chemical characteristics; dosing regimen and route of administration; manufacturing process characteristics (e.g., batch size, contact times, holding times, and temperatures); and component pre-treatment steps (e.g., sterilization and flushing).

Most gaps are identified in one or more of the following categories:

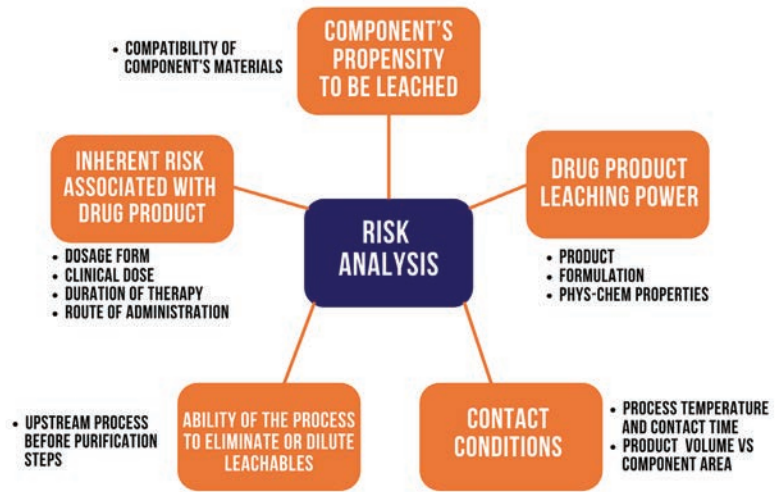
- Incorrect calculation of Analytical Evaluation Threshold (AET) and Process AET
- Incorrect selection of toxicological limits, such as the Safety Concern Threshold (SCT) or Threshold of Toxicological Concern (TTC)
- Extraction conditions (e.g., temperature, time, ratio) not covering the actual in-process parameters
- Extracting solvents not representing or bracketing the actual product formulation

If the extractables data is determined to be suitable for the end user's specific application, the data should be evaluated by a toxicologist in order to determine if the compounds that could potentially

leach into the finished drug product would pose a safety concern for patients.

Risk assessment

Whenever a gap is identified in the gap analysis, and before the generation of any process-specific extractables and leachables data, it is possible to use a science-driven and risk-based approach to identify the correct testing strategy. This risk assessment process enables the end user to prioritize the items to be tested and select the most appropriate analytical approach.

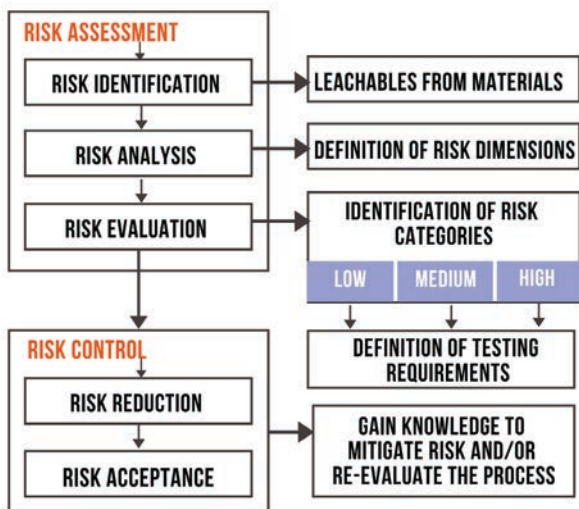


Risk management is defined in ICH guideline Q9 as a process for the “assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle”. There are multiple steps in the process, from risk assessment to the generation of an effective risk control strategy. Below, the risk management process presented in ICH Q9 has been adapted for in-process manufacturing materials:

For each product-contacting material, the risks are identified and analysed (**Risk Identification and Risk Analysis**) to determine the likelihood that compounds leached from the manufacturing components under typical conditions of use will enter into the process stream and accumulate in the drug product at potentially toxic or drug-altering concentrations. The likelihood of this happening is defined as the leaching propensity and can be influenced by several

variables. Each component is then categorized based on its risk as part of the **risk evaluation**. Acceptance criteria for high, medium and low risk categories can be customized by the end user, although they should be scientifically justifiable.

The scope of the subsequent **risk control** phase is to define a testing strategy that will support risk reduction and lead to risk acceptance. Typically, little or no further testing is required for low risk items. Testing requirements will increase for medium and high risk items. Regardless, the required testing for each risk category should be justified. The generation of extractables data can involve a wide range of analytical methodologies, from scouting techniques (e.g., NVR and TOC) to more complex analytical techniques, such as chromatography and mass spectrometry. The need for a full E&L assessment, including the evaluation of leachables in the actual product, is often reserved for higher risk materials.



It is recommended that each pharmaceutical company adopt a consistent risk control approach across all manufacturing processes. Consistently defining how to evaluate the single-use systems and determine the necessary amount of testing required simplifies both the change management process as well as the implementation of new manufacturing lines. It will also enable the development of an internal extractables database for various materials and enable the utilization of a bracketing approach. For example, if a material has been assessed previously under more extreme manufacturing conditions, that prior assessment may be leveraged to minimize the amount of additional testing required.

Generation of new extractables data

When new extractables data needs to be generated, it is essential to define the correct testing conditions. Selection of the extractions solvents, time, temperature and surface area to solution volume ratio is critical to ensure the extracts are generated properly. The extracts are then analysed by multiple analytical techniques. For a full E&L evaluation, the testing typically includes gas chromatography mass spectrometry (GC/MS), liquid chromatography mass spectrometry (LC/MS), and inductively coupled plasma (ICP). The Analytical Evaluation Threshold (determined based on the therapeutic indication of the drug and the total bulk volume of the batch) is used to determine when extracted compounds need to be identified and reported for further toxicological evaluation.

Toxicological evaluation

A toxicological evaluation of all extracted compounds above the Analytical Evaluation Threshold (AET) for each analytical method should be carried out to identify any potential hazards. A systematic evaluation of the potential adverse health effects resulting from human exposure to extracted compounds is performed and a Tolerable Exposure (TE) value is defined for each compound. For each compound, these Tolerable Exposures are then compared to the Maximum Daily Intake (MDI), taking into account any dilution that may occur throughout the manufacturing process and the total bulk size. In addition, the final product's dosing regimen, therapeutic indication, and route of administration is considered. The purpose of such an assessment is to identify which of the extractable compounds could pose a toxicological risk for the patient.

Leachables studies

When compounds are identified through the toxicological evaluation as posing a risk to patient safety, additional mitigation measures may be required. These additional steps are not uncommon for materials, such as the bulk intermediate storage vessels, that may have extended contact with the process stream. Special consideration should be given to items, such as sterilizing filters, that may be used multiple times in the process and/or are in close proximity to the final filling step. Mitigation procedures, such as the addition of a flushing step, should be evaluated to determine if they are effective in reducing the accumulation of leachables in the final packaged product. If mitigation steps are not feasible or effective, then the final product may need

to be tested for the leachable(s) of concern prior to releasing the product to ensure there are no risks to patient safety.

Product-contact surfaces and container closure system extractables: a holistic approach

Components used to package pharmaceutical drug products must be evaluated for extractable compounds. This evaluation often entails testing the components to identify which compounds are likely leachables and thus require targeted testing in the final product. A non-targeted screening for leachables in the final packaged product can also be performed to detect any impurities that do not correspond to extractables from container closure system. These impurities could belong to a subset of compounds not previously detected in the initial extractables screening or they have leached from components in the manufacturing process.

A comprehensive risk evaluation of all in-process materials is critical to ensure such potentially toxic compounds are identified early in the drug development process. Early identification will ensure there are no unexpected impurities in the final drug product, minimizing additional costs or delays. Furthermore, any additive effects (i.e., the same compound leaching from in-process materials and packaging) can be considered in this stage, adding an additional margin of safety for the patients.

Conclusions

An adequate evaluation of the suitability of disposable items for a specific manufacturing process is required by regulators to ensure an adequate level of protection to patients. Such assessment requires thorough knowledge of the process equipment, materials of construction and product formulation combined with expertise in analytical techniques and toxicology. Although these activities may consume time and resources, they will help avoid delays later on. Adequate management of the whole project should be in place to minimize the impacts on the pharmaceutical product development and approval.

Why Choose Eurofins BioPharma Product Testing?

A collaborative approach between all involved parties is key to a well-designed testing strategy. Eurofins provides support for the risk management process through a dedicated Consultancy team. In addition, with over 20 years of experience and FDA-audited E&L laboratories that meet GMP requirements,

Eurofins conducts hundreds of controlled extraction studies each year along with the associated leachables stability studies. In-house toxicologists work closely with the analytical chemists to perform safety assessments. Every project is assigned to a dedicated Project Manager that can act as single point of contact for the Client and coordinate the activities through all the steps of the evaluations.

Regulatory References

International Standards

- ICH Q9 Guideline on quality risk management
- ISO 10993 part 13: Identification and quantification of degradation products from polymeric medical devices
- ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

Regulatory References

- US FDA 21 CFR Part 211.65: Equipment construction
- US FDA 21 CFR Part 211.94: Drug Containers
- US FDA 21CFR600.11 - Establishment Standards for Biological products
- EU GMP, Medicinal products for human and veterinary use, European Commission, Volume 4, chapter 3

Other References

- USP <665> Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products
- USP <1665> Characterization of Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products.
- PDA Technical Report n. 66 Application of Single-Use Systems in Pharmaceutical Manufacturing
- BPOG Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing
- BPOG Best Practices Guide for Evaluating Leachables Risk from Polymeric Single-Use Systems Used in Biopharmaceutical Manufacturing
- Biophorum Best Practices Guide for Extractables Testing of Polymeric Single-Use Components in Biopharmaceutical Manufacturing
- BPSA Recommendations for Extractables and Leachables Testing