Provantage® Services

Extractables and leachables validation services

Merck Millipore is a division of MERCK

Extractables and leachables validation services

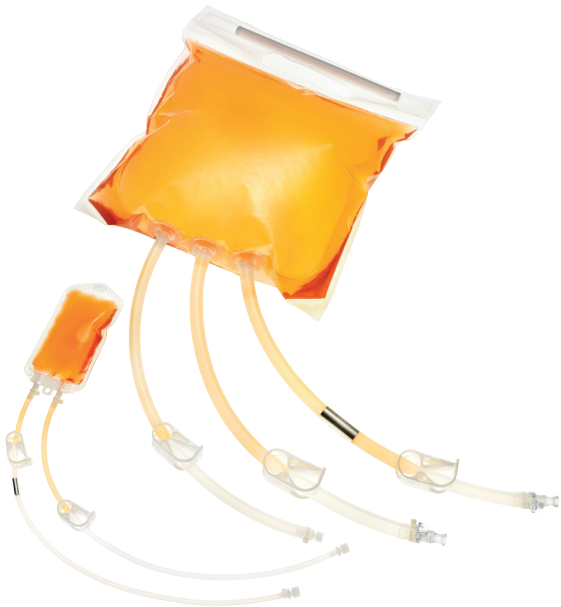
Demonstrate that the plastic/elastomeric product-contact material will not adversely affect the safety of your drug product

GMP guidelines around the world require that surfaces that come into contact with drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, purity, or quality of the drug product beyond the official or other established requirements.

Filters, containers and other components constructed of plastic and/or elastomeric materials are used extensively in biopharmaceutical manufacturing processes. When these components are used in direct contact with process intermediates and final drug product they can leach chemical compounds. It is the responsibility of drug manufacturers to prove that the presence of leached compounds does not present any safety hazard to their patients. The execution of an extractables and leachables evaluation is the means by which this critical safety question is answered.

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. The objective of the extractables and leachables evaluation is to effectively combine existing data sources, analytical study results, process and product knowledge, and toxicology in order to demonstrate that the product-contact materials will not adversely affect the product's safety.

Provantage® Services provide extractables and leachables validation services to mitigate the risk associated with implementing and using single-use assemblies/components in your production process.



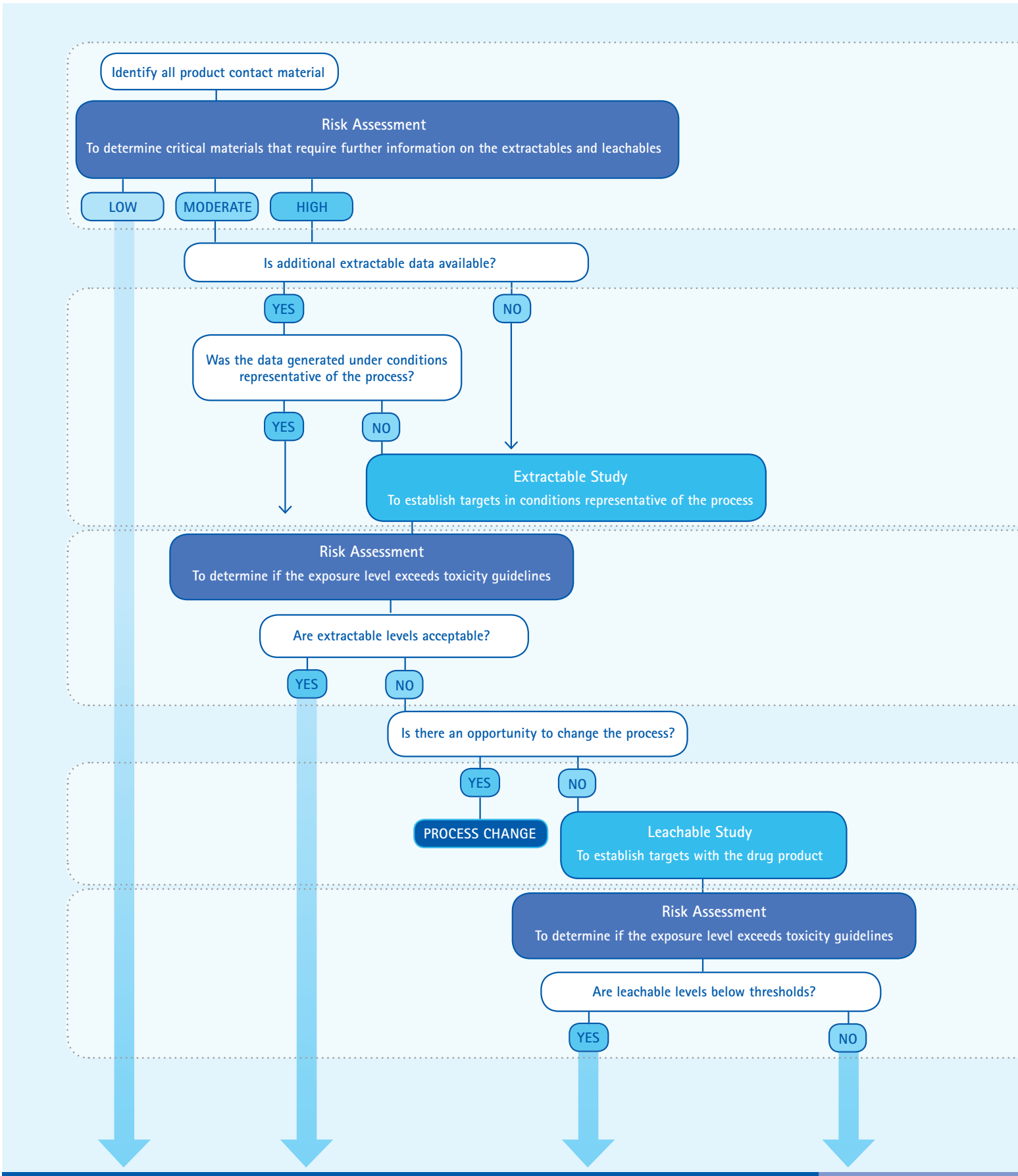
Unparalleled support from our lab to yours

We will guide you through a step-wise approach following recommendations from industry and regulatory guidance:

- Product Contact Material Safety Risk Assessment and Consultancy
- Extractable Certification or Testing if needed
- Extractable Toxicity Assessment
- Leachable Study and Toxicity Assessment when required

Our validation consultants will work with you to understand your process, and then by using our in-depth knowledge of our products, help you assess the overall risk of the single-use components and prepare an appropriate extractables and leachables data package that is needed to assess the patient's safety risk.

Industry & Regulatory Guidance for E&L Evaluation



Provantage® Approach and Services

• Risk Assessment Report	**Product Contact Material Safety Risk Assessment**
• Extractables Certificate • Extractables Study	**Extractables Data Packages**
• Risk Assessment Report • Extractables Data Report • Toxicological Evaluation Report	**Extractables Toxicity Risk Assessment**
• Leachables Study • Flushing Study	**Leachables Data Packages**
• Risk Assessment Report • Extractables and Leachables Data Report • Toxicological Evaluation Report	**Leachables Toxicity Risk Assessment**

The E&L evaluation decision tree presented above is aligned with the E&L evaluation approach recommended by the Bio-process Systems Alliance. The presented approach, which is both step-wise and risk based, is aligned with the expectation of regulatory authorities that the E&L evaluation process remains focused on the extractable and leachable substances risk to patient safety.

A risk-based approach

Product Contact Material Safety Risk Assessment

A Provantage® specialist will work closely with you to assess the risk of your single-use system (SUS) within your process according to regulatory and industry guidelines.

We will help you conduct a step-by-step risk assessment approach and:

- Assess the criticality of your process step and SUS
- Build a rationale to:
  - Identify single-use components that can be supported with existing whitepaper extractables data
  - Identify critical single-use components that will require further extractables data
- Document all of these steps in a report

Extractables Data Package

A Provantage® specialist will compile existing data and execute extractable testing, if necessary, to establish targets in conditions representative of your worst-case process conditions.

This includes:

- Rationale for selected analytics
- Selection of model solvent(s) and definition of worst-case conditions
- Materials, test procedure, analytical methods
- Approval by the customer for test execution
- Execution of testing as required
- Delivery of a cGMP auditable certificate or report

Extractables Toxicity Risk Assessment

With the extractable data package, a toxicologist will help you to assess the risk of your single-use system within your process according to the toxicity of the extracted chemical compounds.

The outcome of this service will either:

- Prove the safety of the single-use system and approve it to be used within your manufacturing process, or
- Point to the need for further evaluation including the development of a data set more realistic to your process by completing a flushing or leachable substances study

You will receive a report with data supporting this outcome.

Flushing Study

A Provantage® specialist will help you develop and qualify a flushing procedure that is compatible with your process conditions and will reduce the amount of extractable compounds coming from your single-use system.

Leachables Evaluation – Conducted with the drug product

A Provantage® specialist will execute leachable testing with your drug product under your process conditions to identify leachates and quantify them.

This includes:

- A preliminary evaluation is conducted to verify that target extractable compounds can be identified through the product formulation. Once the preliminary evaluation is complete, leachable testing design can begin
- Design of drug product testing for leachables, materials, test procedure, and analytical methods
- Approval by the customer for test execution
- Execution of testing as required
- Delivery of a cGMP auditable certificate or report

Leachables Toxicity Risk Assessment

With leachables data, a toxicologist will help you assess the risk of your single-use system within your process according to the toxicity of the leached chemical compounds.

The outcome of this service will either:

- Prove the safety of the single-use system and approve it to be used within your manufacturing process
- Identify the need for a process change

You will receive a report with data supporting this outcome.

References

- Mobius® Validation Services tech brief, TB10010000
- Extractables and Leachables for Filters, Bags, and Other Components used in Biopharmaceutical Manufacturing Processes tech brief, PB10010000

www.merckmillipore.com/provantage

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