Extractables and Leachables from Medical Devices

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• Introduction

Leachables are compounds that migrate from the medical device into a patient. There are two possible routes of entry for leachables: direct patient tissue contact or by first migrating into a drug product which then carries the leachable into the patient. Leachables present a potential risk to the patient both from the toxicity of the leachable and in the second route of entry, from impacting the stability or efficacy of the drug product. Examples of common organic leachables can be seen in **Table 1**.

Table 1. Examples of Common Organic Leachables

Class	Specific Example	Structure of Specific Example
Lubricants	Oleamide	
Plasticizers	Bis(2-ethylhexyl) phthalate	
"Small" antioxidants	Butylhydroxytoluene (BHT)	
"large" antioxidants	Irganox 1010	
Slip Agents	Stearic Acid	
Organic impurities (alkanes, alcohols and aldehydes)	Butanol	

• ISO 10993-18:2020

Extractables and leachable testing is part of the chemical characterization of medical devices described in ISO 10993-18:2020. As described in ISO 10993-18:2020, there are four goals of extraction studies done as part of the chemical characterization:

- to evaluate the compositional aspects of the medical device (exhaustive extraction)
- to determine the "worst-case scenario" of all possible extractables that could potentially become leachables (exaggerated or accelerated extraction).
- to determine only the extractables from the medical device that could become leachables under the conditions of clinical use (simulated extraction)
- be able to correlate extractables results with results from biological testing.

In addition, FDA and other global regulatory authorities recognize the need for reducing the amount of animal testing. So well designed extractables and leachables study plans can be often be used in lieu of biocompatibility testing that involves animals.
For a long term implanted medical device, ISO 10993-18 recommends Exhaustive extraction. For other medical devices, this extraction may not be needed based upon the intended use of the device.
At the end of the exaggerated extraction, the list of extractables generated represents a "worst-case scenario" of potential leachables. The ISO 10993-18 guidance recommends that a toxicological risk assessment be done on all of the observed extractables according to ISO 10993-17. If the toxicological risk assessment finds that the risk from the observed extractables is acceptable, then the risk assessment

can be considered complete without further testing. If the toxicological risk assessment finds that the risk from the observed extractables is not acceptable, the ISO 10993-18 guidance recommends proceeding to the simulated extraction to better determine the extractables likely to be present under clinical conditions.

• Experimental Overview

• Types of Extractions

• Exhaustive Extraction

The exhaustive extraction is the most aggressive of the extractions with the goal being to extract the maximum amount of each extractable from the device. The extraction conditions are set to be as aggressive as possible without leading to the swelling, dissolution or destruction of any component of the medical device.

The ISO 10993-18:2020 guidance recommends using two solvents for an exhaustive extraction; one polar and one non-polar. The polar solvent will be water for most medical devices. The common non-polar solvents used for the exhaustive extraction are hexane or toluene. Other solvents can be used and the selection of the non-polar solvents should be based upon the composition of the medical device and the potential for the solvent to interfere with the analytical methods. Although not recommended by ISO 10993-18:2020, the FDA has requested on specific occasions for individual manufacturers of medical devices used to deliver a drug product to perform the exhaustive extraction using the drug product or a solvent that simulates the drug product. When this request is encountered, Pine Lake Laboratories has the expertise to recommend an extraction solvent based on the properties of the drug product.

The types of extraction used in an exhaustive extraction will most likely be reflux, Soxhlett extraction, shake flask extraction, or oven incubation. All of these extraction types are aggressive and the selection is based upon the medical device and the extraction solvents to be used.

Once the extraction solvent and extraction type have been selected, the extraction will need to be proven to be exhaustive. To be exhaustive, an extraction is repeated on the same sample until the extractables in a subsequent extraction cycle are less than 10% of the level of extractables observed in the initial cycle. The ISO 10993-18:2020 guidance does allow for gravimetric analysis to be used to establish the number of cycles required to meet the exhaustive extraction criteria. Gravimetric analysis is a quick and simple analysis but it lacks the sensitivity and specificity of the analytical methodologies used later for extractables analysis. So for some medical devices, establishing the extraction as exhaustive by gravimetric analysis of the extracts may be appropriate but for other devices other techniques may be needed. This is especially the case if the drug product is used as the extraction solvent. Using all of the analytical methods later used for extractables analysis would give a complete demonstration that all observed extractables have met the exhaustive extraction requirement, however this approach is extremely time consuming and expensive. At Pine Lake Laboratories, we have had success using one chromatographic method with a universal detector (GC-FID) for organic extractables and a screening method for

elemental impurities (ICP-MS) for inorganic extractables. This approach is considerably more sensitive than gravimetric analysis without the cost of performing all of the extractables analyses to demonstrate the extraction is exhaustive.

- **Exaggerated Extraction**

The exaggerated extraction is less aggressive than the exhaustive extraction with the goal being to extract only the potential leachables from the device. The extraction conditions are set to capture all possible leachables while minimizing the extraction of compounds unlikely to leach from the medical device during clinical use. The extractables observed should represent the "worst-case scenario" of potential leachables and is expected to contain less extractables than in the exhaustive extractions.

In exaggerated extractions both polar and semi polar solvents are needed. For the polar solvents, water should be selected but an evaluation at an exaggerated pH may also be needed. Depending upon the medical device, acidified or basified water may also be required as extraction solvents. The common semi polar solvents used for the exhaustive extraction are methanol and isopropanol. Other organic solvents can be used and the selection of the semi polar solvents should be based upon the composition of the medical device and the potential for the solvent to interfere with the analytical methods.

For an exaggerated extraction the medical device is usually extracted in a sealed container by oven extraction with agitation. The time and temperature of the extraction are determined based upon the composition of the medical device and its intended use. When determining the extraction time and temperature, consideration needs to be made for the potential for the extractables to degrade after extraction. Degraded extractables do not accurately predict the potential leachables and therefore the extraction time and temperature need to minimize the risk of degradation.

- **Simulated Extraction**

The simulated extraction is the mildest of the extractions with the goal of the extraction to closely mimic the intended conditions of clinical use. When designing a simulated extraction, conditions should be made for the most likely route for the leachable to enter the patient (Figure 1). There are two possible routes of entry for leachables: direct patient tissue contact or by first migrating into a drug product which then carries the leachable into the patient.

Figure 1: **Simulated Extraction Study Design Based Upon** Leachable Route of Entry into Patient **from a Medical Device**

When direct patient tissue contact is the route for the leachable to enter the patient, the study is designed to mimic the tissue environment to be encountered by the device. In this study only one solvent is used and it is selected based upon the tissue to be encountered. For example, if the medical device will have blood contact, the solvent would be a mixture of ethanol and water with similar solvent strength to blood. The extraction temperature will most likely be 37˚C and the extraction time would be based upon intended clinical use.

When migration into a drug product is the route for the leachable to enter the patient, the study is designed to mimic the drug product. In this study only one solvent is used

and it is selected based upon the drug product. The extraction will most likely be done under ambient conditions and the extraction time would be based upon intended clinical use.

- **Extractable Analysis**

The sample extracts are analyzed by GC-MS, LC-MS and ICP-MS. The goal of these analysis is to identify as many extractables as possible and to semi-quantitatively determine the level of each extractable. Since the methods are designed to detect unknowns, these methods cannot be validated. Results from these analyses are reported as the amount of the extractable (usually in µg) per weight (usually in g) or surface area (usually in cm^2) of the medical device.

C. Analytical Evaluation Threshold

At the completion of the extractables analysis, a list of extractables is generated. The challenge at this point is to only report extractables that present a toxicological risk. To evaluate the toxicity of each observed extractable, the dose based threshold (e.g.safety concern threshold) is used. The dose base threshold (DBT) is the highest acceptable exposure of a patient to a leachable and is usually expressed in terms of µg of leachable per day.

The analytical evaluation threshold (AET) is calculated as follows:

Where
DBT = dose base threshold in µg/day
A = number of medical devices extracted
B= extraction volume (mL)
C = number of devices a patient would be exposed to in one day
UF = uncertainty factor
The AET will have units of µg/mL. Any extractable observed at a concentration at or above the AET would need to be identified, quantitated and considered for evaluation for toxicological risk.

• Conclusion

The above extraction studies described in ISO 10993-18:2020 are needed to address the potential risk to patients from leachable from medical devices. When properly executed, these studies will identify the potential leachables that could occur under the clinical use of the device and thus provide the needed results for an accurate toxicological risk assessment.

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VI. References

- ISO 10993-18:2020: Chemical Characterization of Medical Device Materials Within a Risk Management Process

About the Author

Kurt L. Moyer has more than 30 years of pharmaceutical and medical device development experience spanning all areas from discovery support to marketed products. His primary expertise is in the areas of extractables and leachables, method development and validation, identification of impurities and metabolites, and GLP/GMP compliance. Prior to joining Pine Lake Laboratories, Dr. Moyer served as a Senior Research Investigator for Sanofi Aventis and a Research Scientist for the DuPont Pharmaceutical Company. Dr. Moyer received his Ph.D. in biochemistry from Villanova University.	

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