EXTRACTABLES AND LEACHABLES FOR MEDICAL DEVICES: MEETING THE 510 (k) REQUIREMENTS

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BIOGRAPHICAL NOTE

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ABSTRACT

Recent changes in the FDA's 510(k) requirements for medical device applications have spawned many inquiries from clients on how to address the request for extractables, leachables and drug compatibility data. Meeting the expectations of the CDRH can be challenging in that any given study design is not universally applicable to all devices. A good study design requires elements of the best practices documented in ISO-10993-12, the PQRI guidance for E&L testing of OINDP as well as any specific requests for drug compatibility data from CDRH.

A hybridized study design, incorporating the essential regulatory elements, has been developed and successfully implemented for a variety of medical device applications. The rationale behind selection of the elements, overall experimental design strategy and interpretation of the resulting data will be presented.

INTRODUCTION

Extractables and leachable testing is required by the CDRH in the FDA for many medical devices. Experimental design for evaluation of extractable and leachables from medical devices can be done based on the most likely route for a leachable to enter the body. One route of entry is for leachables from a medical device to enter a drug product that carries the leachable into a patient. Examples of medical devices were this is the leachable route of entry include infusion pumps, syringes, and syringe filters. For leachables in this category, both the toxicity of the leachable and the potential impact of the leachable on the drug product need to be considered. The second route of entry is direct migration of the leachable from the medical device into the patient from direct tissue contact. Examples of medical devices where this is the main leachable route of entry include dental implants, artificial joints, stents, bandages, and contact lens. For some medical devices, both routes of entry for leachables are possible. Examples of medical devices where both routes of entry are possible include drug releasing implants and stents. If both routes of entry are possible, follow the second experimental design for direct migration route of entry. If leachables from a medical device are unlikely to enter the body from one of these two routes, an evaluation of extractables and leachables is probably not necessary.

Until recently, only medical devices where the leachable route of entry was from direct tissue contact were required to perform extractable and leachable testing. This requirement has changed as evidenced in the below example of a recent response from the FDA to a 510 (k) for an infusion pump:

> *"For each route of administration identified in your statement of intended use, you should identify an FDA approved drug or biologic to demonstrate that at least one such product is approved for infusion through the proposed route of administration and at the proposed dosage.*

If your infusion pump includes a reservoir, we recommend that you provide stability and compatibility data for each drug or biologic that you have identified above, which assesses the stability and compatibility for the recommended use period and conditions included in your labeling.

In addition to demonstrating that the drug or biologic retains its specifications, we recommend that you include a safety evaluation of any leachables, extractables, impurities and degradants. Analytical methods should be used to identify and quantify impurities, degradants, leachables and foreign particulates in the effluent."

There are two important requests in this FDA response to the 510 (k). The first request is to assess the stability and compatibility of each drug or biologic intended to be used with the medical device. The second is a safety evaluation of any leachables, extractables, impurities and degradants from the medical device into the drug product.

To address extractables testing for medical devices, in the FDA Modernization Act of 1997, the FDA recognized ISO 10993-12 Titled "Sample Preparation and Reference Materials". In this document are clearly defined extraction experiments for extractable and leachable evaluations. Some of the definitions and experiments in ISO 10993-12 are similar to the definition of an extractable and the forced extraction studies described in the PQRI guidance for E&L testing of OINDP. Acceptance criteria for extractables and leachables are not defined in ISO 10993-12.

Based upon the similarities between ISO 10993-12 and the PQRI guidance for E&L testing of OINDP, a study design for medical devices where the route of entry for leachables is in a drug product will be presented that includes elements of both documents. The study design to be presented for medical devices where the leachable route of entry was from direct tissue contact will be based only on ISO 10993-12.

STUDY DESIGN

Extractables and leachables study design for medical devices where the route of entry for leachables is in a drug product

Before starting to evaluate drug compatibility and leachables from the medical device, an FDA approved drug(s) intended for use with the medical device must be selected. If the device is intended for just one drug, like an insulin pump, the selection of the drug is obvious. If the device can be used with multiple drugs and multiple routes of administration, select a total of three drugs that are commonly used from the three most common routes of administration. For example, if evaluating an infusion pump that is intended to deliver drugs intravenously and as an epidural, pick two common drugs for intravenous infusion and one for epidural infusion. Once the drug(s) has been selected, pick the simplest formulation of the drug to evaluate drug compatibility and leachables.

To address drug compatibility and leachables from the medical device, the experimental approach is divided into two steps. The first step is the determination of extractables from the medical device in controlled extraction studies. Based upon these results, analytical methods are then developed to be used to evaluate leachables in the second step. The second step is the evaluation of leachables from the medical device into the drug product, and the evaluation of drug stability in the medical device.

Only the components of the medical device that directly contact the drug product need to be included in the controlled extraction study although other components can be included if deemed to present a significant risk. Separating components of the medical device for extractions will facilitate the identification of extractables, but the medical device can be extracted intact if separation is not practical.

An overview of the controlled extraction study can be found in **Table 1** and is similar to what is done for a sample container closure system following the PQRI guidance for E&L testing of OINDP. The medical device is extracted in a polar solvent and a non-polar solvent with the solvents selected based on the representative drug products. The extraction type is based on the solvent type and the analytical methods for analysis of extractables are the same for all extractions. Extractables are identified by MS and quantitated against structurally similar standards.

Table 1. Overview of Controlled Extraction Study

Solvent	Extraction Type	Analytical Methods
1. Polar – buffer(s) that match (or bracket) the pH and ionic strength of the drug product vehicle(s), water 2. Non-polar – 50/50 Ethanol/water if drug product contains surfactants, IPA if drug product contains no surfactants	1. Neat solvents : Soxhlett 2. Mixed solvents and buffers: Batch extraction with agitation or reflux	1. Volatile organic extractables by GC-MS 2. Non-volatile organic extractables by LC-MS 3. Inorganic extractables by ICP-MS (aqueous extract only)

Once the extractable profile of the medical device has been determined, analytical methods are then developed that can analyze for the extractables present as leachables in the representative drug products. Hopefully GC-FID and HPLC-UV methods can be developed for the organic leachables, but detection by MS may still be needed based upon the extractables identified and the number of unknowns. For both methodologies the drug may present significant interference for detection of potential leachables and extensive sample preparations, like liquid-liquid extractions, may be required. For inorganic leachables, ICP-MS is commonly used. All of these methods should be validated for accuracy, precision, specificity, LOD/LOQ and linearity. Acceptance criteria for validation should be set based upon the demonstrated performance of the method and the intended use of the method.

Analytical assay methods are also needed to demonstrate the stability and compatibility of each drug with the medical device. If available, the USP method for the drug product should be used. If a USP method is not available for the drug product, an analytical assay method will need to be developed and validated.

Once all methods are in place, the experimental steps shown in **Table 2** are followed.

Table 2. Steps in Study To Determine Drug Compatibility and Leachables from Medical Device

1. Load drug product into each configuration of the medical device to be evaluated
2. Dispense drug at clinically relevant rate for a clinically relevant time (or store in device for a clinically relevant time) under ambient conditions
3. A control of the drug product that has not been exposed to the medical device is stored for the same time under the same conditions
4. Collect representative aliquots at end (and intermediate time points depending upon length of time dispensed).
5. Assay dispensed sample and control. Calculate the difference between the two.
6. Analyze dispensed sample and control by leachables method. Exclude any leachables that are also observed in control at a similar level.
7. Repeat for each representative drug

Acceptance criteria are not universally defined. For assay we recommend setting the difference between the control and the sample to be the same as the USP acceptance criteria for assay. For example, if the USP method has the assay value for a drug product to be +/- 10.0 % of label claim, the acceptance criteria for compatibility should be that the assay value for the sample be within +/- 10.0% of the assay value of the control. For leachables and medical device impurities we recommend using the same acceptance criteria as process impurities of 0.05% of the drug product label claim.

Extractables and leachables study design for medical devices where the leachable route of entry is from direct tissue contact

To address extractables and leachables, two different extraction studies are done. The first experiment is an exaggerated extraction study which is defined in ISO 10993-12 as “any extraction that is intended to result in a greater amount of a chemical constituent being released as compared to the amount generated under the simulated conditions of use”. An exaggerated extraction study is a forced extraction study to generate a complete extractable profile for hazard identification and is required by ISO 10993-12 to be exhaustive. The

second experiment is a simulated use experiment which is defined in ISO 10993-12 as “evaluating leachable material levels available to the patient or user from devices during the routine use of a device using an extraction method that simulates product use.” The experimental conditions in a simulated use experiment are modeled after the intended tissue environment for the device with the goal of determining leachable exposure to the patient.

An overview of the exaggerated extraction study can be found in **Table 3**. The key decision in study design is solvent selection. For an exaggerated extraction study, the extraction solvents are selected based upon the anticipated tissues the device will encounter. The extraction type is based on the solvent type and the analytical methods for analysis of extractables are the same for all extractions. For exaggerated extractions, the extraction must be proven to be exhaustive, therefore extraction time is established experimentally. Extractables are identified by MS and quantitated against structurally similar standards.

Table 3. Overview of Exaggerated Extraction Study

Solvent	**Extraction Type**	**Analytical Methods**
1. Polar – water, phosphate buffered saline, culture media without serum 2. Non-polar - vegetable oil, ethanol/water, ethanol/saline, polyethylene glycol 400, dimethyl-sulfoxide, culture media with serum.	1. Low boiling neat solvents : Soxhlett 2. Mixed solvents, buffers and high boiling neat solvents: Batch extraction with agitation or circulation	1. Volatile organic extractables by GC-MS 2. Non-volatile organic extractables by LC-MS 3. Inorganic extractables by ICP-MS (aqueous extract only)

An overview of the simulated use extraction study can be found in **Table 4**. Again the key decision in study design is solvent selection. Like the exaggerated extraction study, the extraction solvents are selected based upon the anticipated tissues the device will encounter and the results of the exaggerated extraction study. The extraction type is batch extraction with agitation and the analytical methods for analysis of leachables are the same for all solvents. The extraction conditions should be the highest temperature listed that does not exceed the glass transition temperature of the material. Leachables are identified by MS and quantitated against structurally similar standards.

Table 4. Overview of Simulated Use Extraction Study

Solvent	**Extraction Type**	**Extraction Conditions (select one)**	**Analytical Methods**
1. Polar – water, physiological saline, culture media without serum 2. Non-polar - vegetable oil, ethanol/water, ethanol/saline, polyethylene glycol 400, dimethyl-sulfoxide, culture media with serum.	Batch extraction with agitation	a) 37°C for 72 hours b) 50°C for 72 hours c) 70°C for 24 hours d) 121°C for 1 hour	1. Volatile organic extractables by GC-MS 2. Non-volatile organic extractables by LC-MS 3. Inorganic extractables by ICP-MS (aqueous extract only)

Acceptance criteria for the levels of extractables and leachables in a medical device are not included in ISO 10993-12. A risk based approach method to set acceptance criteria that includes a toxicological evaluation of each extractable and leachable is presented in ISO 10993-17 but this approach may not be recognized by the FDA. A second option would be to use a predefined default level appropriate for the device and its intended use.

If the medical device contains a drug (e.g. a drug releasing implant), sample selection needs to be considered and can be different for the above two extraction studies. Depending upon the amount of drug in or on the device, a “placebo” device without drug may be considered for the exaggerated extraction study to avoid excessive interferences from the drug in the identification of extractables. However, the final medical device including the drug should be used in the simulated use experiment since the presence of the drug could effect the migration of the leachables from the device.

CONCLUSION

Extractables and leachables testing are required by the CDRH in the FDA for many medical devices. A study design was presented that was based on both ISO 10993-12 and the PQRI guidance for E&L testing of OINDP for medical devices where the route of entry for leachables is in a drug product, and a second study design was presented based only on ISO 10993-12 for use on medical devices where the leachable route of entry is from direct tissue contact. Both study designs have been used to support successful 510(k) submissions.

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