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Using Simulation Testing to Increase Efficiency in Extractables and Leachables Testing of Pharmaceutical Product Contact Materials

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Regulatory Background

Best practices for testing of product contact materials should follow the scientific approach originally developed by the Product Quality Research Institute (PQRI) working group for Parenteral and Ophthalmic Drug Products (PODP), and more recently embodied in USP <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* and USP <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* of the US Pharmacopeia.

While the PQRI guidelines, and USP chapters <1663>and<1664> are meant to address final containers and closures, and not necessarily product contact surfaces from the manufacturing process, the regulatory expectations for qualifying final containers are more rigorous than for product contact materials. Therefore, this approach can be considered conservative enough to cover both upstream and downstream processes and materials.

The PODP working group was formed to address extractables and leachables from parenteral and ophthalmic drug products, after an earlier PQRI working group completed its work for Orally Inhaled and Nasal Drug Products (OINDP). The PQRI PODP strives to adapt the best practices developed by the OINDP working group for parenteral and ophthalmic drugs. USP <1663> and USP <1664> were then written to embody the PQRI PODP recommendations.

One of the major accomplishments of the OINDP group was establishing the concept of a Safety Concern Threshold (SCT), which is defined as a daily dosage of an extractable above which a toxicology assessment must be performed. The SCT limit for OINDP was set at a dosage of 0.15 μg/day. This meant that extractables below this dosage pose negligible risk (defined as no more than 1 in 1,000,000 chance of cancer) and therefore do not have to be included in a toxicology assessment or even identified.

OINDP drug products are different than most drug products firstly because they have very small dosage sizes and secondly, they are administrated directly to the lungs, organs that are immediately critical to life. Parenteral drugs, on the other hand, have much larger volume dosage forms (up to 5.000 mL), and injections made intravenously or subcutaneously are not considered to have the same immediate negative consequences compared to OINDP.

The PODP working group thus recommended that the SCT for parenteral drugs be set at 1.5 μg/day. From the SCT, an Analytical Evaluation Threshold (AET) can be determined. The AET is the concentration below which the chemist can ignore an extractable. In a

manufacturing process, we apply the concept of the SCT by starting at the patient and working upstream to determine an AET concentration that takes into account the effects of the manufacturing process. As an example, if a sterile filter is used to filter 1,000 doses of drug product during the final fill step, the mass of extractables from that filter would be spread across all of the doses thereby leading to a higher AET.

PQRI PODP Recommendations

The PQRI PODP working group recommended assessing the safety of a material with three distinct tests. Table 1 shows these steps along with the comparable nomenclature from USP <1663> and USP <1664>.

Table 1. *PQRI Recommendation for Material Assessments for Extractables/Leachables*

PQRI – PODP Nomenclature	USP Nomenclature	Outcome
Controlled Extraction Study	Extractable Study	Extractables as Potential Leachables
Simulation Study	Simulation Study	Extractables as Probable Leachables
Migration Study	Leachable Study	Leachables

The PQRI defined Extractables Testing as a Controlled Extraction Study (CES) in which a test article is extracted with a wide range of pure solvents at conditions that are deemed more harsh than would logically be seen in a drug product. The goal is to find all the compounds that could possibly migrate from the material as potential leachables. In order to achieve this, harsh solvents are used (alcohol, hexane, very high pH, very low pH, etc.), and the test conditions are at higher temperatures. By using harsh conditions, a long list of potential leachables is created.

Rather than proceed directly to a leachable study, the PODP working group recommended that a simulation study be performed to determine a list of those extractables as probable leachables. Normally for a simulation test, the number and concentration of extractables detected is much lower. This is because the test solutions and conditions are based on the actual worst case conditions for that drug product, which is typically less aggressive than extractables conditions.

Simulations are accomplished by creating a formulation that closely resembles the extractive propensity of the drug product, but without analytical interferences. The design space of the simulation test is schematically shown in Figure 1, with the large circles representing the extractables tests with pure solvents. The size of the circles corresponds with number of extractables that are detected. The Simulation test is represented by a smaller circle because there are fewer detected extractables.

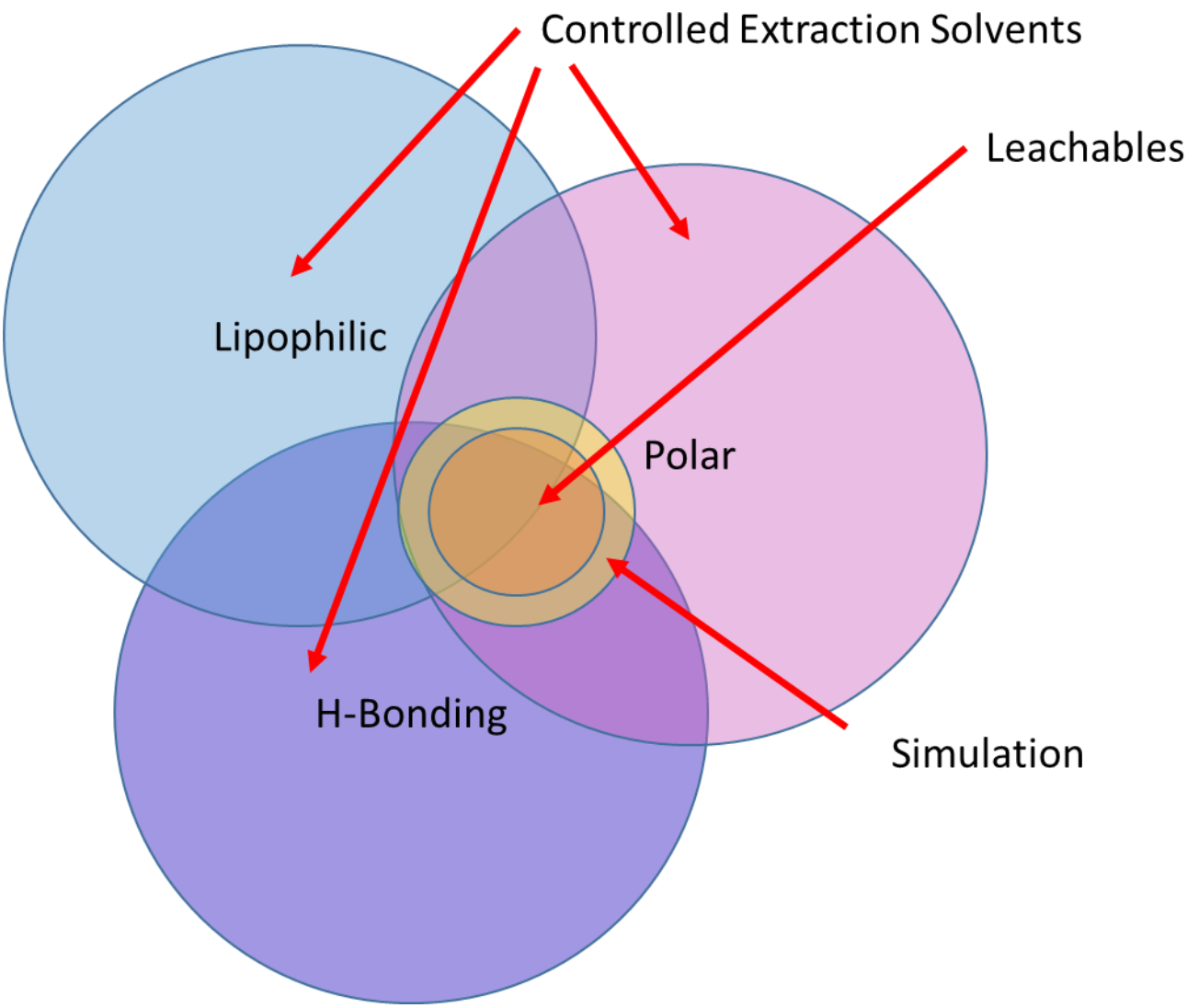

Figure 1. *Schematic of Three Levels of PQRI Testing*

Source: Thomas Feinberg: Presentation at USP-PQRI Symposium, Dec 2013

For most product contact materials, the evaluation stops at a simulation test, provided that a toxicology assessment of the simulation extractables as probable leachables does not indicate a potential safety concern.

A Migration Study, known in USP <1664> as a Leachable Study, is usually only preformed on final containers and directly targets several extractables in the actual drug product. Analytical interferences can be avoided because targeted analytical methods can be developed specifically to avoid analytical interferences.

For instance, interference in LC-UV-MS can be eliminated by having the MSD scan only for ions associated with the molecular weight of the target analyte. Ions from the drug product are ignored, and therefore a clean chromatogram can be acquired.

Justifications for a Simulation Test

While it is preferred to use the actual drug formulation in a simulation test, it is often not feasible without significant reduction in sensitivity. Compounds found in many drug formulations that cause analytical interference include proteins, solubilizing agents such as polysorbate 80, and other ingredients.

These compounds lead to segments of the liquid or gas chromatograms where it is not possible to determine if an extractable is present. The ingredients of a drug product can also impact the performance of the chromatography columns, causing the system to fail a performance check after a series of injections.

This is implied under the heading in USP <1664> titled "Additional Considerations: Simulation Studies"

> *"Occasions may arise in which it is not analytically feasible (due to challenging thresholds) to successfully discover and identify all actual leachables in a drug product leachables study. This circumstance can be managed if the activities of discovery and identification of probable leachables are accomplished in an extraction study, where samples and analyte concentrations are more easily manipulated to achieve analytical expediency."*

This can be interpreted that a simulation study is used when one cannot be assured of detecting (discovering) and identifying all actual leachables in the drug formulation.

In the same section, USP <1664> also states:

> *"To the extent that the simulation study mimics the drug product leachables study, the potential safety or quality impact of a compound as an extractable is an estimate of the potential safety or quality impact of the compound as an actual leachable. If it can be established that a compound quantitated as an extractable under these conditions has an acceptably small impact on safety and quality, then it follows that the same compound as a leachable in the drug product formulation may be assumed to have a similarly low impact on safety and quality. The acceptability of this approach for any particular drug product needs to be scientifically justified by the drug product applicant."*

This implies that extractables that do not impact safety or quality do not have to be addressed in a leachable study. We can then assume that if all extractables detected in a simulation study do not impact safety or quality, a leachable test is not necessary.

It is our experience, based on several experiences of our clients, that leachables studies for product contact materials are typically nonessential since the detected extractables generally do not impact safety or quality. This means that the detected extractables are either below the AET, or if they are above the AET, they do not pose a safety or quality risk.

Therefore, it is recommended to use a simulation solution that mimics worst case extractable potential of the actual drug formulations. The module would be used in a worst case condition with regard to time, temperature, pretreatment steps and processing configuration.

Conclusions

The PODP guidelines represent a rational, systematic approach to assessing extractables and leachables, first by identifying all potential extractables from a test article using an Extractable Study, and second by assessing the safety risk from contamination by compounds that are extracted under “real world” conditions using a Simulation Study. This approach limits the need to conduct a Leachable/Migration Study only to cases where the AET is exceeded, or where the potential for toxicity from target leachables is high even below the AET. Simulation Studies should thus be considered a highly useful mechanism for increasing efficiency in testing for extractables and leachables.

