**Experimental Protocol for Qualitative Controlled Extraction Studies on Material Test Articles:**

**Representative of Prefilled Syringe (PFS) and Small Volume Parenteral (SVP) Container Closure Systems:**

**Extraction Methods and Analytical Testing Procedures**

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### Introduction: PODP Working Hypothesis

Threshold concepts that have been developed for safety evaluation and safety qualification of leachables in OINDP can be extrapolated to the controlled extraction of drugs from container closure systems. These leachables are not intended for oral use and would be expected to be released into the aqueous environment, including water and biologic fluids, and would not have the same characteristics unique to various PODP types. The "good science" test demonstrated practices that were established for OINDP pharmaceutical development process can be extrapolated to container closure systems for PODP!

### Overview

The PODP Parenteral and Ophthalmic Drug Products (PODP) Leachables and Extractables Working Group developed an experimental protocol as a means of establishing Best Demonstrated Practices for the performance of Controlled Extraction Studies, specifically relevant for PODP container closure systems and dosage forms. This protocol considered the processes by which a Controlled Extract is generated, the processes by which a Controlled Extract is analyzed and processes by which the test results are evaluated and interpreted, specifically within the context of the Working Group’s approved Work Plan and experimental hypothesis.

### Test Articles Representing PODP Materials

The following primary target elements were included in the ICP analysis: Al, As, B, B2, BG, Cr, Ca, Mg, Mn, Na, K, Fe, Ni, Co, Cu, Zn, V, Ti, Nb, Mo, Hg, and Pb. These second element elements are those that were captured in the OINDP included 8B, 10B, 11B, 12B, 13B, 14B, 15B, and 16B. These second element elements are those that were captured in the OINDP included 8B, 10B, 11B, 12B, 13B, 14B, 15B, and 16B.

### Analytical Test Procedures, Organic Extractables

**Gas Chromatography (GC):**
- Semi-volatiles

**Liquid Chromatography (LC):**
- Semi-volatiles, non-volatiles

**Gas Chromatography with Headspace Sampling (GC-MS):**
- Volatiles

### Analytical Test Procedures, Trace Element and Metallic Extractables

**GC/MS:**
- Low density polyethylene (LDPE)

**LC/TOF-MS:**
- Polyethylene (PE)

**LC/MS:**
- Polyethylene (PE)

### Experimental Workflow

**Overall Study Design Matrix**

**Additional Aspects of the Study Design and Implementation**

1. Multiple layers of quality control.
2. Standardized methods (modified appropriately as necessary).
3. Use of instrumentation qualified per participating lab’s procedures.
4. System suitability testing.
5. Concentration estimation via internal standards (chromatographic assay).
6. Reporting limit of 10 µg/l, although lower levels were reported consistent with method capabilities.
7. Identifications made based on OINDP Best Demonstrated Practices.