Parenteral and Ophthalmic Drug Products (PODP) Leachables and Extractables Working Group: Study Protocol – Stage 2; *Experimental Protocol for Simulation Study of Blow-Fill-Seal (BFS) PODP Container Closure Systems*, Introduction and Experimental Design

Dennis Jenke and Thomas Egert

Members, PQRI Extractables and Leachables Working Group, PODP Chemistry Team

Introduction

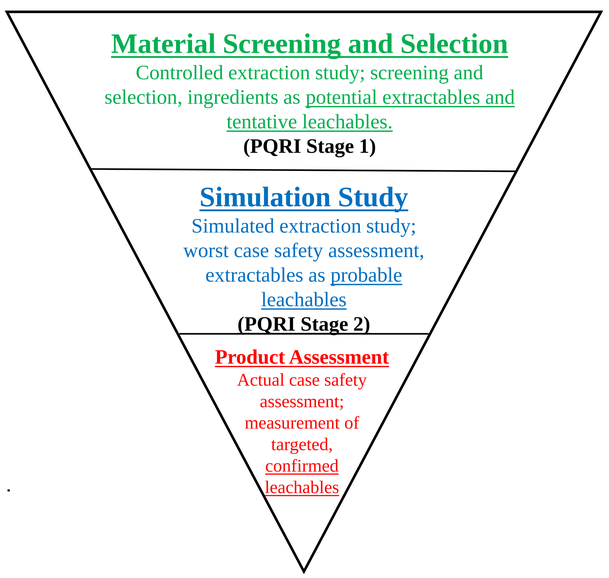
Substances leached by drug products from their container closure systems can affect the product's safety and efficacy. Regulatory documents provide some guidance regarding the chemical and toxicological safety assessment of such substances.

In 2006, the Product Quality Research Institute (PQRI) issued a document entitled "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products", which provided a scientific rationale and process to identify, quantify and establish the safety of leachables and/or extractables in OINDP. Included therein were protocols for establishing Best Demonstrated Practices to perform Controlled Extraction Studies, specifically relevant to OINDP dosage forms.

The PQRI Parenteral and Ophthalmic Drug Products (PODP) Leachables and Extractables Working Group is developing, executing and reporting studies to establish Best Demonstrated Practices for chemically assessing PODP container closure systems and dosage forms. Figure 1 illustrates the Chemical Assessment Process. A recently reported PODP Stage 1 study[1,2] considered Material Characterization including the processes by which a Controlled Extract is generated, by which a Controlled Extract is analyzed and by which the test results are evaluated and interpreted. An ongoing Stage 2 study considers the Simulation Study, specifically establishing the extractables profile of an experimental container closure system constructed from some of the examined in the Stage 1 study. This experimental container closure system (Figure 2) specifically mimics a Blow-Fill-Seal (BFS) packaging system, such as those used with many ophthalmic products, consisting of a BFS bottle, its associated cap, a closure gasket and an affixed printed label.

Figure 1. The Chemical Assessment Triad[3]

A simulation study is a bridge between material characterization, which establishes extractables that are tentative leachables, and product assessment, which measures confirmed leachables. A simulation study mimics the product assessment by using simulating solvents to facilitate the analytical tasks and extraction conditions which accelerate the product use conditions. The simulation study may be the basis of a preliminary toxicological assessment and can be used to establish target leachables for product assessment. A simulation study that includes multiple time points is also called a **Migration Study.**



Purpose

The purpose of the PODP Stage 2 experiments is to generate data from a Simulation Study to investigate the hypotheses that:

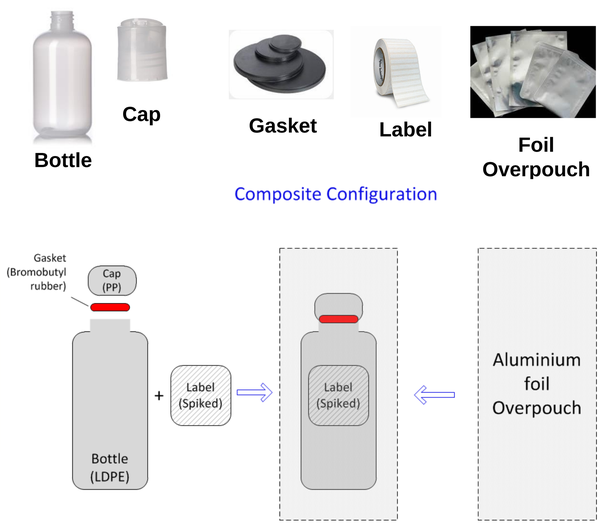
- Threshold concepts that have been developed for safety qualification of leachables in OINDP can be extrapolated to the evaluation and safety qualification of leachables in PODP, with consideration of factors and parameters such as dose, duration, patient population and product dependent characteristics unique to various PODP types.
- The science-based best demonstrated practices established for the OINDP pharmaceutical development process can be extrapolated to PODP container closure systems.
- Threshold and best practices concepts can be integrated into a comprehensive process for characterizing container closure systems with respect to leachable substances and their associated impact on PODP safety.

Experimental – Test Articles

Table 1. Test Article.

Type	Use	Format	Description
Low density polyethylene (LDPE)	Bottle or Vial	Bottle	4 oz LDPE, part B347A (Container & Packaging Supply)
Polypropylene (PP)	Cap	Cap	PP, Part L764(Container & Packaging Supply)
Adhesive Label	Label on Container Surface	Label Sheets	Substrate: Unknown Adhesive: Acrylic polymer(s), residual monomers, water, ammonia (99.55%); wetting agent, Surfynol 336, at 0.4% containing 577-11-7 (> 25%), 9014-85-1 (> 25%); Biocide, Kathon LX, at 0.05% containing Chloro-2-methyl-4-isothiazolin-3-one (26172-55-4), 1.1-1.4%,2-Methyl-4-isothiazolin-3-one (2682-20-4), 0.3 - 0.5%, Magnesium Chloride (7786-30-3), 1.0 - 1.2%, Magnesium nitrate (10377-60-3), 1.4 - 2.0% Copper nitrate (3251-23-8) 1,500 - 1,700 ppm,Water, 95 - 97% Printing ink: Irgacure 369 (119313-12-1) and Irgacure 1173 (7473-98-5), photoinitiators; Trimethylolpropane triacrylate (TMPTA, 15625-89-5), Tripropylene glycol diacrylate (TPGDA, 42978-66-5), Glycerol propoxy triacrylate (GPTA, 52408-84-1), monomers; HQME/Mequinol (150-76-5), stabilizer; Carbon black (1333-86-4),Phthalo blue (147-14-8),Carbazole violet (215247-95-3), pigments Varnish : Unknown
Rubber (Elastomer) (RE)	Closures	Gasket liner	Brominated isobutylene isoprene copolymer (57.3%); calcined aluminum silicate, 38.2%, titanium dioxide, 1.2%; paraffinic oil, 1.2%; zinc oxide, 0.6%; polyethylene, 0.6%; SRF Carbon block mixture, 0.4%; calcined magnesium oxide, 0.3%; 4,4'-dithiodi-morpholine/polyisobutylene, 0.3%

Figure 2. Test System and Components

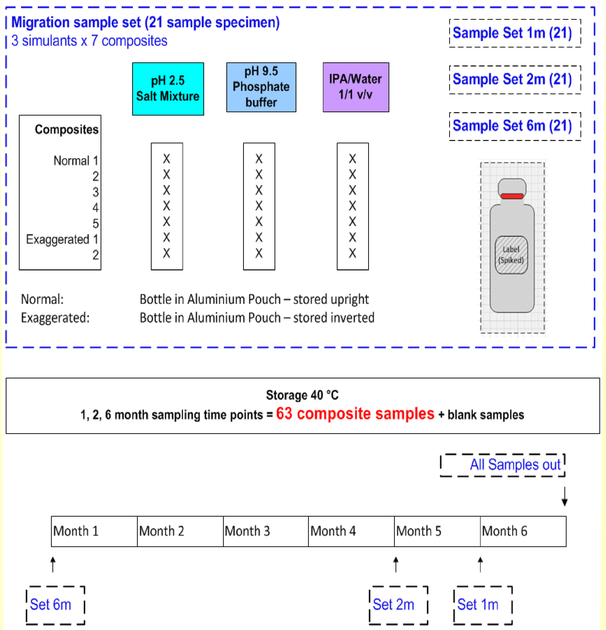


Note: Labels were spiked with four target compounds, typical of adhesives, to ensure that there would be compounds to follow (Methylethyl ketone, Irgacure 1173, Benzophenone, Dipropylene gylcol diacrylate).

Experimental – Migration Conditions

- Three Simulating Solvents; pH 2.5 salt mixture, pH 9.5 phosphate buffer, 1/1(v/v) IPA/water.
- Test Unit Preparation:
  - Bottles filled with their nominal volume (100 mL) of extracting solution.
  - Gasket placed inside of cap and cap attached to filled bottle, closing bottle.
  - Label spiked and then affixed to outside of bottle.
  - Filled and labeled bottle placed into foil overpouch.
  - Overpouched test unit placed in oven to initiate extraction.
- Test Unit Storage: 1, 2 or 6 of storage at 40°C; test units stored either upright or inverted.
- Initiation of extraction staggered for each interval so that test units matured at the same time.
- After completion of storage, the contents of three individual test units were combined to produce composite samples with sufficient volume to allow for testing.
- Composite samples were tested.

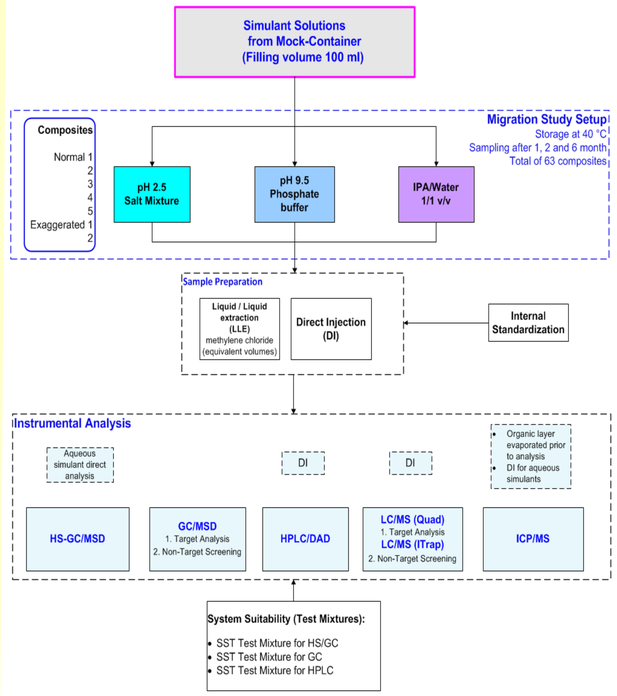
Figure 3. Extraction (Migration) Conditions



Experimental – Analytical Testing

1. Gas Chromatography (GC/FID/MS) with Headspace sampling for volatile extractables.
2. Gas Chromatography (GC/FID/MS) via direct injection (after solvent exchange and evaporative concentration) for semi-volatile extractables.
3. Liquid chromatography (LC/UV/MS) via direct injection for non-volatile extractables.
4. Atomic spectroscopy (ICP/MS) for extracted elemental impurities.

Figure 4. Analytical Testing



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