Simulated Leaching (Migration) Study for a Model Container-closure System Applicable to Parenteral and Ophthalmic Drug Products (PODPs)

Dennis Jenke, Thomas Egert, Alan Hendricker, et al.

**PQRI SPECIAL CONTRIBUTION DISCLAIMER:** The following article is an invited contribution submitted by the Product Quality Research Institute (PQRI) Leachables and Extractable Working Group. The article was internally reviewed by PQRI and by the author’s affiliated organizations and not peer-reviewed by the PDA Journal.

Observations made, opinions expressed, and conclusions drawn in this article reflect the views of the authors acting in their role as members of the PQRI Extractables and Leachables Working Group and should not be construed to represent the views or policies of their affiliated organizations.

**Simulated Leaching (Migration) Study for a Model Container-closure System Applicable to Parenteral and Ophthalmic Drug Products (PODPs)**

Dennis Jenke1*, Thomas Egert2, Alan Hendricker3, James Castner4, Tom Feinberg5, Christopher Houston6, Desmond G. Hunt7, Michael Lynch8, Kumudini Nicholas9, Daniel L. Norwood5, Diane Paskiet10, Michael Ruberto11, Edward J. Smith12, and Frank Holcomb13

Author Affiliations:

Product Quality Research Institute (PQRI) Leachables and Extractables Working Group: Parenteral and Ophthalmic Drug Products (PODPs), 2107 Wilson Blvd, Suite 700, Arlington, Virginia 22201-3042, USA; 703-248-4719, Fax: 703-525-7136; email: PennV@pqri.org

1Baxter Healthcare Corporation, Round Lake, IL, USA
2Boehringer Ingelheim Pharmaceuticals, Inc., Ingelheim/Rhein, Germany
3Becton Dickinson, Research Triangle Park, NC, USA
4Pharma Interface Analysis, LLC,
5Scio Analytical Consulting, Chapel Hill, NC, USA
6juvo BioScience, Rush, NY, USA
7United States Pharmacopeia, Rockville, MD, USA
8Pfizer, Groton, CT, USA
9Bureau of Pharmaceutical Sciences, Health Canada, Ottawa, ON, Canada
10West Pharmaceutical Services, Lionville PA, USA
11Materials Needs Consulting LLC, Montvale, NJ, USA
12Packaging Science Resources, King of Prussia, PA, USA
13United States Food and Drug Administration, Washington, DC, USA

*Corresponding author: Dennis Jenke, Baxter Healthcare, 25212 West Illinois Route 120, Round Lake, IL 60073, dennis_jenke@baxter.com
Abstract

A simulating leaching (migration) study was performed on a model container-closure system relevant to parenteral and ophthalmic drug products (PODP). This container-closure system consisted of a linear-low density polyethylene bottle (primary container), a polypropylene cap and an elastomeric cap liner (closure), an adhesive label (labeling) and a foil overpouch (secondary container). The bottles were filled with simulating solvents (aqueous salt/acid mixture at pH 2.5, aqueous buffer at pH 9.5, and 1/1(v/v) IPA/water), a label was affixed to the filled and capped bottles, the filled bottles were placed into the foil overpouch and the filled and pouched units were stored either upright or inverted for up to 6 months at 40°C. After storage, the leaching solutions were tested for leached substances using multiple complementary analytical techniques to address volatile, semi-volatile, and non-volatile organic and inorganic extractables as potential leachables.

The leaching data generated supported several conclusions, including that (a) the extractables (leachables) profile revealed by a simulating leaching study can qualitatively be correlated with compositional information for materials of construction, (b) the chemical nature of both the extracting medium and the individual extractables (leachables) can markedly affect the resulting profile and (c) while direct contact between a drug product and a system’s material of construction may exacerbate the leaching of substances from that material by the drug product, direct contact is not a prerequisite for migration and leaching to occur.
Lay Abstract

The migration of container-related extractables from a model pharmaceutical container closure system and into simulated drug product solutions was studied, focusing on circumstances relevant to parenteral and ophthalmic drug products. The model system was constructed specifically to address the aspect of migration of extractables from labels applied to the outside of the primary container. The study demonstrated that (1) the extractables that do migrate can be correlated to the composition of the materials used to construct the container closure systems, (2) the extent of migration is affected by the chemical nature of the simulating solutions and the extractables themselves, and (3) even though labels may not be in direct contact with a contained solution, label-related extractables can accumulate as leachables in those solutions.

Key words: extractables, leachables, simulation studies, parenteral and ophthalmic drug products (PODPs), leaching (migration) study
Introduction

Most pharmaceutical products are packaged in a container closure system to preserve and protect the product during its manufacturing, distribution, storage and use. During this period of contact, the pharmaceutical product and its packaging system can interact, potentially affecting product quality and safety. For example, substances in the container closure system can leach from the system and become entrained in the product, thus becoming foreign impurities (leachables) in the product. The need to establish what effect, if any, that such foreign impurities have on product quality and safety is well established in the regulatory literature [1-3] and the means of establishing the effect have been the focus of numerous authoritative texts on the subject [for example, 4 – 8].

A comprehensive strategy for assessing the potential safety and quality risk posed by such foreign impurities generally involves three stages; materials characterization, which is the procurement of knowledge about the composition and general properties of a container closure system’s materials of construction, extractables profiling of the container closure system and/or its components (via a controlled extraction simulation study) and, as necessary and appropriate, leachables profiling of the pharmaceutical product (leachables migration study). Material characterization establishes those chemical entities (including additives and ingredients) that are present in the material and which may be extracted from the material, thereby creating a basis for the selection (and justification) of appropriate materials of construction. The controlled extraction simulation study establishes that container closure system extractable profile which is relevant to the clinical use of the pharmaceutical product (and thus which closely mimics the pharmaceutical product’s leachables profile). Thus the controlled extraction simulation study can assist in materials and packaging component selection as well as contribute to the packaging system’s quality and safety impact assessment. Profiling the pharmaceutical product for leachables during the course of a long-term stability study (leachables migration study) provides additional information for quality and/or safety assessment.

In situations of challenging detection limits for leachables, and certain other circumstances, a simulation study can be used either to focus the leachables study or even in place of the leachables study. A simulation study is a type of extraction or leaching study which employs simulating solvents, which are intended to closely mimic the actual drug
product vehicle and its leaching potential and accelerated leaching conditions. Extractables, leachables and simulation studies are described in two recent United States Pharmacopeia (USP) informational general chapters [7,8]. In addition to leachables, which can accumulate in a drug product from direct contact with the packaging system, the USP recognizes the term “migrants”, which can accumulate in a drug product after crossing a barrier (e.g., from a label through a plastic bottle).

The Product Quality Research Institute (PQRI) has been an active participant in the effort to develop effective, science-driven and risk-based strategies for the safety qualification of container closure systems for pharmaceutical products. For example, in 2006, PQRI issued the report “Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products,” which provides a scientific rationale and process to address packaging systems use for Orally Inhaled and Nasal Drug Products (OINDP) [4]. This report includes best demonstrated practices for addressing extractables and leachables, specifically relevant to the OINDP dosage forms. More recently, the PQRI expanded its efforts to include parenteral and ophthalmic dosage forms (PODP). One aspect of the PQRI PODP activity was to develop and examine the three stage approach discussed previously. To this end, the PQRI PODP Leachables and Extractables Working Group initiated a study which generated and interpreted data from controlled extraction studies performed on multiple polymeric and elastomeric materials of construction commonly encountered in PODP packaging systems (stages 1 and 2). In this study, the test materials were subjected to different extraction conditions and the resulting samples (i.e., extracts) were then characterized for extracted substances to establish the material’s general extractables characteristics. [9]

Continuing its assessment, the PQRI PODP team performed a second study to address the third stage, leaching (migration) study, via a controlled simulation study. [10] In this study, a model container closure system, more or less consistent with systems used with PODPs, was constructed from either materials that the PODP team had characterized in its previous study or which were characterized as part of this study. This model container closure system was then filled with simulating solvents relevant to liquid PODP dosage forms and the filled units were subjected to a leaching (migration) study.
The purpose of this report is to discuss the design and results of the PODP leaching (migration) study, specifically considering the role of such a study in the safety assessment of a container closure system used for PODP products.

**Experimental**

**Test Article (see Figure 1)**

The model container closure system consisted of a low density polyethylene (LDPE) bottle (4 oz Natural LDPE, Boston Round Bottle; Container & Packaging Supply, part B347A), a polypropylene (PP) cap (20-410 Natural Smooth Disc Top; Container & Packaging Supply, part L764), an adhesive label (UPM Raflatac), a rubber gasket (Brominated isobutylene isoprene copolymer) and a foil overpouch (Figure 1). The components of the model container closure system were used as received.

**Leaching (Migration) Simulation Study**

**General**

The test units for the leaching (migration) study were prepared as follows. Individual bottles were filled with extraction solvent (nominal 100 mL), a rubber gasket was inserted on the top of the neck of the bottle and the cap was tightly screwed down on the gasket. Spiked labels were manually applied to the outer surface of the bottles and the labelled bottles were placed in a foil pouch, which was subsequently closed by heat-sealing.

The leaching (migration) study was performed twice. The first study, with relatively fewer and later time points, served the purpose of range finding. The results of this range finding study facilitated the optimization of the experimental design. The second study, with relatively more frequent and earlier time points, reflected the optimized experimental design. Because the leaching (migration study) employed simulating solvents (as opposed to a drug product) and accelerated storage conditions, it is properly termed a simulation study.

**Leaching Solvents**

The leaching solvents were as follows.

- **Water pH 2.5:** A salt/acid solution was prepared containing 0.01 M KCl and 0.003 M HCl. The pH was
adjusted to 2.5 as needed.

Water pH 9.5: A buffer solution was prepared containing 0.066 M dibasic sodium phosphate and monobasic 0.0045 M sodium phosphate. The pH was adjusted to 9.5 with 1N NaOH.

50:50 Isopropanol (IPA): water: Equal volumes of IPA and water were mixed. These leaching solvents were chosen as PODPs are primarily aqueous and formulated between these pH extremes. The 1:1 IPA:water mixture represents a PODP that contains an organic surfactant or solubilizing agent.

*Leaching Conditions*

Leaching was conducted at 40 °C (humidity not controlled) for up to 6 months. These leaching conditions were chosen as they are generally accepted to be the proper acceleration of a 2 year ambient temperature product shelf-life. In the range finding study, test units were stored in either an upright and inverted configuration, as the inverted configuration results in direct contact between the rubber gasket and the fill solution. The optimized study included only inverted test units.

The time points for the range finding study included 1, 2 and 6 months of storage. The time points used in the optimized study included 0.75, 2, 5, 12, 25, 70, 98, 105 and 180 days of storage.

*Label Spiking*

Four compounds were spiked onto the bottle-contacting surface of the label prior to placing the label onto the bottle. These four compounds (see Table 1) were chosen as they possess a range of physiochemical properties and are known substances associated with labels. The labels were spiked with these substances so that the pool of label-related extractables was sufficiently high that they could be effectively quantified in the fill solutions.

Spiking was accomplished as follows. For the range finding study, a mixed standard of the spiking compounds was prepared at a nominal concentration of 250 mg/mL, except for MEK which was used as the dilution solvent (at a level of approximately 615 mg/mL). Immediately before placing the label on the bottle, 2 drops of 2.5 µL each of
the mixed standard spiking solution were placed onto the back of the label on the adhesive layer. The label was then immediately pressed and sealed to the filled bottle, followed by sealing the labelled bottle in the foil pouch.

The spike level was chosen so that spiked substances could be readily detected if migration occurred. A 5 µL spike of a 250 mg/mL solution equates to a spike amount of 1250 µg for the semi-volatile compounds and 3080 µg for the MEK. If a 10% migration rate was obtained in this study, then the resulting concentration of the compounds in the extraction solvents would be 1.25 µg/mL for each semi-volatile target (1250 µg x 0.10 (10% migration) / 100 mL (total solution volume) = 1.25 µg/mL) and 3.08 µg/mL for MEK). Such accumulation levels were detectable and within the operating range of the analytical techniques used in this study.

An alternate spiking process was used for the optimized study. In this case, the spiking standard was prepared to contain approximately 50 mg/mL of each spike compound, using PEG 200 as the solvent. A 10 µL aliquot of the viscous spiking standard was evenly distributed on the inner adhesive surface of the label, which was immediately placed on a filled bottle which in turn was then immediately sealed into a foil overpouch. Assuming a migration rate of 100%, this spike would result in a fill solution containing approximately 5 µg/mL of each spike compound.

Solvent Blanks
Solvent blanks were obtained by storing portions of unused leaching solvent in inert containers (glass for pH 2.5 and IPA/water, Teflon for pH 9.5).

Leachate Analysis: Range Finding

Test Methods
The leachates (and solvent blanks) were analyzed for organic and inorganic extractables (simulated leachables) using methods that are typically employed for the purpose of extractables screening. Generally speaking this included gas chromatography with headspace sampling and mass spectrometric detection (HS-GC-MS) for volatile substances, direct injection GC/ MS for semi-volatile substances and high performance liquid chromatography with both UV absorption and mass spectrometric detection (HPLC-DAD-MS) for non-volatile substances. Extractables
(simulated leachables) were also measured based on their elemental constituents via inductively coupled plasma mass spectrometry (ICP-MS).

**Sample Processing Prior to Analysis**

Solvent switching was performed on all leachates intended for GC-MS analysis. A portion of each leachate was liquid-liquid extracted with an equivalent volume of methylene chloride. The organic layer was analyzed directly. For HS-GC-MS and HPLC-DAD-MS analysis all extracts were analyzed directly. For ICP-MS, the leachates were analyzed directly, except the IPA:Water extracts in which case the IPA was evaporated off prior to analysis. The ICP-MS samples were acidified prior to analysis.

**Test Systems and Operating Conditions**

As the purpose of this study was range finding, the specific analytical instruments and test method operating conditions used in the chromatographic analyses performed in this study are not fully reported as the instruments, methods and operating conditions used in the optimized study are more relevant. As the ICP-MS analyses were only performed during range finding, the analytical details for this analysis are shown in Table 2.

**Extract Analysis; Optimized Study**

**Test Methods**

The leachates (and solvent blanks) were analyzed for targeted organic extractables using appropriate gas (GC) and liquid (LC) chromatographic methods developed for this purpose.

**Sample Processing Prior to Analysis**

Samples (leachates and blanks) were prepared for the GC analysis by transferring 200 µL of the sample, 100 µL of an internal standard solution (39 µg/mL 2-Fluorobiphenyl in methanol), and 800 µL isopropanol into a 2 mL sample vial. The vials were capped and vortexed briefly. Samples were prepared for LC analysis by transferring 100 µL of an internal standard solution (106 µg/mL Irganox 415 in methanol) and 1000 µL of the extract into a 2 mL sample vial. The vials were capped and vortexed briefly.
Test Systems and Operating Conditions

The specific analytical instruments and test method operating conditions used in chromatographic analyses performed in the optimized study are delineated in Tables 3 and 4.

Results and Discussion; Ranging Finding

Organic Extractables

Figure 2 illustrates the leaching trends of one of the intentionally added label-related extractables (MEK). The migration of MEK through the LDPE bottle and into the leachate occurs quite rapidly and migration is essentially complete and asymptotic levels were achieved at the first time point (1 month). Because MEK is label-related, the accumulation levels of this spiked extractable was not affected by whether the filled bottles were stored upright (no direct contact between the extracting solution and the elastomeric gasket or PP cap) or inverted (direct contact between the extracting solution and the elastomeric gasket or PP cap). Similar leaching (migration) profiles were obtained for the other spiked label-related extractables.

As the spiked extractables where intentionally added to the labels, it is possible to determine their extent of leaching. If 100% leaching of the spiked compounds (Irgacure 1173, DGPTA and Benzophenone) were to occur and the migration was strictly in the direction of the solution (and not outwards through the label), a solution concentration of 12.5 µg/mL would result. Under such an assumption, the extents of leaching for Irgacure 1173, DPGDA and Benzophenone were calculated to be 26%, 27% and 48%, respectively, in the IPA/Water extracts.

The accumulation level of both label- and container-related extractables is illustrated in Figure 3. While the accumulation levels of the highly water-soluble label targets (Irgacure 1173 and DPGDA) were generally similar in the aqueous and organic solvents, the poorly water-soluble, non-polar container-related organic extractables, such as the nonyl phenol isomers, benzophenone and Irganox 1076, only accumulated in the IPA/water leachates in measureable quantities. The accumulation levels of the label- and bottle-related extractables were not affected by
whether the filled bottles were stored upright (no direct contact between the extracting solution and the elastomeric
gasket or PP cap) or inverted (direct contact between the extracting solution and the elastomeric gasket or PP cap).

These data established two areas for optimization in the second study reported herein. Firstly, it is clear that fully
establishing the leaching (migration) profile would require test intervals much earlier and more frequent than were
used in the range finding study. Secondly, the label spiking was found to be sub-optimal. Specifically, the levels at
which extractables were spiked onto the label were too high and the spiking of the label did not produce an even
distribution of the spiked compounds across the surface area of the label. While the leaching of the spiked
extractables was readily followed in the range finding study, it was not possible to follow the leaching of
extractables which were both spiked into the label or were intrinsic to the label as the levels of the spiked
extractables were significantly greater than the levels of the intrinsic extractables. Furthermore, the leaching of the
spiked compounds was mechanistically constrained by their uneven distribution on the label. Thus the spiking
levels were reduced and the spiking process was modified in the optimized study.

Additionally, the leaching trends noted in the range finding study established the approximate levels to which the
extractables accumulated in the fill solutions. Knowing the approximate accumulation levels facilitated the
development of analytical methods which had the necessary sensitivity, specificity, accuracy and precision to
support the target extractables testing that was used in the optimized leaching (migration) study.

**Elemental Extractables**

While the ICP-MS testing was performed a using “periodic table” scan of 70 elements (see Table 2 for the list of
elements included in the scan), extractables containing most of these elements were not detected in any of the
leachates. Those elements which were present in the leachates at measurable levels included B, Mg, Al, Si, K, Ca,
Ti, Zn and Br. The likely source of most of these elements is the elastomeric gasket; B and Br from the rubber
itself, Ti from the titanium dioxide used as a colorant, Ca and Zn as counter-ions in the fatty acid salts used as
lubricants, Al and Si from the elastomer’s calcined aluminum silicate and Mg from the material’s calcined
magnesium oxide.
The following observations were made concerning the leaching behavior of the elemental extractables (see Figures 4 and 5):

1. The element-containing extractables were leached in higher quantities at lower pH.
2. The levels of element-containing extractables were larger, inverted (exaggerated) versus upright test units. This is consistent with the elastomeric gasket being the source of these extractables, as the gasket is in direct solution contact in the inverted configuration.
3. Complete leaching of the element-containing extractables was not achieved under the conditions of this study. While the leaching plots typically reflect an approach to asymptotic concentrations, the asymptotic behavior was not achieved for most element-containing extractables and thus the levels of these extractables would continue to increase for longer storage durations. Nevertheless, the most rapid leaching of the metallic extractables occurred in the early stages of the extraction study (less than 1 month contact). Conversely, the leaching of the non-metallic extractables (B and Br) at low pH did not achieve asymptotic behavior over the course of the study, suggesting that either (a) the pool of these extractables is larger than the pool of the metallic extractables (b) the mechanism of leaching is different than the metallic extractables or (c) a combination of both.

Figure 6 documents the maximum levels of the element-containing extractables, aqueous versus IPA/water leaching solutions. In general, the metallic extractables form two groups with respect to their relative leached levels, aqueous leachates versus IPA/water leachates. One group, reflecting Al, K, Ti and Zn, accumulated at higher levels in the aqueous leachates (more specifically, the low pH aqueous leachates). A second group, including Ca, Mg and Si, accumulated at either similar or higher levels in the IPA/water leachates. It is likely that this different behavior reflects a different leaching mechanism. For example, it is likely that the element-containing extractables that accumulated to higher levels at the low pH aqueous leachates were leached from the test article via a process of either ion exchange or dissolution of an inorganic oxide. On the other hand, the metallic extractables that accumulated to higher levels in the IPA/water leachates were leached from the test article in the form of an organic compound that is more soluble in IPA/water than it is in water.
Unlike the metallic extractables, Br-containing extractables accumulated at much higher levels, IPA/water versus aqueous. This behavior could reflect the leaching of Br-containing hydrocarbon oligomers by the IPA/water extraction medium.

**Results and Discussion, Optimized Study**

**Establishing Targeted Extractables**

It is reasonable and appropriate to suggest that there be a relationship between (1) the ingredients intentionally added to a material of construction, (2) the extractables that are revealed when the material (or a component or system containing the material) is characterized by a controlled simulation study, and (3) the leachables that are present in a pharmaceutical product stored in the system constructed from the material. Going forward, one would expect that the ingredients would be indicative of the extractables and that the extractables would be indicative of the leachables. In the reverse direction, one would expect that leachables would be largely explainable on the basis of extractables and that extractables would be largely explainable on the basis of ingredients. In fact these observations are the basis of extractables and leachables correlations. Furthermore, these observations establish why a three-stage assessment process including material selection (based on ingredients), system qualification (based on extractables) and product assessment (based on either leachables or simulating extractables) is an appropriate means of developing and qualifying safe and effective packaged pharmaceutical products.

Information that can guide the selection of target extractables in the optimized leaching (migration) study is contained in Tables 5 through 7. Specifically, Table 5 contains compositional information that was obtained from the vendors of the materials that made up this study’s test system while Table 6 contains the extractables profiles that were obtained for these materials via controlled extraction studies. Table 7 qualitatively reconciles the compositional and extractables information and uses this information to select those extractables which were targeted in the optimized leaching (migration) study. It should be noted that these targeted substances are termed targeted extractables because the optimized leaching (migration) study is a simulation of the actual clinical use of the test system. Had this leaching (migration) study been performed with a specific drug product under the actual conditions of storage and use of that drug product, then the targeted substances would have been termed target leachables.
As seen in Table 7, the extractables profiles for the test system’s individual materials of construction can be well-correlated to the materials’ composition, known or speculated. For example, while the vendor of the polyethylene bottle did not provide its compositional information, it is reasonable to suspect that the polyethylene was formulated to contain one or more antioxidants and in fact commonly employed antioxidants were present in the material’s extractables profile. Considering a material whose composition was well known, the rubber material’s extractables can generally be linked to its intentional ingredients.

Several factors are relevant when selecting extractables to target in a leaching (migration) study. Generally speaking, the overriding factor for the selection of target substances (either extractables or leachables) is the potential for the substance to adversely affect some quality attribute (including safety) of either the pharmaceutical product or the packaging system. As performing an impact assessment was not within the scope of this study, this means of selecting targets was not used. Rather, targets were chosen based on secondary considerations, including:

- Measured level in the leachates (based on the generalization that the extractables at the highest levels tend to have the greatest impact potential and are the most readily measurable),
- Analytical expediency, and
- Ability to represent a particular compound class or a particular source ingredient.

**Leaching Profiles for the Label-related Targeted Extractables**

Leaching profiles for the three spiked label-related target extractables are shown in Figures 7 through 9. The profiles of the individual extractables are both similar and dissimilar, consistent with the chemical nature of the extractable and the extracting matrix. As all three extractables are highly soluble in the IPA/water extraction medium, it is to be expected that all three extractables would have similar leaching profiles in this medium. This is the case, as shown in Figure 10, which indicates that the leaching of these three extractables is essentially complete after approximately 20 days of storage, at which point an equilibrium level is achieved. This equilibrium level, approximately 4200 ng/mL, is comparable to the total pool of these spiked substances, which was approximately 5000 ng/mL.
While the behavior of these three extractables is similar in the IPA/water medium, their behaviors are very different in the aqueous extracts. As Irgacure 1173 is both highly water soluble and non-ionic, its leaching is very similar in all three leachate matrices (Figure 7). As benzophenone is less water soluble, its equilibrium level in the aqueous leachates is lower than its equilibrium level in the IPA/water leachate (Figure 8).

The leaching profiles obtained for dipropylene glycol diacrylate (DPGDA, Figure 9) are quite different than the profiles for the other spiked label-related extractables, as the profiles are quite different in all three leachate media. Since this extractable is both highly water soluble and non-ionic, it is reasonable to expect that it would exhibit similar behavior to Irgacure 1173, where the profiles in all three leachate media are essentially the same. The lower and decreasing levels observed in the pH 2.5 and especially the pH 9.5 leachates suggest that this extractable is degraded by an acid- and base-catalyzed process.

The behavior of a fourth label-related extractable, 2,4,7,9-tetramethyl-5-decyn-4,7-diol, is shown in Figure 11. This targeted extractable differs from the spiked targets in that (a) this extractable is native to the label, and not artificially spiked as were the previously discussed targets and (b) it is a degradation product of, or impurity in, one of the constituents of the label’s adhesive (Surfynol PSA 336). As a degradation product, its leaching would be slower than the spiked extractables because it leaching rate reflects the combination of its production rate and its diffusion rate whereas the leaching rate of the spiked extractables reflects solely the diffusion rate. Nevertheless, this extractable achieves its equilibrium level in solution after approximately 105 days of storage. Because this non-ionic extractable has a low water solubility, its equilibrium level in the aqueous leachates is similar at both low and high pH media but lower than its equilibrium level in the IPA/water medium.

Leaching Profiles for the Cap-related Targeted Extractables

Due to the nature of the test system, the cap is an indirect solution contact component of the system. This observation is significant as it is the explanation for the behavior of the cap-related target extractables. Although Irganox 1010, Irgafos 168 and Irgafos 168 oxide were targeted, these substances did not accumulate in the extraction
media at any point in the migration study. As these substances are large molecules with low volatility, their migration from the cap and through the barriers (either the bottle or the liner) was anticipated to be very slow. Additionally, their solubility in aqueous solutions is very low and even if they did migrate to the point where they achieved solution contact, they would not dissolve in the aqueous media to any measurable extent.

On the other hand, ethyl-4-ethoxybenzozate was readily measurable in the IPA/water leachate throughout the course of the leaching (migration) study (Figure 12). As this compound is smaller, more soluble and more volatile than the other cap-related targets, it is reasonable to expect that it would migrate faster than the other targets. In fact, the chemical properties of this target are similar to those of benzophenone, a spiked label-related target and thus it is reasonable to expect that the ethyl-4-ethoxybenzozate would have the ability to migrate out of the cap, through the bottle and into the fill solution. Of course, such a process for ethyl-4-ethoxybenzozate would be slower than for benzophenone given ethyl-4-ethoxybenzozate’s longer, and likely more complex, migration pathway.

As shown in Figure 12, ethyl-4-ethoxybenzozate does not accumulate in the aqueous leachates to appreciable levels. Although this behavior does not reflect the relatively high aqueous solubility of this compound (which is greater than 300 mg/L), it could be explained by either acid- and base-catalyzed decomposition of the benzoate, the small surface area of contact between the fill solution and the cap, and/or the partitioning of this compound into the other components of the container closure system, such as the bottle.

**Leaching Profiles for the Gasket-related Targeted Extractables**

The leaching profiles of the single measured gasket-related extractable, the C21 oligomer, are shown in Figure 13. This oligomer accumulates in the fill solutions at very low levels, even in the case of the IPA/water fill solution. This behavior suggests that the various container closure system components have a strong affinity for this oligomer and thus that the oligomer partitions primarily into these components, thereby limiting its accumulation in the fill solutions.

**Leaching Profiles for the Bottle-related Targeted Extractables**
Due to the large contact surface area between the bottle and the leaching solution, relative to the other components of the test system, and their relatively large total pools in the bottle, it is reasonable to expect that bottle-related extractables would quickly accumulate in the fill solutions in readily measurable quantities. This expectation is realized for the three targeted bottle-related extractables in the IPA/water leachate, as shown in Figures 14 through 16. Given the very limited aqueous solubility of Irganox 1076, it is expected that its accumulation in the aqueous leachates would be low and this was the outcome that was observed. The low accumulation levels of trinonylphenylphosphate in the aqueous leachates reflect both the limited aqueous solubility of this compound and its hydrolytic degradation in aqueous solutions. Given its higher aqueous solubility, 4-nonylphenol accumulated at measurable concentrations in the aqueous leachates and as it is non-ionic there was no difference in its leaching behavior as a function of extraction solution pH. However, its relatively low accumulation levels in the aqueous leachates and the rapidity with which the plateau in the leaching (migration) profile is achieved indicate that 4-nonylphenol partitions preferentially into the bottle material, as opposed to partitioning into the fill solution.

**Conclusions**

The results of the simulated leaching (migration) study performed on a model container closure system that is more or less relevant for parenteral drug products supports the following generalizations:

1. The extractables profile revealed by performing such a simulation study on a packaging system can qualitatively be correlated with compositional information obtained for the system’s materials of construction.
2. The chemical nature of the extracting/leaching medium can markedly affect the extractables and the leachables profiles.
3. The chemical nature of the extractable itself can markedly affect its leaching (migration) profile.
4. An extractable’s leaching (migration) profile reflects the interplay between the chemical natures of the leaching medium and the extractable (items #2 and #3 previous).
5. Element-containing extractables are leached from materials in different forms and by different mechanisms, depending on the chemical nature of the leaching medium and the chemical form of the extractable’s source material.
6. While direct contact between a drug product and a system’s material of construction may exacerbate the leaching of substances from that material by the drug product, direct contact is not a prerequisite for extraction to occur. Thus label- and certain cap-related extractables were able to breach the barrier provided by the LDPE bottle and accumulate in the leaching solutions. Furthermore, while gasket-related extractables accumulated to higher levels when the model packaging system was stored inverted versus upright, some leaching was noted even in the upright (non-direct solution contact) configuration.

7. That LDPE is a poor barrier to volatile and semi-volatile extractables, as this study established that the migration and leaching of label-related extractables was quite rapid.

Furthermore, this study establishes that a simulated leaching (migration) study can produce an extractables profile that could reasonably be expected to mimic the leachables profile of a packaged pharmaceutical product.

References


<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS #</th>
<th>Supplier/Purity</th>
<th>Structure/Info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl ethyl ketone (MEK)</td>
<td>78-93-3</td>
<td>Fluka (St. Louis, Mo), &gt;99.5%</td>
<td><img src="image1" alt="Structure of MEK" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemical Formula: $\text{C}_3\text{H}_6\text{O}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exact Mass: 72.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aqueous solubility: &gt;10000 mg/L(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Log Po/w: 0.47(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vapour pressure: 115 torr</td>
</tr>
<tr>
<td>Irgacure 1173 (Ic1173)</td>
<td>7473-98-5</td>
<td>Sigma-Aldrich (St. Louis, Mo), &gt;85%</td>
<td><img src="image2" alt="Structure of Ic1173" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemical Formula: $\text{C}<em>{18}\text{H}</em>{22}\text{O}_2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exact Mass: 164.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aqueous solubility: &gt;4400 mg/L(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Log Po/w: 1.49(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vapour pressure: 0.007 torr</td>
</tr>
<tr>
<td>Benzophenone (BzPh)</td>
<td>119-61-9</td>
<td>Sigma-Aldrich, 99%</td>
<td><img src="image3" alt="Structure of Benzophenone" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemical Formula: $\text{C}<em>{13}\text{H}</em>{12}O$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exact Mass: 182.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aqueous solubility: 150 mg/L(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Log Po/w: 3.21(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vapour pressure: 0.008 torr</td>
</tr>
<tr>
<td>Dipropylene glycol diacrylate (DGPDA)</td>
<td>57472-68-1</td>
<td>TCI America (Portland, OR), &gt;85%</td>
<td><img src="image4" alt="Structure of DGPDA" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemical Formula: $\text{C}<em>{12}\text{H}</em>{9}\text{O}_5$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exact Mass: 242.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aqueous solubility: &gt;969 mg/L(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Log Po/w: 1.30(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vapour pressure: Not available</td>
</tr>
</tbody>
</table>

\(^1\)Value obtained from Advanced Chemistry Development, ACD/Labs Software V11.02.
### Table 2: Instrument Parameters; Inductively Coupled Plasma-Mass Spectrometry (ICP-MS).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Operating Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP-MS</td>
<td>Agilent (Santa Clara, CA) 7500A</td>
</tr>
<tr>
<td>Forward Power</td>
<td>1300 watts</td>
</tr>
<tr>
<td>Integration Time</td>
<td>0.1 seconds per point</td>
</tr>
<tr>
<td>Rinse Time</td>
<td>180 seconds</td>
</tr>
<tr>
<td>Rinse Rate</td>
<td>0.5 rps</td>
</tr>
<tr>
<td>Uptake Time</td>
<td>45 seconds</td>
</tr>
<tr>
<td>Uptake Rate</td>
<td>0.5 rps</td>
</tr>
<tr>
<td>Stabilization Time</td>
<td>20 Seconds</td>
</tr>
<tr>
<td>Analysis Pump Rate</td>
<td>0.1 rps</td>
</tr>
<tr>
<td>All Other Settings</td>
<td>Determined by Tune</td>
</tr>
<tr>
<td>Elements Scanned</td>
<td>Li, Be, B, Na, Mg, Al, Si, K, Ca, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge, As, Se, Br, Rb, Sr, Y, Zr, Nb, Mo, Ru, Rh, Pd, Ag, Cd, In, Sn, Sb, Te, I, Cs, Ba, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Th, and U</td>
</tr>
</tbody>
</table>

### Table 3. Typical Operating Parameters, GC/MS Analyses

<table>
<thead>
<tr>
<th>Operating Parameter</th>
<th>Operating Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column</td>
<td>Restek (Bellefonte, PA) Rtx®-VMS, 30m x 0.25mm, 1.4 µm film thickness</td>
</tr>
<tr>
<td>Oven Program</td>
<td>Start at 40°C, hold for 4 min; ramp at 25°C/min to 220°C; ramp at 5°C/min to 250°C; ramp at 25°C/min to 260°C, hold for 8 min</td>
</tr>
<tr>
<td>Carrier Gas</td>
<td>He at 1.8 mL/min</td>
</tr>
<tr>
<td>Injection</td>
<td>Splitless; 0.25 μL</td>
</tr>
<tr>
<td>Injector Temperature</td>
<td>280°C</td>
</tr>
<tr>
<td>MS Transfer Line Temperature</td>
<td>260°C</td>
</tr>
<tr>
<td>MS Detection Details</td>
<td>EI (70.3 ev), mass range 29 – 550 amu</td>
</tr>
<tr>
<td>Instrumentation Used</td>
<td>Agilent (Santa Clara, CA) 7890 GC / 7683B autosampler / 7000B Triple Quadrupole MS (Agilent Mass Hunter B.07.01 data system)</td>
</tr>
</tbody>
</table>
Table 4. Typical Operating Parameters, LC/UV/MS Analyses

<table>
<thead>
<tr>
<th>Operating Parameter</th>
<th>Operating value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column</td>
<td>Agilent Zorbax Eclipse Plus C18, 100 x 3.0 mm, 3.5μm particles</td>
</tr>
<tr>
<td>Column Temperature</td>
<td>50°C</td>
</tr>
<tr>
<td>Mobile Phase Components</td>
<td>A = 10 mM ammonium acetate, B = acetonitrile</td>
</tr>
<tr>
<td>Mobile Phase Gradient</td>
<td>Time</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>21.0</td>
</tr>
<tr>
<td></td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td>26.0</td>
</tr>
<tr>
<td>Mobile Phase Flow Rate</td>
<td>0.8 mL/min</td>
</tr>
<tr>
<td>Injection Volume</td>
<td>10 μL</td>
</tr>
<tr>
<td>Detection, UV</td>
<td>205 –400 nm; step = 2 nm</td>
</tr>
<tr>
<td>Detection, MS</td>
<td>API-ES or AP-Cl, positive ion and negative ion (targeted m/z for each targeted analyte)</td>
</tr>
<tr>
<td>Instrumentation Used</td>
<td>Agilent 1200 LC (vacuum degasser, binary pump, heated column compartment) / Model G1315A diode array detector / 6120 mass selective detector (MSD). Agilent Chemstation rev B.04.03-SP2 data system</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Bottle</td>
<td>Not provided</td>
</tr>
<tr>
<td>Cap</td>
<td>Not provided</td>
</tr>
<tr>
<td>Rubber Liner</td>
<td>Brominated isobutylene isoprene copolymer (57.3%); Calcined aluminium silicate, 38.2%; Titanium dioxide, 1.2%; Paraffinic oil, 1.2%; Zinc oxide, 0.6%; Polyethylene, 0.6%; SRF Carbon black mixture, 0.4%; Calcined magnesium oxide, 0.3%; 4,4'-Dithiodimorpholine/polyisobutylene, 0.3%</td>
</tr>
<tr>
<td>Label</td>
<td>Adhesive:</td>
</tr>
<tr>
<td></td>
<td>Surlynol PSA 336 Surfactant (wetting agent); Dioctylsulfosuccinate, Sodium Salt; Ethoxylated 2,4,7,9-tetramethyl 5 decyn-4,7-diol</td>
</tr>
<tr>
<td></td>
<td>Biocide:</td>
</tr>
<tr>
<td></td>
<td>Chloro-2-methyl-4-isothiazolin-3-one; 2-Methyl-4-isothiazolin-3-one; Magnesium chloride; Magnesium nitrate; Copper nitrate</td>
</tr>
<tr>
<td></td>
<td>Ink:</td>
</tr>
<tr>
<td></td>
<td>Modified Polyester; Irgacure 369; Irgacure 1173; Trimethylolpropane triacrylate; Tripropylene glycol diacrylate; 3-Glyceryl triacrylate (propoxylated); Carbon Black; Phato Blue; Carbazole Violet; Tale</td>
</tr>
</tbody>
</table>
Table 6. Extractables Profiles; Materials of Construction, Established Via a Controlled Extraction Study.

<table>
<thead>
<tr>
<th>Material</th>
<th>Extractable Name</th>
<th>CAS RN</th>
<th>Level, µg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottle</td>
<td>4-Nonylphenol isomers</td>
<td>84852-15-3</td>
<td>4200</td>
</tr>
<tr>
<td></td>
<td>Irganox 1076</td>
<td>2082-79-3</td>
<td>10000</td>
</tr>
<tr>
<td></td>
<td>Trinonylphenylphosphate</td>
<td>26569-53-9</td>
<td>NE(^1)</td>
</tr>
<tr>
<td>Cap</td>
<td>Irganox 1010</td>
<td>6683-19-8</td>
<td>310</td>
</tr>
<tr>
<td></td>
<td>Irgafos 168</td>
<td>31570-04-4</td>
<td>5000</td>
</tr>
<tr>
<td></td>
<td>Irgafos 168 oxide</td>
<td>95906-11-9</td>
<td>2200</td>
</tr>
<tr>
<td></td>
<td>Monostearin</td>
<td>123-94-4</td>
<td>1200</td>
</tr>
<tr>
<td></td>
<td>Ethyl-4-ethoxybenzoate</td>
<td>23676-09-7</td>
<td>300</td>
</tr>
<tr>
<td>Label</td>
<td>Dioctylsulfosuccinate, sodium salt</td>
<td>577-11-7</td>
<td>1900</td>
</tr>
<tr>
<td></td>
<td>2,4,7,9-Tetramethyl-5-decyn-diol</td>
<td>126-86-3</td>
<td>700</td>
</tr>
<tr>
<td></td>
<td>Octadecanoic (Stearic) acid</td>
<td>57-11-4</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Hexadecanoic (Palmitic) acid</td>
<td>57-10-3</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Hexanedioic acid, bis(2-methylpropyl) ester</td>
<td>141-04-8</td>
<td>10</td>
</tr>
<tr>
<td>Rubber liner(^2)</td>
<td>Octadecanoic (Stearic) acid(^6)</td>
<td>57-11-4</td>
<td>&gt; 1000</td>
</tr>
<tr>
<td></td>
<td>Hexadecanoic (Palmitic) acid(^6)</td>
<td>57-10-3</td>
<td>&gt; 1000</td>
</tr>
<tr>
<td></td>
<td>C-21 Oligomers(^4)</td>
<td>---</td>
<td>10 – 1000</td>
</tr>
<tr>
<td></td>
<td>Dimethyterephthalate</td>
<td>120-61-6</td>
<td>100 – 1000</td>
</tr>
<tr>
<td></td>
<td>Oleamide</td>
<td>301-02-0</td>
<td>100 - 1000</td>
</tr>
<tr>
<td></td>
<td>Octadecane</td>
<td>593-45-3</td>
<td>100 – 1000</td>
</tr>
<tr>
<td></td>
<td>Octacosane</td>
<td>630-02-4</td>
<td>10 – 100</td>
</tr>
<tr>
<td></td>
<td>1-(4-Morpholinyl)-octanoic acid</td>
<td>5299-54-7</td>
<td>10 – 100</td>
</tr>
<tr>
<td></td>
<td>Morpholine</td>
<td>110-91-8</td>
<td>10 – 100</td>
</tr>
<tr>
<td></td>
<td>Tetracosane</td>
<td>646-31-1</td>
<td>10 – 100</td>
</tr>
<tr>
<td></td>
<td>10-Oxo-octadecanoic acid</td>
<td>870-10-0</td>
<td>10 – 100</td>
</tr>
<tr>
<td></td>
<td>4,4'-Diocetyl diphenylamine</td>
<td>101-67-7</td>
<td>10 – 100</td>
</tr>
<tr>
<td></td>
<td>Hexadecanamide</td>
<td>629-54-9</td>
<td>10 – 100</td>
</tr>
<tr>
<td></td>
<td>Docosane</td>
<td>629-97-0</td>
<td>10 - 100</td>
</tr>
<tr>
<td></td>
<td>Nonadecanoic acid</td>
<td>646-30-0</td>
<td>10 – 100</td>
</tr>
<tr>
<td></td>
<td>Bromine(^3)</td>
<td>---</td>
<td>21(^5)</td>
</tr>
<tr>
<td></td>
<td>Potassium(^3)</td>
<td>---</td>
<td>7(^5)</td>
</tr>
<tr>
<td></td>
<td>Aluminum(^3)</td>
<td>---</td>
<td>4(^5)</td>
</tr>
<tr>
<td></td>
<td>Magnesium(^3)</td>
<td>---</td>
<td>4(^5)</td>
</tr>
<tr>
<td></td>
<td>Calcium(^3)</td>
<td>---</td>
<td>4(^5)</td>
</tr>
</tbody>
</table>

\(^1\)NE = level not established in this study.
\(^2\)Data from reference 9.
\(^3\)Only the Rubber liner was tested for extractable elemental entities.
\(^4\)For example, 1-Isopropenyl-2,2,4,4-tetramethyl-6-(2,2,4-trimethyl-pentyl-1-)cyclohexane. Certain of these oligomers were halogenated.
\(^5\)Measured in aqueous extracts only.
\(^6\)Various aliphatic esters of these compounds were also identified.
<table>
<thead>
<tr>
<th>Component</th>
<th>Ingredient</th>
<th>Extractable</th>
<th>Targeted Extractable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottle (PE)</td>
<td>Antioxidants(^3)</td>
<td>Irganox 1076</td>
<td>Irganox 1076</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-Nonylphenol isomers</td>
<td>4-Nonylphenol isomers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trinonylphenolphosphate</td>
<td>Trinonylphenolphosphate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trinonylphenolphosphate</td>
<td>---</td>
</tr>
<tr>
<td>Cap (PP)</td>
<td>Antioxidants(^3)</td>
<td>Irganox 1010</td>
<td>Irganox 1010(^5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irgafos 168</td>
<td>Irgafos 168(^3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irgafos 168 oxide</td>
<td>Irgafos 168 oxide(^3)</td>
</tr>
<tr>
<td></td>
<td>Catalyst(^3)</td>
<td>Ethyl-4-ethoxybenzoate</td>
<td>Ethyl-4-ethoxybenzoate</td>
</tr>
<tr>
<td></td>
<td>Antistat(^3)</td>
<td>Monostearin</td>
<td>Monostearin(^6)</td>
</tr>
<tr>
<td>Liner (Rubber)</td>
<td>Brominated isobutylene isoprene copolymer</td>
<td>Br, B</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrocarbon Oligomers</td>
<td>C21 Hydrocarbon Oligomer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Octadecane, Octacosane, Tetraicosane, Docosane</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Calcined aluminosilicate</td>
<td>Al, Si</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Titanium dioxide</td>
<td>Ti</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Zinc oxide</td>
<td>Zn</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Calcined magnesium oxide</td>
<td>Mg</td>
<td>---</td>
</tr>
<tr>
<td>Processing Aids(^3)</td>
<td>Palmitic acid</td>
<td>Palmitic acid(^8)</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Stearic acid</td>
<td>Stearic acid(^8)</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>10-Oxa-octadecanoic acid</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Oleamide</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Nonadecanoic acid</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Hexadecanamide</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Paraffinic oil</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>SRF Carbon black mixture</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Unknown Source</td>
<td>Dimethylterephthalate</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>1-(4-Morpholinyl)-octanoic acid</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Morpholine</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
Table 7. Reconciliation of Ingredients, Extractables and Targeted Extractables (continued).

<table>
<thead>
<tr>
<th>Component</th>
<th>Ingredient</th>
<th>Extractable</th>
<th>Targeted Extractable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Label Adhesive</td>
<td>Ethoxylated 2,4,7,9-Tetramethyl-5-decyn-4,7-diol</td>
<td>2,4,7,9-Tetramethyl-5-decyn-4,7-diol</td>
<td>2,4,7,9-Tetramethyl-5-decyn-4,7-diol</td>
</tr>
<tr>
<td></td>
<td>Diocetyl sulfosuccinate, sodium salt</td>
<td>Diocetyl sulfosuccinate, sodium salt</td>
<td>Diocetyl sulfosuccinate, sodium salt</td>
</tr>
<tr>
<td></td>
<td>Surfynol PSA 336 surfactant</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>---</td>
<td>---</td>
<td>Benzophenone⁷</td>
</tr>
<tr>
<td>Label, Ink</td>
<td>Irgacure 369</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Irgacure 1173</td>
<td>---</td>
<td>Irgacure 1173⁴</td>
</tr>
<tr>
<td></td>
<td>Trimethylolpropane triacrylate</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Tripropylene glycol diacylate</td>
<td>---</td>
<td>Dipropylene glycol diacylate⁴</td>
</tr>
<tr>
<td></td>
<td>3-Glyceryl triacrylate (propoxylated)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Modified polyester</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Label, Biocide</td>
<td>Chloro-2-methyl-4-isothiazolin-3-one</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>3-Methyl-4-isothiazolin-3-one</td>
<td>5-Ethyl-n-propylthiazole</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Magnesium chloride</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Magnesium nitrate</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Copper nitrate</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Label</td>
<td>Unknown</td>
<td>1, (1,4-Dimethyl)-3-cyclohexen-1-yl Ethanol</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N-acetyl-N-(hydroxyl phenyl)-butanamide</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-Propenoic acid, 2-ethylhexyl ester</td>
<td>---</td>
</tr>
</tbody>
</table>

¹As specified by the component’s vendor; see Table 5.
²As revealed by a controlled extraction study; see Table 6.
³Although this ingredient was not specified by the component’s vendor, this ingredient is commonly employed with this type of material.
⁴Targeted as a spiked compound.
⁵Although these extractables were targeted, their leaching was limited and their levels in the fill solutions were at or near the analytical method’s quantitation limit. Thus, leaching (migration) profiles were not generated for these extractables.
⁶Although this extractable was targeted, it undergoes transesterification in the presence of IPA. Thus, leaching (migration) profiles for this extractable were not generated.
⁷Although this extractable was not linked to the label by either its vendor or in the extraction study, it was added to the label as a spiked target due to its known association with label adhesives and well-documented migration and leaching behavior.
⁸Although these extractables were targeted, the resulting data suggested that analytical issues were encountered during the testing of the fill solutions. Thus, leaching (migration) profiles were not generated for these extractables.
<table>
<thead>
<tr>
<th><strong>Compound</strong></th>
<th><strong>CAS #</strong></th>
<th><strong>Information</strong></th>
<th><strong>Structure/Info</strong></th>
</tr>
</thead>
</table>
| 2,4,7,9-Tetramethyl-5-decyn-4,7-diol (TMDD)      | 126-86-3  | Chemical Formula: C_{14}H_{26}O_{2}  
Molecular weight: 226.35  
Aqueous solubility: 10 mg/L \(^1\)  
Log P\(_{\text{o/w}}\): 4.37\(^1\)  
Vapor pressure: 3.0 \times 10^{-3} \text{torr} | ![Structure](image1.png) |
| Dioctylsulfosuccinate, sodium salt               | 577-11-7  | Chemical Formula: C_{20}H_{38}O_{7}S.Na  
Molecular weight: 444.56  
Aqueous solubility: 18 g/L \(^1\)  
Log P\(_{\text{o/w}}\): 2.4\(^1\)  
Vapor pressure: N/A                                      | ![Structure](image2.png) |

See Table 1 for additional information for other Label-related extractables (benzophenone, Irgacure 1173).
<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS #</th>
<th>Information</th>
<th>Structure/Info</th>
</tr>
</thead>
</table>
| Irganox 1010              | 6683-19-8 | Chemical Formula: C\textsubscript{73}H\textsubscript{108}O\textsubscript{12}  
Molecular weight: 1177.63  
Aqueous solubility: 0.02 µg/L\textsuperscript{1}  
Log P\textsubscript{o/w}: 18.83\textsuperscript{1}  
Vapor pressure: < 10\textsuperscript{-14} torr | ![Chemical Structure] |
| Irgafos 168               | 31570-04-4 | Chemical Formula: C\textsubscript{42}H\textsubscript{63}O\textsubscript{3}P  
Molecular weight: 646.45  
Aqueous solubility: 0.7 µg/L\textsuperscript{1}  
Log P\textsubscript{o/w}: 13.7\textsuperscript{1}  
Vapor pressure: 1.8 x 10\textsuperscript{-13} torr | ![Chemical Structure] |
| Irgafos 168 oxide         | 95906-11-9 | Chemical Formula: C\textsubscript{42}H\textsubscript{63}O\textsubscript{4}P  
Molecular weight: 662.45  
Aqueous solubility: 0.3 µg/L\textsuperscript{1}  
Log P\textsubscript{o/w}: 11.4\textsuperscript{1}  
Vapor pressure: 3.7 x 10\textsuperscript{-13} torr | ![Chemical Structure] |
| Ethyl-4-ethoxybenzoate    | 23676-09-7 | Chemical Formula: C\textsubscript{13}H\textsubscript{14}O\textsubscript{3}  
Molecular weight: 194.23  
Aqueous solubility: 370 mg/L\textsuperscript{1}  
Log P\textsubscript{o/w}: 3.43\textsuperscript{1}  
Vapor pressure: 5.2 x 10\textsuperscript{-3} torr | ![Chemical Structure] |
<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS #</th>
<th>Information</th>
</tr>
</thead>
</table>
| Monostearin               | 123-94-4 | Chemical Formula: C\textsubscript{21}H\textsubscript{42}O\textsubscript{4}  
Molecular weight: 358.56  
Aqueous solubility: 3 mg/L\textsuperscript{1}  
Log P\textsubscript{o/w}: 7.09\textsuperscript{1}  
Vapor pressure: 4.2 x 10\textsuperscript{-11} torr |

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS #</th>
<th>Information</th>
</tr>
</thead>
</table>
| C21 Rubber Oligomer       | N/A   | Chemical Formula: C\textsubscript{21}H\textsubscript{40}  
Molecular weight: 376.24  
Aqueous solubility: N/A  
Log P\textsubscript{o/w}: N/A  
Vapor pressure: N/A       |

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS #</th>
<th>Information</th>
</tr>
</thead>
</table>
| Palmitic acid             | 57-10-3 | Chemical Formula: C\textsubscript{16}H\textsubscript{32}O\textsubscript{2}  
Molecular weight: 256.42  
Aqueous solubility: 5.4 mg/L\textsuperscript{1}  
Log P\textsubscript{o/w}: 6.81\textsuperscript{1}  
Vapor pressure: 3.5 x 10\textsuperscript{-5} torr |

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS #</th>
<th>Information</th>
</tr>
</thead>
</table>
| Stearic acid              | 57-11-4 | Chemical Formula: C\textsubscript{18}H\textsubscript{36}O\textsubscript{2}  
Molecular weight: 284.48  
Aqueous solubility: 1.2 mg/L\textsuperscript{1}  
Log P\textsubscript{o/w}: 7.83\textsuperscript{1}  
Vapor pressure: 8.6 x 10\textsuperscript{-6} torr |
<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS #</th>
<th>Information</th>
<th>Structure/Info</th>
</tr>
</thead>
</table>
| Irganox 1076 (Ix 1076)      | 2082-79-3 | Chemical Formula: C_{35}H_{62}O_{3}  
Molecular weight: 530.87  
Aqueous solubility: 0.4 µg/L \(^1\)  
Log P\(_{ow}\): 13.5 \(^1\)  
Vapor pressure: 1.6 x 10^{-13} torr | ![Chemical Structure](image) |
| 4-Nonylphenol               | 104-40-5 | Chemical Formula: C_{15}H_{24}O  
Molecular weight: 220.35  
Aqueous solubility: 2 to 20 mg/L \(^1\)  
Log P\(_{ow}\): 6.1 \(^1\)  
Vapor pressure: 8.5 x 10^{-5} torr | ![Chemical Structure](image) |
| Trinonylphenolphosphite (TNPPsite) | 26523-78-4 | Chemical Formula: C_{45}H_{69}O_{3}P  
Molecular weight: 689.00  
Aqueous solubility: <0.05 mg/L \(^1\)  
Log P\(_{ow}\): 8.0 \(^1\)  
Vapor pressure: N/A | ![Chemical Structure](image) |

\(^1\) Value obtained from Advanced Chemistry Development, ACD/Labs Software V11.02.
\(^2\) N/A = Information not available.
**Figure Captions**

**Figure 1.** The Individual Components of the Model Container Closure System. The bottle used is shown with the label already applied. The major ingredients or extractables from the individual components of the test system are listed. The foil overpouch, used primarily as a barrier to reduce solvent loss from the test article, is not shown.

**Figure 2.** Leaching (migration) Profile for Methylethyl ketone during the Range Finding Study. The leaching of this label-related extractable was relatively rapid and was essentially completed by the first time point. The accumulation of this uncharged extractable is only marginally affected by the pH of the extracting medium.

**Figure 3.** Maximum Accumulation Levels for the Organic Extractables Measured during the Range Finding Study.

**Figure 4.** Leaching Profiles for Elemental Extractables, Range Finding Study, pH 2.5.

**Figure 5.** Leaching Profiles for Bromine, Range Finding Study.

**Figure 6.** Maximum Accumulation Levels the Elemental Extractables Measured during the Range Finding Study.

**Figure 7.** Leaching Profile of a Spiked Label Extractable, Irgacure 1173, Optimized Study. The leaching of this non-ionic, highly water soluble and stable extractable is similar in all three leachate media.

**Figure 8.** Leaching Profile of a Spiked Label Extractable, Benzophenone, Optimized Study. The different leaching behavior of this extractable in the aqueous leachate matrices likely reflects its limited aqueous solubility.

**Figure 9.** Leaching Profile of a Spiked Label Extractable, Dipropylenglycol diacrylate (DPGDA), Optimized Study. The different leaching behavior of this highly water soluble, non-ionic extractable in the aqueous leachate matrices likely reflects its acid- and base-catalyzed degradation.

**Figure 10.** Leaching Profile of Three Spiked Label Extractables in Isopropanol/Water, Optimized Study. All three spiked extractables behave similarly in this leachate matrix, achieving an equilibrium state after roughly 20 days of storage.

**Figure 11.** Leaching Profile of a Native Label Extractable, 2,4,7,9-Tetramethyl-5-decy-4,7-diol (TMDD), Optimized Study. The different leaching behavior of this extractable in the aqueous extraction matrices likely reflects its limited aqueous solubility.

**Figure 12.** Leaching Profile of a Cap-related Extractable, Ethyl-4-ethoxybenzoate, Optimized Study. The significantly lower levels of this extractable in the aqueous, versus the IPA/water, leachates is a manifestation of this compound’s propensity to partition into the various components of the container closure system. Thus it leaches from the cap and then preferentially partitions into the other system components (e.g., bottle) as opposed to the fill solution.

**Figure 13.** Leaching Profile of a Liner-related Extractable, C21 Rubber Oligomer, Optimized Study. The leaching behavior of this extractable reflects its limited aqueous solubility and strong partitioning into the various components of the container closure system.

**Figure 14.** Leaching Profile of a Bottle-related Extractable, Irganox 1076, Optimized Study. The different leaching behavior of this extractable in the aqueous leachate matrices likely reflects its very limited aqueous solubility.
**Figure 15.** Leaching Profile of a Bottle-related Extractable, Trinonylphenylphosphite, Optimized Study. The low accumulation levels of this extractable in the aqueous leachate matrices reflect both its limited aqueous solubility and its hydrolytic degradation in aqueous solutions.

**Figure 16.** Leaching Profile of a Bottle-related Extractable, 4-Nonylphenol, Optimized Study. The significantly lower levels of this extractable in the aqueous, versus the IPA/water, leachates is a manifestation of this compound’s propensity to partition into the various components of the container closure system.
Figure 1.

PP Screw Cap
- Ethyl-4-ethoxybenzoate (EEBz)
- Irganox 1010 (Ix1010)
- Irgafos 168 (Is168)
- Irgafos 168 oxide (Is168ox)
- Monostearin

LDPE Bottle:
- 4-Nonylphenol (mix. of isomers) (4-NP)
- Irganox 1076 (Ix 1076)
- Trinonylphenolphosphite (TNPPite)

Bromombutyl Rubber Liner
- Palmitic acid (PA)
- Stearic acid (PA)
- C21-Oligomer

Label (Adhesive)
NATIVE:
- 2,4,7,9-Tetramethyl-5-decyn-4,7-diol (TMDD)
- Dioctyl sulfosuccinate sodium salt (DOSS)

SPIKED:
- 2-Butanone (MEK)
- Irgacure 1173 (Ic1173)
- Dipropylenglycol diacrylate (DPGDA)
- Benzophenone (BzPh)
Figure 2.

![Graph showing relative peak intensity against storage duration at 40°C. The x-axis represents storage duration in months, ranging from 0 to 6. The y-axis represents relative peak intensity, ranging from 0 to 160,000,000. Two curves are plotted: one for pH 9.5 and the other for pH 2.5.](image)

Figure 3.

![Bar graph showing concentration in µg/mL. The x-axis lists various compounds: Irgacure 1173, DGPTA, benzophenone, nonyl phenols, benzoic acid, 4 ethoxy-ethyl ester, and Irganox 1076. The y-axis shows concentration ranging from 0 to 25. Two bars are plotted: one for aqueous and another for IPA/Water.](image)
Figure 4.

![Graph showing the concentration of various elements (Boron, Magnesium, Aluminum, Silicon, Calcium, Titanium, Zinc) over a duration at 40°C (Months).]

Figure 5.

![Graph showing the concentration of Bromine at pH 2.5 (Normal) and pH 9.5 (Normal and Exaggerated) over a duration at 40°C (Months).]
Figure 6.

![Bar chart showing concentrations of various elements in different solvents.](image-url)
Figure 7.

Ic 1173 (Exp #2)

Level in Simulant (ng/ml)

Aq pH 2.5
Aq pH 9.5
IW

days
Figure 8.

Benzophenone (Exp #2)

Level in Simulant (ng/ml)

Aq pH 2.5
Aq pH 9.5
IW

Level in Aqueous Simulants (ng/ml)

Days
Figure 9.

DGPDA (Exp #2)

Level in Simulant (ng/ml)

- Aq pH 2.5
- Aq pH 9.5
- IW

days

on January 31, 2021
Figure 11.
Figure 12.

Et-4-EthBzate (Exp #2)

Level in Simulant (ng/ml)

Aq pH 2.5
Aq pH 9.5
IW

days

on January 31, 2021
Figure 13.

C21 Ru Oligomer (Exp #2)

Level in Simulant (ng/ml)

Aq pH 2.5
Aq pH 9.5
IW

days

0 50 100 150 200

0 20 40 60 80 100
Figure 14.

Ix 10^76 (Exp #2)

Level in Simulant (ng/ml)

Aq pH 2.5
Aq pH 9.5
IW

days
Figure 15.
Figure 16.

4-Nonylphenol (Exp #2)

Level in IW (ng/ml)

Aq pH 2.5
Aq pH 9.5
IW

Level in Aqueous Simulants (ng/ml)

days

on January 31, 2021Downloaded from
An Authorized User of the electronic PDA Journal of Pharmaceutical Science and Technology (the PDA Journal) is a PDA Member in good standing. Authorized Users are permitted to do the following:

- Search and view the content of the PDA Journal
- Download a single article for the individual use of an Authorized User
- Assemble and distribute links that point to the PDA Journal
- Print individual articles from the PDA Journal for the individual use of an Authorized User
- Make a reasonable number of photocopies of a printed article for the individual use of an Authorized User or for the use by or distribution to other Authorized Users

Authorized Users are not permitted to do the following:

- Except as mentioned above, allow anyone other than an Authorized User to use or access the PDA Journal
- Display or otherwise make any information from the PDA Journal available to anyone other than an Authorized User
- Post articles from the PDA Journal on Web sites, either available on the Internet or an Intranet, or in any form of online publications
- Transmit electronically, via e-mail or any other file transfer protocols, any portion of the PDA Journal
- Create a searchable archive of any portion of the PDA Journal
- Use robots or intelligent agents to access, search and/or systematically download any portion of the PDA Journal
- Sell, re-sell, rent, lease, license, sublicense, assign or otherwise transfer the use of the PDA Journal or its content
- Use or copy the PDA Journal for document delivery, fee-for-service use, or bulk reproduction or distribution of materials in any form, or any substantially similar commercial purpose
- Alter, modify, repackage or adapt any portion of the PDA Journal
- Make any edits or derivative works with respect to any portion of the PDA Journal including any text or graphics
- Delete or remove in any form or format, including on a printed article or photocopy, any copyright information or notice contained in the PDA Journal