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RESEARCH

Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products

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ABSTRACT: Polymeric and elastomeric materials are commonly encountered in medical devices and packaging systems used to manufacture, store, deliver, and/or administer drug products. Characterizing extractables from such materials is a necessary step in establishing their suitability for use in these applications. In this study, five individual materials representative of polymers and elastomers commonly used in packaging systems and devices were extracted under conditions and with solvents that are relevant to parenteral and ophthalmic drug products (PODPs). Extraction methods included elevated temperature sealed vessel extraction, sonication, refluxing, and Soxhlet extraction. Extraction solvents included a low-pH (pH = 2.5) salt mixture, a high-pH (pH = 9.5) phosphate buffer, a 1/1 isopropanol/water mixture, isopropanol, and hexane. The resulting extracts were chemically characterized via spectroscopic and chromatographic means to establish the metal/trace element and organic extractables profiles. Additionally, the test articles themselves were tested for volatile organic substances.

The results of this testing established the extractables profiles of the test articles, which are reported herein. Trends in the extractables, and their estimated concentrations, as a function of the extraction and testing methodologies are considered in the context of the use of the test article in medical applications and with respect to establishing best demonstrated practices for extractables profiling of materials used in PODP-related packaging systems and devices.

KEYWORDS: Extractables, Leachables, Plasticized poly (vinyl chloride), Polycarbonate, Low-density polyethylene, Rubber, Cyclic olefin copolymer, Polymer analysis.

LAY ABSTRACT: Plastic and rubber materials are commonly encountered in medical devices and packaging/delivery systems for drug products. Characterizing the extractables from these materials is an important part of determining that they are suitable for use. In this study, five materials representative of plastics and rubbers used in packaging and medical devices were extracted by several means, and the extracts were analytically characterized to establish each

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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.

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material's profile of extracted organic compounds and trace element/metals. This information was utilized to make generalizations about the appropriateness of the test methods and the appropriate use of the test materials.

Introduction

Many pharmaceutical products are manufactured, stored, delivered, and/or administered in a packaging system or via a medical device with polymeric and elastomeric components. Interactions between the product and packaging systems or delivery devices can affect the quality of the product or, less frequently, the packaging system or device itself. From the perspective of the packaged drug product, interactions between the product and its packaging system (or device) are either additive (e.g., a packaging system constituent is added to the product due to the interaction) or reductive (e.g., a product constituent is reduced, in either level or action, due to the interaction). The additive interaction reflects a single physicochemical process; extractables (organic and/or inorganic chemical entities) from the packaging system (or device) migrate out of the system and accumulate as leachables in the product. It has been well established that leachables in products can affect the product's safety and/or efficacy, and regulatory guidances include recommendations regarding the analysis and toxicological safety assessment (i.e., qualification) of such substances (1–4). To comply with regulations and to establish the safety impact of packaging, numerous medical polymers and elastomers have been characterized for their extractable substances and many pharmaceutical products have been characterized for polymer- and elastomer-related leachables. Nevertheless, there is little consistency in the design and execution of these various studies, and while the studies are driven by the general principles of good science, it is not clear what principles and practices reflect and establish good scientific methods and processes.

In 2006, the Product Quality Research Institute (PQRI) issued its report Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products (5), which provides a scientific rationale and process to identify, quantify, and establish the safety of leachables and/or extractables in orally inhaled and nasal drug products (OINDPs). This report includes best demonstrated practices for performing controlled extraction studies, specifically relevant to the OINDP dosage forms. To establish thresholds and best demonstrated practices for performing controlled extraction studies specifically relevant for polymers and elastomers used in container closure systems for parenteral and ophthalmic dosage products (PODPs), the PQRI PODP Leachables and Extractables Working Group initiated a study which considered the processes by which extracts are generated and analyzed and the means by which the test results are evaluated and interpreted. The purpose of this present study was to generate and interpret data from controlled extraction studies performed on multiple polymeric and elastomeric materials of construction commonly encountered in PODP packaging systems. These materials were subjected to different extraction conditions and the resulting samples (i.e., extracts) were then characterized for extracted substances to establish how the different experimental parameters affected the resulting extractables profiles. Thus, this study was designed and executed to be exploratory in nature and differs significantly, in terms of design, execution, and interpretation, from studies whose objective is to establish the suitability for use of marketed packaging.

This report presents the test results for the five materials of construction investigated and discusses the results within the overall context of establishing best demonstrated practice recommendations for extractables characterization in PODP-related packaging systems, components, and materials of construction.

Experimental

Objective

The overall objective of this study was to produce comprehensive, albeit semi-quantitative, extractables profiles for a series of PODP-relevant materials of construction. These profiles were generated using solvents and extraction techniques relevant to typical PODP dosage forms and formulations. To meet this objective, five materials representative of those used in PODP packaging were examined: poly (vinyl chloride) (PVC), brominated isobutylene-isoprene rubber, low-density polyethylene (LDPE), polycarbonate (PC), and a cyclic olefin copolymer (COC).

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Test Articles

Test articles were provided as resin beads, plaques, or sheets rather than molded components. While these materials are representative of those used in PODP packaging, none of these raw materials are used in any commercial packaging systems. Compositions of the test articles were provided by each material's supplier and no attempt was made to definitively establish that the supplier information was comprehensive. Thus, it is possible that each material contained unspecified additives and processing aids which could appear as extractables. Test articles were used as received and were not subjected to additional potentially chemically modifying processing steps (e.g., sterilization by gamma irradiation).

Extraction

All extraction and extract characterizations were conducted under a protocol generated by the PQRI PODP Working Group (6). Extraction conditions were chosen to be appropriate for PODP packaging systems and relevant to PODP formulations. Thus, overly aggressive extractions that could lead to partial solubilization of any test articles were not used in this study. However, as no single extraction technique and method can solubilize all potentially relevant extractables, multiple extraction processes (combinations of extraction solvent, extraction method, and extraction conditions) were used. Additionally, as no single analytical technique can identify and quantify all unknown extractables, orthogonal methods were used to maximize the likelihood that all predominant extractables were detected and appropriately evaluated. Overlap between methods produces corroborating data that demonstrate the validity of the procedures.

Extraction Solvents and Methods: To establish best demonstrated practices for OINDPs, the PQRI Leachables and Extractables Working Group performed extractions with a particular focus on metered dose inhalers (MDIs) whose drug product vehicle is typically an organic solvent (5). Because many PODP dosage forms are aqueous, this present study focused on water as an extraction solvent. The extraction solvents used in this current study were

- Water at pH 2.5 (HCl/KCl mixture); justified as few therapeutic products are formulated at a pH lower than 2.5. The extraction solvent contained 0.01 M KCl and 0.003 M HCl at a typical pH of 2.5 ± 0.1.

- Water at pH 9.5 (phosphate buffer); justified as few therapeutic products are formulated at a pH higher than 9.5. This extraction solvent contained 0.0045 M and 0.066 M concentrations of monobasic and dibasic sodium phosphate salts, respectively, and was titrated to a final pH of 9.5 with 1 N NaOH.

- 1/1 (v/v) isopropanol (IPA)/water; justified as a simulant for aqueous formulations containing solubilizing agents and also provides for trend analysis between IPA and water alone. This solvent was prepared by mixing equal volumes of IPA and water.

- Organic solvents, including hexane and IPA.

This study included extraction techniques typically used in OINDP extractables characterization studies, such as Soxhlet and reflux (5). However, because a significant number of PODPs are terminally sterilized aqueous formulations, extraction methods compatible with aqueous extraction media (i.e., sealed vessel, sonication) were also included in this study. Finally, all test articles were thermally analyzed for volatile extractables by gas chromatography (GC) with headspace sampling.

Not all of the above extraction methods were combined with all extraction solvents. For example, completely organic solvents were not coupled with sealed vessel or sonication extraction because PODP dosage forms do not generally include autoclaved organic solvents. Aqueous extraction solvents were not coupled with Soxhlet or reflux extraction. Details of the extraction study design with respect to test articles, solvents, methods, and conditions are summarized in Table I.

Extraction Parameters: The magnitude of this study was such that it required the combined efforts of six participating laboratories to fulfill its objectives. Although extracts were generated and tested according to protocol (6), minor deviations in particular method details and extraction procedures were occasionally made by individual participating laboratories to accommodate different laboratory facilities and instrumentation. It is the intent of this report to summarize the general procedures used across laboratories without delving into the relatively minor differences between them.

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TABLE I
Overview of Study Design and Extraction Parameters

Typical Sample Preparation		5 g test article/200 mL extraction solvent										1 g/20 mL vial
Extraction Method		Soxhlet		Reflux			Sonication		Sealed Vessel			
Extraction Solvent		IPA	Hexane	IPA	Hexane	IPA/W	pH 2.5	pH 9.5	pH 2.5	pH 9.5	IPA/W	Headspace
Test Article	PVC	X	X	X	X	X	X	X	X	X	X	X
	Rubber	X	X	X	X	—	X	X	X	X	X	X
	LDPE	X	X	X	X	—	X	X	X	X	X	X
	PC	X	X	X	X	X	X	X	X	X	X	X
	COC	X	X	X	X	—	X	X	X	X	X	X
Extraction Parameters		16–24 h		2–3 h		2 h	0 °C 2 h		Autoclave at 121 °C 1 h		55 °C 3 days	80 °C 2 h
Analytical Method	GC/FID or GC/MS	X (1)	X (1)	X (1)	X (1)	X (1,2)	X (1,2)	X (1,2)	X (1,2)	X (1,2)	X (1,2)	—
	LC/UV/MS	X (1)	X (1)	X (1)	X (1)	X	X	X	X	X	X	—
	ICP/MS	—	—	—	—	—	X	X	X	X	—	—
	Headspace GC/MS	—	—	—	—	—	—	—	—	—	—	X

Notes: An "X" denotes a material/solvent/analytical method combination for which testing was performed, a "—" denotes a combination not tested.
IPA = isopropanol, IPA/W = 50/50 isopropanol/water
1. Sample processing included concentration (see text).
2. Sample processing included solvent-switching for improved compatibility between solvent and analytical method as well as analysis of TMS-derivatized and underivatized extracts (see text).

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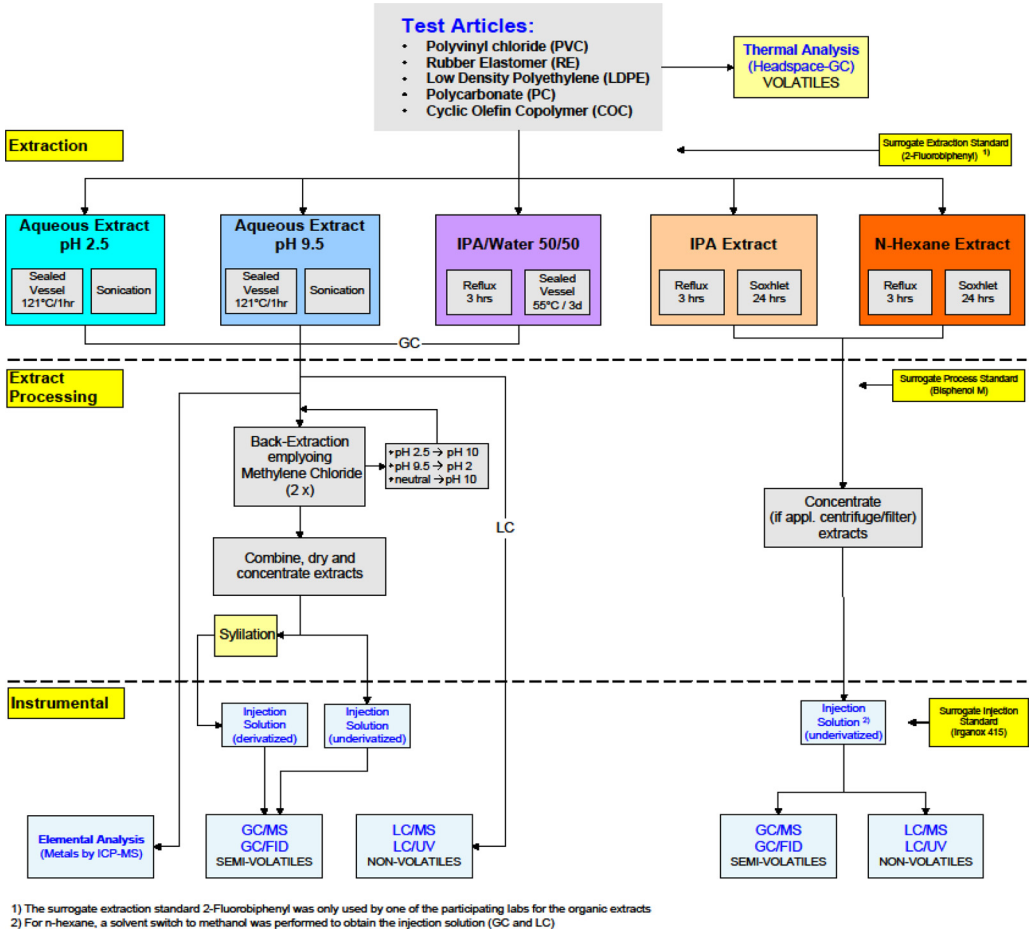

Figure 1

Flow Diagram Showing the Analysis Process for the Test Articles and their Associated Extracts. See also Table I.

Sample weight, extracting solvent volume, and sample extract concentration factors were established so that individual extractables present above a reporting threshold of 10 µg/g (ppm, 0.001% by weight) could be discovered, identified, and quantified. Toward this end, extractions were conducted with a test article to solvent ratio targeted at 5 g to 200 mL. Where necessary, test articles were reduced in size by cutting them into smaller pieces prior to extraction. Aggressive size reduction methods such as grinding were avoided. All extractions were conducted in duplicate and blanks (negative controls) were prepared in duplicate for all solvent/method combinations and processed in the same manner as test articles. At the conclusion of each extraction, extracts were cooled to room temperature, decanted from the extracted test article, and preserved for analysis in an appropriate vessel with minimal headspace.

Table I summarizes key parameters for all extractions including weights, volumes, times, and temperatures. Note that for sealed vessel extractions, glass containers (250 mL media bottles with polypropylene screw caps) were used to generate extracts intended for organic analysis (i.e., chromatographic methods) while Teflon vessels were utilized to generate extracts for inorganic (metals) analysis. Glass is a potential problem in metals analysis, especially with solvents at higher pH, due to potential leaching of targeted extractables from glass (e.g., Si, B, Al, Na). Teflon vessels can create potential problems with organic extractables due to possible adsorption of the extractables.

For sonication extractions, the temperature of the bath was maintained at approximately 0 °C (range of 0–2 °C) by continuously adding ice to the bath. This was

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TABLE II
Typical Operating Parameters, GC/FID and GC/MS Analyses

Operating Parameter	Operating Value (Aqueous Extracts)	Operating Value (Organic Extracts)
Column	J&W (Folsom, CA) DB-5HT, 30 m × 0.25 mm, 0.1 μm film thickness	J&W DB-5HT, 30 m × 0.25 mm, 0.25 μm film thickness
Oven Program	Start at 40°C, hold for 1 min; ramp at 10°C/min to 280°C, hold for 2 min; ramp at 15°C/min to 310°C, hold for 3 min	Start at 50°C, hold for 1 min; ramp at 12 °C/min to 315 °C, hold for 16 min
Carrier Gas	He at 1 mL/min	He at 1.2 mL/min
Injection	Splitless; 2 μL	Split (1:5); 1 μL
Injector Temperature	300°C	300 °C
FID Detector Temperature:	350°C	N/A
MS Transfer Line Temperature	310°C	180 °C
MS Detection Details	70 eV (+EI), mass range of 33–650 amu (5.0 min or 7.5 min solvent delay used for un-derivatized or derivatized samples)	70 eV (+EI), mass range of 33–650 amu (3.0 min solvent delay)
Instrumentation Used	1. Agilent (Santa Clara, CA) 6890 GC/7683 autosampler/5973 MSD Simultaneous FID and MS via flow splitter (MSD Productivity Chemstation software) 2. Agilent 6890 GC/CTC Analytics CombiPal aitosampler/Waters (Millford, MA) GCT Premier TOF-MS (Waters MassLynx 4.1 software)	Agilent 6890 GC/7683 autosampler/973 or XL5975C MSD (MSD Productivity Chemstation software)

intended to address concerns about the consistent application of energy during sonication.

Extract Processing Prior to Analysis

All samples were visually inspected prior to analysis to ensure that they were free from obvious particulate matter. Samples containing visible particulate matter, and portions of their associated extraction blanks, were handled either by filtration or by allowing the particulates to settle and carefully obtaining clear sample aliquots for testing. Samples that contained particulate matter included the reflux and Soxhlet extracts of PVC and the pH 9.5 sealed vessel extracts of the PVC and rubber.

In certain cases, additional processing of the extracts was carried out prior to analysis, in order to concentrate extractables and create samples more compatible with a particular analytical method, for example, trimethylsilyl (TMS) derivatization. This was particularly true in cases where aqueous extraction solvents were analyzed by GC. Scenarios where extracts required additional processing are explicitly given in Figure 1. Details of the processing steps are described in the following text.

Internal Standards: In cases where extracts underwent concentration or solvent switching (Figure 1) prior to GC analysis, a minimum of two internal standards were introduced. The first, a surrogate internal standard, was added to the extract prior to additional processing (solvent switching, concentration, derivatization) to monitor the performance of these procedures. The surrogate internal standard compound was 4,4'-(*m*-phenylene-diisopropylidene)diphenol (Bisphenol M), chosen because it was sufficiently stable, soluble in all extraction solvents, amenable to back-

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TABLE III
Typical Operating Parameters, LC/UV/MS Analyses

Operating Parameter	Operating value	
Column	Agilent Zorbax Eclipse Plus C_{18}, 100 × 3.0 mm, 3.5 μm particles	
Column Temperature	40–50 °C	
Mobile Phase Components	A = 10 mM ammonium acetate, B = acetonitrile	
Mobile Phase Gradient	Time (min)	% B
	0.0	5.0
	8.4	100.0
	35.0	100.0
	36.0	5.0
	39.0	5.0
Mobile Stage Flow Rate	0.8 mL/min	
Injection Size	10–50 μL	
Detection, UV	205–300 nm; spectra recorded at λ = 210, 220, 230, 250, and 270 nm; 205 nm for variable wavelength detector	
Detection, MS	API-ES or APCI, positive ion and negative ion (mass range 80–1500)	
Instrumentation Used	1. Agilent 1100 LC (vacuum degasser, binary pump, heated column compartment)/Model ATG1315A diode array detector/1100 mass selective detector (MSD). Agilent Chemstation rev A.10.02 software. 2. Agilent 1100 LC (vacuum degasser, binary pump, heated column compartment, variable wavelength detector)/Applied Biosystems (Foster City, CA) Mariner TOF-MS (APCI mode). Agilent Chemstation rev A.10.02 and Applied Biosystems Data Explorer version 4.0.0.1 software. 3. Agilent LCs (binary pump, autosampler, heated column compartment)/ Thermo Finnigan (Waltham, MA) LCQ Deca XP Max ion trap MS or Thermo Finnigan LTQ FT Ultra MS or Waters Q-TOF Premier TOF-MS. Thermo Finnigan Xcalibur and Waters MassLynx software.	
Sample Preparation	None, direct injection	

extraction from aqueous extracts by organic solvents, semi-volatile, amenable to all detection principles, selectively detectable, and amenable to TMS derivatization.

At the final stage of sample processing (after solvent switching and/or concentration), an injection internal standard was introduced to monitor instrument performance. The injection internal standard used in this study was 4,4'-(*m*-4,4'-thiobis(3-methyl-6-*t*-butylphenol) (Irganox 415), chosen because it was sufficiently stable, soluble in the final extract, semi-volatile, amenable to all detection methods, and selectively detectable.

Although their concentrations varied across laboratories, both internal standards were nominally prepared at 50 μg/mL in methanol. In some laboratories, internal standards were also introduced prior to extraction (e.g., the 2-fluorobiphenyl noted in Figure 15), but such additions went beyond the scope of the original protocol (6).

Solvent Switching: Solvent switching was performed on all aqueous extracts intended for GC analysis. Briefly, a 50.0 mL aliquot of extract was combined with a nominal 1.0 mL volume of surrogate internal standard and back-extracted twice with 25.0 mL dichloromethane (DCM). Next, the pH of the extract was adjusted to the opposite extreme (pH 2.5 extracts were adjusted to ~10, pH 9.5 extracts were adjusted to ~2) and back-extracted two more times with DCM. All four resultant DCM extracts were pooled and concentrated (see the following text). In the case of IPA/water extracts intended for GC analysis, the same back-extraction procedure was followed except that the initial round of DCM

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TABLE IV
Composition of the Diluted Grob Mix used to Assess GC System Suitability

Components of the Grob Mix	Concentration, μg/ml (ppm) in the System Suitability Test Sample
L(+)-2,3-Butanediol	27
n-Decane	14
2,6-Dimethylaniline	16
2,6-Dimethylphenol	16
Methyl decanoate	21
Methyl docecanoate	21
Methyl undecanoate	21
Nonanal	20
1-Octanal	18
n-Undecane	14

extraction was conducted after acidification of the original extract.

Extract Concentration: For aqueous or mixed IPA/water extracts switched into DCM, pooled DCM fractions were dried with anhydrous sodium sulfate and evaporatively concentrated (e.g., Turbovac) to less than 0.5 mL. An aliquot of injection internal standard (nominally, 0.5 mL) was then added to the concentrated DCM extract and the final volume adjusted to 1.0 mL. A similar concentration strategy was followed for organic extracts without solvent switching.

TMS Derivatization: Aqueous and IPA/water extracts analyzed by gas chromatography were tested with and without derivatization of extractables to their TMS analogs. Derivatized samples were prepared by combining 0.5 mL of concentrated extract in DCM with 100 μL dimethylformamide in an amber autosampler vial. Once the vial contents were evaporated to near-dryness under flowing nitrogen, a 100 μL aliquot of N,O-bis(trimethylsilyl)-trifluoroacetamide (BSTFA) containing 1% trimethylchlorosilane (TMCS) (Supelco, Bellefonte, PA) was added to the mixture, the vial capped, and the mixture was allowed to react at 70 °C for 1 h. DCM was added to each autosampler vial to increase the final volume to 0.5 mL for injection.

Table I describes which combinations of extraction solvent, extraction method, and analytical method utilized these additional processing steps. The analytical processes used to test the extracts are delineated graphically in Figure 1.

Instrumental Methods

Consistent with the PQRI-OINDP recommendations (5), multiple analytical techniques were used to discover, identify, and quantify the extractables present in each extract of PODP materials. Not all analytical methods were used to characterize all extracts (see Table I); for example, elemental analyses were performed only on aqueous extracts.

Typical instrument parameters for extract analyses are described as follows. Individual laboratories used the instrumentation available to them, resulting in different (but equivalent) equipment being used across laboratories. Thus, minor variations in operating parameters for chromatographic methods were sometimes necessary to produce the desired chromatographic performance in each laboratory. In all cases, however, the chromatographic runs performed for this study met previously established system suitability requirements (6).

Gas Chromatographic Methods—GC/Flame Ionization Detection (GC/FID), GC/Mass Spectrometry (GC/MS): GC with appropriate sample processing and detection strategies (GC/FID and GC/MS) was used to assess volatile and semi-volatile extractables.

TABLE V
Operating Conditions, ICP-MS System for Elemental Analysis

Parameter	Setting
Forward Power	1300 watts (7500 a), 1500 watts (7500 c)
Acquire Integration Time	0.10 seconds per point
Integration Mode	Auto
Replicates	1
Points per Peak	6
Rinse Time	180 s
Rinse Rate	0.5 rps
Uptake Time	35 s
Uptake Rate	0.5 rps
Stabilization Time	20 s
Analysis Pump Rate	0.1 rps
Sample Introduction	Polypropylene Spray Chamber, Platinum Injector
Nebulizer	Cross Flow
Nebulizer Flow rate	1.1 L/min
Other Settings	Determined by tune results

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TABLE VI
Operating Parameters, Headspace GC-FID-MS Analysis for Volatiles

Operating Parameter	Operating Value
Headspace Autosampler	
Oven Temperature	80 °C
Loop Temperature	120 °C
Transfer Line Temperature	155 °C
Carrier gas	He at 2.4 mL/min, constant flow
Equilibrium Time	120 min
Inject time	0.5 min
Loop equilibration time	0.30 min
Loop fill time	0.30 min
Vial pressurization time	0.30 min
Gas Chromatograph	
Column	J&W DB-WAXETR, 60 m × 0.32 mm I.D., 1 μm film
Oven Program	Start at 35 °C, hold for 7 min. Ramp at 1 °C/min to 40 °C, hold for 15 min. Ramp at 10 °C/min to 100 °C. Ramp at 25 °C/min to 240 °C, hold for 5 min.
MS Ionization Mode	EI+, 70 eV
MS Transfer Line Temp.	240 °C
MS Detection Mass Range	25 – 200 amu
Solvent Delay	0 min
FID Temperature	260 °C
FID Hydrogen Flow	40.0 mL/min
FID Air Flow	400.0 mL/min
FID Mode:	Constant Makeup Flow
FID Makeup flow:	30.0 mL/min
FID Makeup gas:	Helium
Splitter make up gas	Helium at 4.0 psi

For GC/MS analyses, no data were collected while injection solvent was in the ion source of the mass spectrometer. As shown in Table I, aqueous and IPA/water extracts were solvent-switched, concentrated, and TMS-derivatized prior to analysis. For GC/FID or GC/MS analyses of organic extracts generated by Soxhlet or reflux, extracts were concentrated and internal standards were used. No derivatization or solvent switching was deemed necessary for these samples. Typical operating conditions and instrumentation for all GC experiments are summarized in Table II.

High-Performance Liquid Chromatography/UV Absorbance/Mass Spectrometry (LC/UV/MS) Methods: Reversed-phase high-performance liquid chromatography (LC) with diode array UV (LC/UV) and mass spectrometry (LC/MS) detection was used to assess relatively non-volatile extractables. Aqueous and IPA/water extracts were injected neat (no additional processing). The LC/UV/MS analyses of organic solvent extracts (reflux and Soxhlet) were preformed on the same fortified and concentrated samples that were used in the GC analyses of those extracts. As noted previously, some extracts contained particulate matter. The entrained particulate matter was either avoided by allowing it to settle or eliminated by filtering the sample prior to analysis.

General operating conditions and instrumentation for the LC/UV/MS analyses are summarized in Table III. In some instances, individual laboratories extended the chromatographic gradient and increased the mass range of the mass spectrometer to capture later-eluting, higher molecular weight extractables.

System Suitability Criteria for the Chromatographic Analyses: For the GC analyses, system suitability involved analysis of a standard mixture of organic compounds, known as the Grob mixture (7), which is a suite of compounds used to establish the performance characteristics of GC columns and methods. The commercially available Grob mixture (Restek, Bellefonte, PA, catalog #565390) was diluted 1/20 with methylene chloride to produce the system

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TABLE VII
Extracted Trace Elements and Metals

Element	Extracted Amount,[d] µg/g									
	PVC		Rubber		LDPE		Polycarbonate		Cyclic Olefin	
	pH 2.5	pH 9.5	pH 2.5	pH 9.5	pH 2.5	pH 9.5	pH 2.5	pH 9.5	pH 2.5	pH 9.5
Ca	1.5	NP[c]	4.07	2.07	NP[c]	NP[c]	6.6	0.80	0.81	1.7
Zn	1.3	0.43	2.89	0.49	0.08	NP[c]	0.12	0.03	0.07	0.03
Br	1.3	0.08	17.5	20.5	0.40	0.08	1.1	0.07	0.54	0.02
Na	0.60	ME[a]	3.05	ME[a]	0.96	ME[a]	1.0	ME[a]	0.96	ME[a]
K	ME[a]	NP[c]	ME[a]	6.84	ME[a]	NP[c]	ME[a]	NP[c]	ME[a]	NP[c]
Fe	0.35	0.15	0.33	0.08[b]	0.12	NP[c]	0.71	0.06	0.24	NP[c]
Mg	0.26	0.21	3.50	2.90	0.18	0.04[b]	0.24	0.17	0.16	0.15
Al	0.14	NP[c]	0.66	3.56	0.09	NP[c]	NP[c]	NP[c]	0.07	NP[c]
Cr	0.02	NP[c]	0.01	0.01	NP[c]	NP[c]	0.07	0.02	NP[c]	NP[c]
Ti	NP[c]	NP[c]	0.29	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Mn	0.02	NP[c]	0.01	NP[c]	0.01	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Si	NP[c]	NP[c]	0.10	0.25	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Sr	0.01[b]	0.02	0.01	0.01	0.01	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Ni	NP[c]	NP[c]	0.01	0.01	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Cu	NP[c]	0.01	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Co	NP[c]	NP[c]	NP[c]	NP[c]	0.01	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
V	0.01	NP[c]	0.01	0.01	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Ba	NP[3]	NP[c]	NP[c]	NP[c]	NP[c]	0.01	NP[c]	NP[c]	NP[c]	NP[c]
As	0.01	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Pb	0.01[b]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Sb	NP[c]	0.01	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]
Mo	NP[c]	0.01	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]	NP[c]

Notes:
[a]ME = this element a component of the extracting solution used and thus was not measurable as an extractable.
[b]Detected in only one of the two replicate extracts.
[c]NP = not present in this extract in measurable quantities.
[d]The reported value is the largest amount measured in either the sealed vessel or sonication extract.

suitability test mixture; see Table IV for its composition. Adequate chromatography was achieved and all system suitability criteria were met for all analyses performed in this study; typical system suitability results have been previously reported (8).

For LC analyses, system suitability involved analysis of a standard mixture of commonly encountered, chemically diverse organic extractables. The test mixture was custom-made by the participating laboratories from standard grade reference materials and included the following compounds; caprolactam, mono-(2-ethylhexyl phthalate), di-(2-ethylhexyl) phthalate, and 4,4'-(1-methylethylidene)bis-phenol (Bisphenol A, BPA) at a concentration of 1 mg/L each and butylatedhydroxytoluene, diphenylamine, and stearic acid at a concentration of 5 mg/L each. For LC analyses using an extended gradient, two additional suitability compounds, 3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid, 1,1'-[2,2-bis[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxopropoxy]methyl]-1,3-propanediyl] ester (Irganox 1010) and 2,4-Bis(1,1-dimethylethyl)-phenol, 1,1',1''-phosphite (Irgafos 168), were added to the mixture at a concentration of 1 mg/L each. The test mix was prepared by appropriate dilution of more concentrated stock solutions, prepared using solvents appropriate for the individual reagents. The final composition of the test mixture was compatible with the mobile phase used in the LC analysis.

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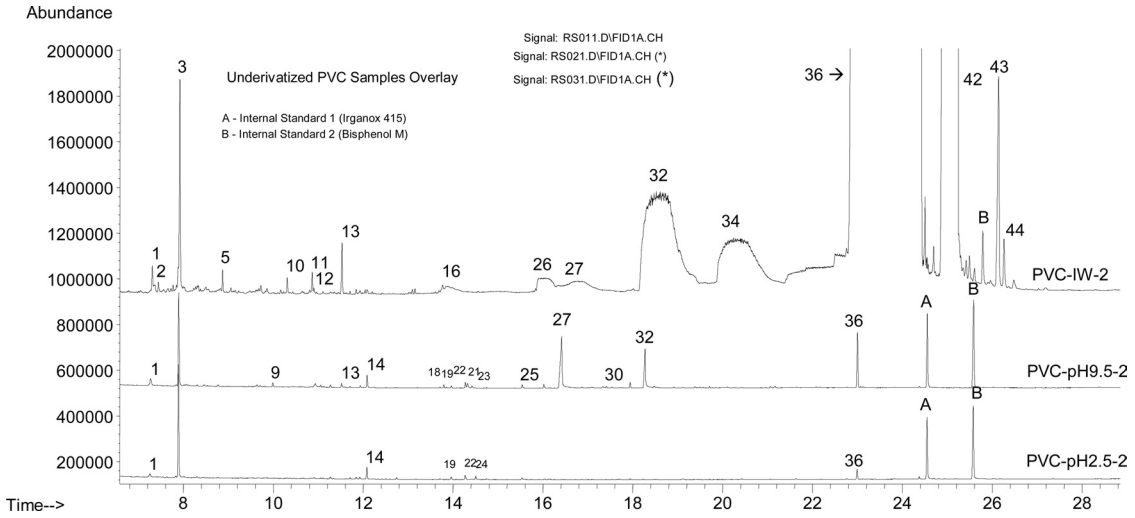

Figure 2

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts for the PVC (underivatized sample preparation). Peaks A and B are the two internal standards (A = Irganox 415 and B = Bisphenol M), reflecting compounds present in the extract at a concentration of approximately 1 mg/L (ppm). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. See Table VIII for a summary of information about the numbered peaks, all of which were ascribed to extracted substances.

Chromatograms for the system suitability test mixtures were examined for the presence of peaks corresponding to each analyte in the mix. Acceptance criteria were as follows:

- Not all compounds were required to produce a response in all chromatograms of a given sample (GC: underivatized and derivatized, LC: UV and +/– mode MS), but all compounds should produce a response in at least one chromatogram.
- All peaks should have a response with a signal to noise ratio (S/N) of 10 or greater.
- The closest eluting pair of peaks shall exhibit a resolution of greater than 1.0.
- All peaks should be well-shaped, with a tailing factor less than 2.0.
- There should be no significant differences (such as changes in retention time, resolution, peak shape and magnitude of response) in the chromatograms obtained at the beginning and the end of the analysis run.

Adequate chromatography was achieved and all system suitability criteria were met for all analyses performed in this study; typical system suitability results have been previously reported (8).

Elemental Analysis: Inductively coupled plasma/mass spectrometry (ICP/MS) was used to detect target elements (i.e., metals) in the aqueous extracts (sealed vessel and sonication extractions). The ICP analyses were performed consistent with USP practices (9). Seventy elements were included in these analyses; those elements present in one or more extracts at reportable levels included Al, As, Ba, Br, Ca, Cr, Co, Cu, Fe, K, Mg, Mn, Mo, Na, Ni, Pb, Sb, Si, Sr, Ti, V, and Zn. Targeted elements that were not reproducibly extracted from any test material at reportable levels included Ag, Au, B, Be, Bi, Cd, Ce, Cs, Dy, Er, Eu, Ga, Gd, Ge, Hg, Hf, Ho, I, In, Ir, La, Li, Lu, Nb, Nd, Pd, Pr, Pt, Os, Rb, Re, Rh, Ru, Sc, Se, Sm, Sn, Ta, Tb, Te, Th, Tl, Tm, U, W, Y, Yb, and Zr. The analysis conditions were such that these elements could be measured at appropriately low levels, typically 0.25 μg/mL or less in the material extracts. As the pH 2.5 and pH 9.5 extracts contained large quantities of sodium and the pH 9.5 extracts contained large quantities of phosphorous, these analytes were not determinable in these extracts.

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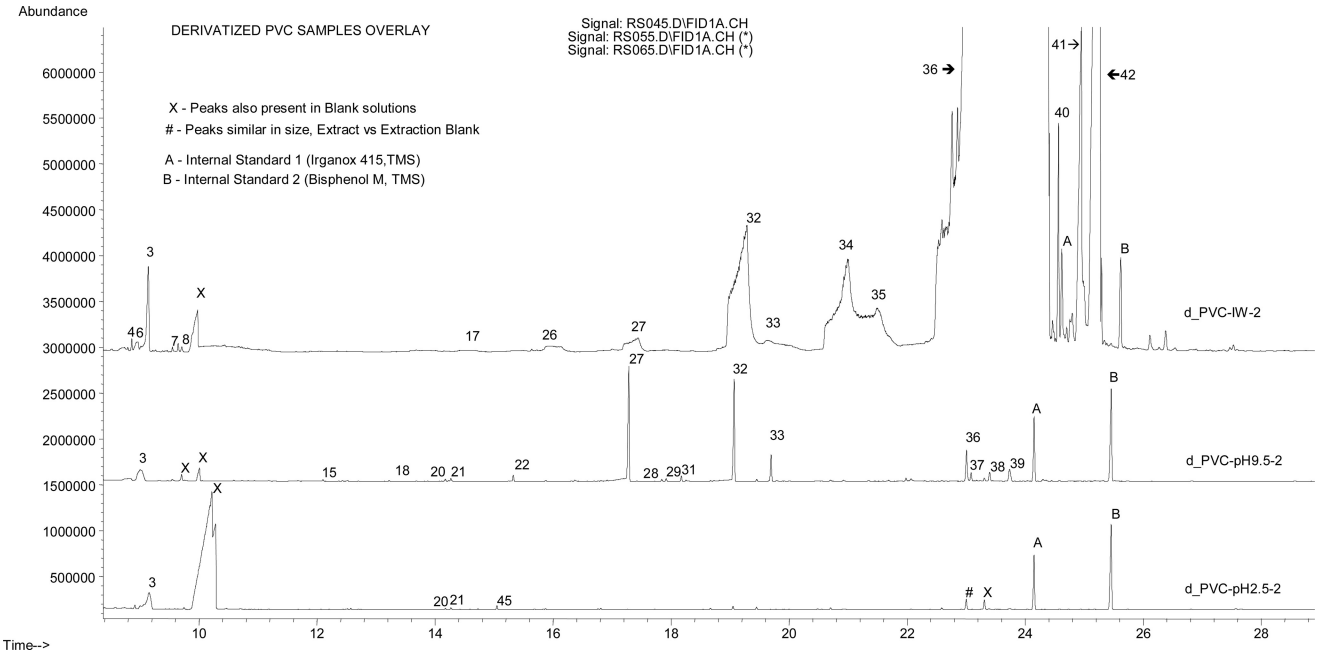

Figure 3

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts for the PVC (derivatized sample preparation). Peaks A and B are the two internal standards (A = Irganox 415 and B = Bisphenol M), reflecting compounds present in the extract at a concentration of approximately 1 mg/L (ppm). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. See Table VIII for a summary of information about the numbered peaks, all of which were ascribed to extracted substances.

Material extracts were acidified prior to analysis via addition of nitric acid; 0.5 mL concentrated nitric acid was added to 10 mL of aqueous extract. The extracts were analyzed by ICP-MS in semi-quantitative mode, calibrated using a 10 μg/L Ce, Co, Li, Th, and Y standard. Distilled, deionized (DI) water was analyzed as a sample blank. The elemental results obtained for the blank were subtracted from all sample results as background. The method blanks were analyzed with the samples and the average result of the method blanks was subtracted from all sample results. A 500 counts per second (CPS) peak threshold was employed during data processing. After the method blank result was subtracted from the sample result, only those elements that had values ≥0.1 μg/L remaining were reported, unless they were eliminated due to confirmation of poly-atomic interference as verified by isotopic abundance ratio template analysis. Data were acquired on Agilent (Santa Clara, CA) models 7500C and 7500A ICP-MS systems; instrument conditions are listed in Table V. System suitability testing for the ICP trace element analysis included the preparation and testing of a system suitability test mixture that contains all the targeted elements listed previously at a concentration of 0.25 mg/L. This criterion was met for all analytical runs performed in this study.

Headspace GC/MS: Direct headspace analysis of materials was employed to detect and quantify their volatile components, which may (or may not) be extractables or leachables. Headspace analysis augments the solvent extraction of materials (and the subsequent analysis of the extracts) because (a) the volatile entities may not be captured in the solvent extract, and/or (b) the volatile entities may not persist in the analytical methods (including associated extract processing) used to test the solvent extracts. The headspace methodology is intended to uncover volatile entities that are present in the test material; it is not intended to produce "volatiles" by causing the test material to thermally decompose. Thus, the headspace "extraction" is accomplished at relatively low temperatures (e.g., 120°C or lower).

Approximately 1 g of sample was weighed into a 20 mL headspace vial. An internal standard spiking solution was added (10 μL), and the vials were capped tightly with a crimp cap. The internal standard spiking solution was prepared by weighing approximately 100

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TABLE VIII
Information for the GC Peaks Associated with Organic Extractables from the PVC Material

Peak #					Highest Concentration in Extract	
Set A[a]	Set B[b]	Set C[c]	Identification[h]	CAS RN	Medium	Type
36	5	14	Di-(2-ethylhexyl) phthalate (DEHP)[e]	117-81-7	IPA	Reflux
41&42	6	18	(z)-13-Docosenamide (Erucamide)[e]	112-84-5	Hexane	Reflux
—	9	15	cis-11-Eicosenamide[f]	10436-08-5	IPA	Reflux
—	8	16	Hexadecanamide[f]	629-54-9	IPA	Reflux
—	No #[d]	8	Isopropyl palmitate[e]	142-91-6	Hexane	Soxhlet
32	2, 10	7	Hexadecanoic (Palmitic) acid[e]	57-10-3	Hexane	Soxhlet
34	4, 11	10	Octadecanoic (Stearic) acid[e]	57-11-4	Hexane	Soxhlet
—	—	13[d]	9-Hexadecenoic acid[g]	2091-29-4	IPA	Reflux
27	—	—	Tetradecanoic (Myristic) acid[f]	544-63-8	IPA/Water	Sealed
—	—	12	Di-(isooctyl) phthalate[g]	27554-26-3	IPA	Soxhlet
—	—	11[d]	Isopropyl stearate[f]	112-10-7	IPA	Soxhlet
—	1	6[d]	Hexadecanoic acid, methyl ester[f]	112-39-0	Hexane	Soxhlet
—	3	—	Octadecanoic acid, methyl ester[f]	112-61-8	IPA/Water	Reflux
43	7	19	9-Octadecenamide (Oleamide)[f]	301-02-0	Hexane	Reflux
—	—	17[d]	Octadecanoic acid, 2-hydroxy-1-(hydroxymethyl) ester[g]	621-61-4	Hexane	Reflux
—	—	5	Benzoic acid, 2-ethylhexyl ester[g]	544-75-7	Hexane	Reflux
—	—	9	Dipropyl phthalate[g]	131-16-8	IPA	Reflux
—	—	20	Tri(2-ethylhexyl)trimelitate[g]	3319-31-1	Hexane	Soxhlet
3	—	1	2-Ethyl-1-hexanol[e]	124-19-6	IPA	Reflux
16	—	4	Butylated Hydroxytoluene (BHT)[e]	128-37-0	Hexane	Soxhlet
13	—	3[d]	Phthalic anhydride[e]	85-44-7	Hexane/IPA	Soxhlet &reflux
—	—	2[d]	Nonanal[e]	124-19-6	Hexane/IPA	Soxhlet &reflux
33	—	—	Mono-(2-ethylhexyl) phthalate (MEHP)[e]	4376-20-9	pH 9	Sealed
26	No #[d]	—	Benzoic acid, 2-ethylhexyl ester[f]	5444-75-7	IPA/Water	Reflux
—	No #[d]	—	Behenic amide[f]	3061-75-4	IPA/Water	Reflux
—	No #[d]	—	Tetradecanoic acid, methyl ester[e]	124-10-7	IPA/Water	Reflux
35	—	—	Oleonitrile[g]	112-91-4	IPA/Water	Sealed
1	—	—	Phenol[g]	108-95-2	IPA/Water	Sealed
6	—	—	1-Octene-1-ol[g]	1184606-14-0	IPA/Water	Sealed
17	—	—	Phthalimide[g]	85-41-6	IPA/Water	Sealed

Notes:
[a]In the sealed vessel aqueous extracts, see Figures 2, 3. These extracts contained several extractables whose peaks are numbered in the chromatograms but whose associated compounds were not established, including peaks 2, 4, 5, 7–12, 14, 15, 18–25, 28–31, 37–40, 44.
[b]In the reflux, IPA/Water extracts, see Figure 6. The first and second numbers refers to the chromatograms for the underivatized and derivatized samples, respectively.
[c]In solvent extracts, Soxhlet and reflux, see Figures 8, 9.
[d]These peaks were present in the extract chromatogram but were not numbered in the relevant Figure.
[e]These identifications are classified as confirmed.
[f]These identifications are classified as confident.
[g]These identifications are classified as tentative.
[h]The chromatograms also contained several peaks whose corresponding compound could not be established; these unknown peaks are not listed in this table.

mg of 1,4-Dioxane into a 50 mL volumetric flask and diluting with polyethylene glycol 200 (PEG 200); thus, each sample vial contains 20 μg of 1,4-Dioxane. Headspace GC/MS analyses were performed with an Agilent G1888 Headspace Autosampler and an Agilent 6890/5975 GC/FID/MS system equipped with an Agilent G3180B Splitter. The operating conditions for the Headspace GC/MS are contained in Table VI.

A custom-made standard mixture was prepared from standard grade reference materials. The individual reagents, including methanol, acetic acid, cyclo-

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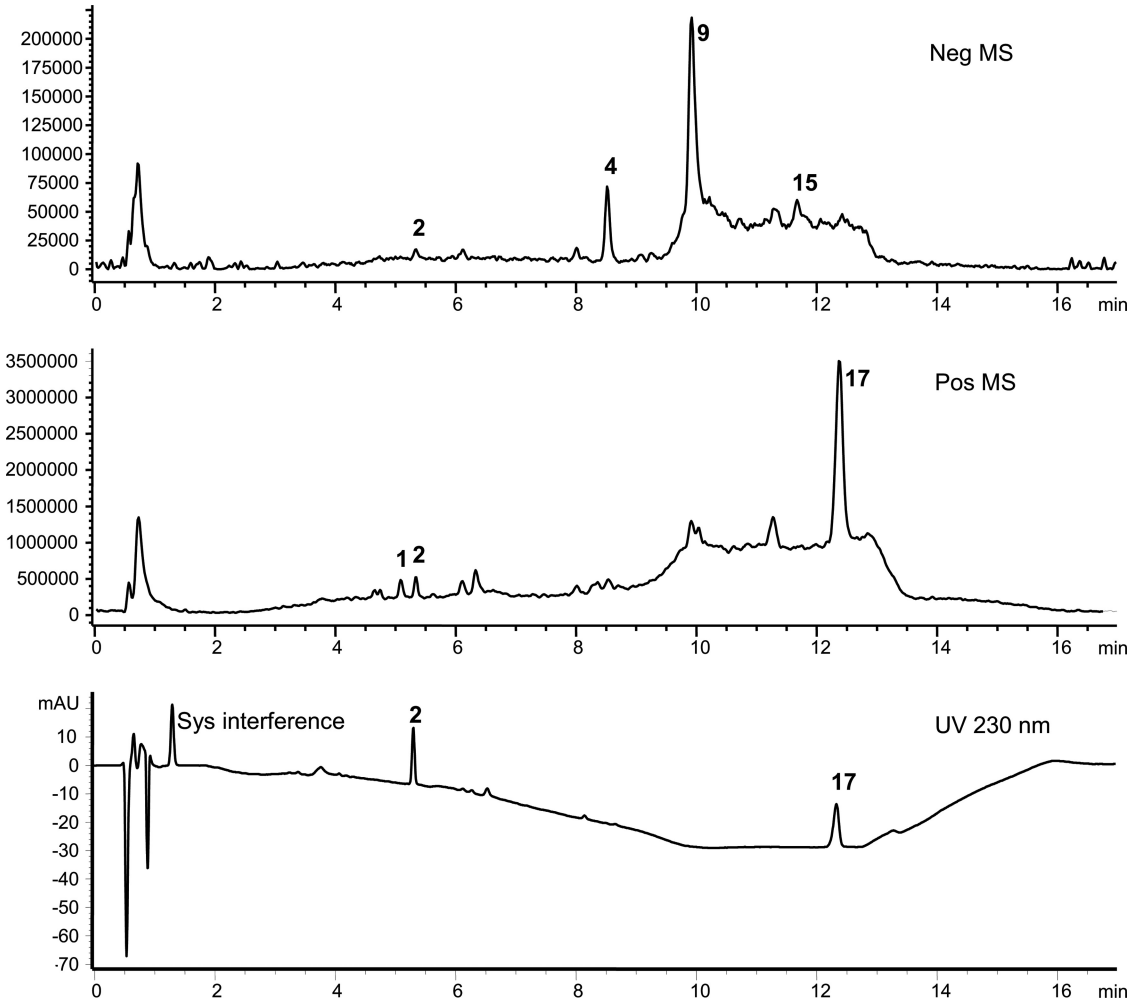

Figure 4

LC/UV/MS chromatograms of the pH 9.5 Sealed Vessel Extracts for the PVC. The chromatograms reflect, from top to bottom, MS detection – ion mode, MS detection, + ion mode, and UV detection at 230 nm, respectively. See Table IX for the identities, as available, for the numbered extractables.

hexanone, toluene, trimethylsilanol, and 2-ethylhexanol, were diluted into PEG 200 at a target concentration of 1 mg/mL (cyclohexanone and toluene) and 2 mg/mL for all other standards. A sensitivity standard was prepared by diluting the stock standard mixture in PEG to a final concentration of 50 μg/mL for cyclohexanone and toluene. Headspace vials were prepared by spiking 10 μL of standard mixture or sensitivity standard into a 20 mL headspace vial and capping tightly with a crimp cap. The final concentration for standard mixture vials was 10 μg/vial for cyclohexanone and toluene, and 20 μg/vial for all other standards. The final concentration for the sensitivity solution was 0.5 μg/vial for cyclohexanone and toluene and 1 μg/vial for all other standards. The test mixture for headspace analysis was prepared to contain the internal standard (1,4-Dioxane).

The chromatograms for the system suitability test mixture were examined for peaks corresponding to each analyte in the mix. The system suitability criteria were the same as those enumerated previously for the other chromatographic analyses. Adequate chromatography was achieved and all system suitability criteria were met for all analyses performed in this study; typical system suitability results have been previously reported (8).

Data Processing:

Identification of Organic Extractables: A primary objective in this study was to establish the identity of extracted chemical entities. Although identification is

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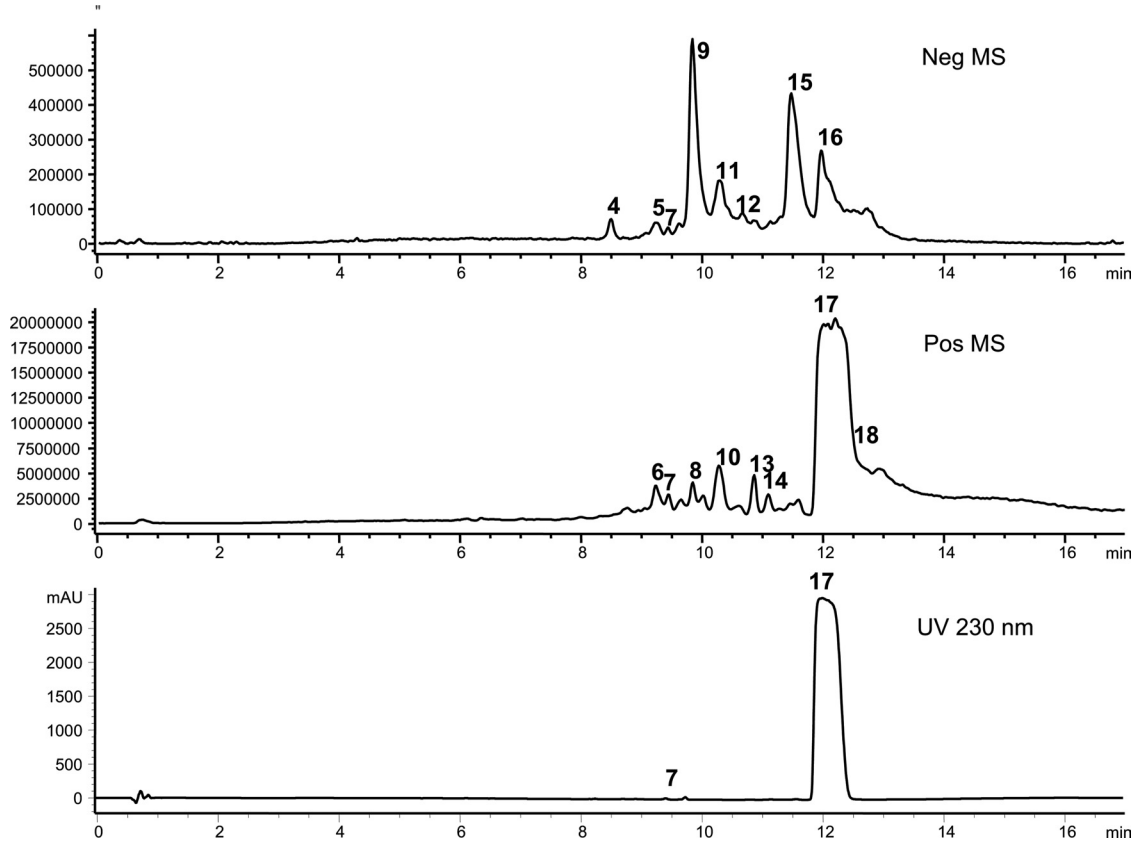

Figure 5

LC/UV/MS Chromatograms of IPA/Water Sealed Vessel Extracts for the PVC. The chromatograms are, from top to bottom, MS detection – ion mode, MS detection, + ion mode, and UV detection at 230 nm. See Table IX for the available identities, for the numbered extractables. Note the much larger response axes (y-axis) for these extracts versus that for the aqueous extracts (e.g., Figure 4).

a fundamental aspect of ICP-MS testing, as the elements of interest are specifically targeted and reported based on their mass spectral properties, chromatographic analyses are designed to separate and respond to a multitude of organic compounds and compound identities must be inferred from the available data. It is generally the case that the accuracy of the inferred identities is based on the amount and quality of the corroborating data. Thus, the inferred identities reported in this study were graded from the perspective of the likelihood that they are correct. The grading scale used in this study, consistent with available best demonstrated practice recommendations (5), were as follows:

- *Confirmed:* corroborating data, including mass spectrometric fragmentation pattern, confirmation of molecular weight (or elemental composition), match in retention time and spectrum with authentic standard were obtained.
- *Confident*: sufficient data to preclude all but the most closely related structures were obtained
- *Tentative*: data that are consistent with a class of molecule only were obtained.

This study was designed to identify extracted substances at a concentration of 10 μg/g or higher. When viable identifications could be made at lower concentrations, they are reported herein. However, speculative identifications made for extractables at levels lower than 10 μg/g are not reported.

Analyte Quantitation: Another study objective was to estimate the extractables' concentrations. Concentration estimates for individual inorganic/elemental extractables are readily obtained via the ICP/MS analyses, as instrumental response was calibrated using single point response factors obtained from external

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TABLE IX
Summary of Identified Organic Extractables from the PVC Material, LC Analysis

Peak #			Identification[d]	CAS RN
Set A[a]	Set B[b]	Set C[c]		
2	—[e]	1	Mono-(2-ethylhexyl) phthalate, MEHP	4376-20-9
4	2	—	Tetradecanoic (Myristic) Acid	544-63-9
9	3	—	Hexadecanoic (Palmitic) Acid	57-10-3
17	4	3	Di-(2-ethylhexyl) phthalate (DEHP)	117-81-7
15	5	—	Octadecanoic (Stearic) Acid	57-11-4
18	6	—	(z)-13-Docosenamide (Erucamide)	112-84-5
6, 7,10–12,14	—[e]	—	Epoxidized Di- and tri-glycerides	—
—	—	2	Unspecified phthalate	—
5	—	—	Pentadecanoic acid	1002-84-2
8	—	—	(z)-9-Octadecenamide (Oleamide)	301-02-0
11	—	—	cis-11-Eicosenamide	10436-08-5

Notes:
[a]In the sealed vessel aqueous extracts, see Figures 4, 5. The chromatograms contained additional peaks whose associated extractables could not be identified; for example, peaks 1, 16.
[b]In the reflux, IPA/Water extracts, see Figure 7.
[c]In solvent extracts, Soxhlet and reflux, see Figure 10. The LC chromatograms also revealed numerous peaks that were associated with fatty acid epoxides. Additional peaks in the chromatograms could not be ascribed to a specific compound.
[d]The identifications for the specific compounds are either confident or confirmed.
[e]A peak for this compound was observed in the MS + ion chromatogram, which is not shown in this article.

standards. A similar situation is encountered for the chromatographic analysis in cases where the identified extractable was present in the system suitability test mixtures. As such circumstances were unintentional and rare, an alternate concentration estimation strategy was employed by using internal standards. Thus, the GC analysis included the addition of at least two internal standards to the sample. As the concentration of the Bisphenol M internal standard in the sample is known and the internal standard's response can be measured, a response factor for the internal standard (ratio of concentration to response) can be calculated. Leveraging the assumption that the response factor is more or less universal for all organic compounds detected by a specific method, this response factor, along with an analyte's response, can be used to estimate the analyte's concentration. Such an approach was universally applied to the GC data, as the assumption of a sufficiently universal response is more readily accepted for GC when FID or electron impact (EI)-MS detection is used. Such an approach was not applied to LC as the assumption of universal response is generally not applicable to UV or API (atmospheric pressure ionization)-MS detection strategies.

Lastly, the extraction procedures, analytical techniques and methods, and analysis conditions described used in this study were not fully and rigorously validated. All the same, the scientific credibility of the data generated in this study was established via the utilization of system suitability testing with all the analysis methods and by the analytical team's expert review of the generated data, consistent with PQRI OINDP recommendations (5).

Test Materials and Their Extractables Profiles

General

Due to the chemical nature of the solvents and physiochemical nature of the extraction processes, one anticipates that the extractables profiles revealed by testing the various extracts would be quite different. This expectation is reinforced by the composition of the test articles. It is generally the case that polymer additives are highly nonpolar, with the individual additives having log $P_{o/w}$ (octanol/water partition coefficients) values typically greater than 4. This is not an unexpected circumstance, as additives are formulated into a material with the

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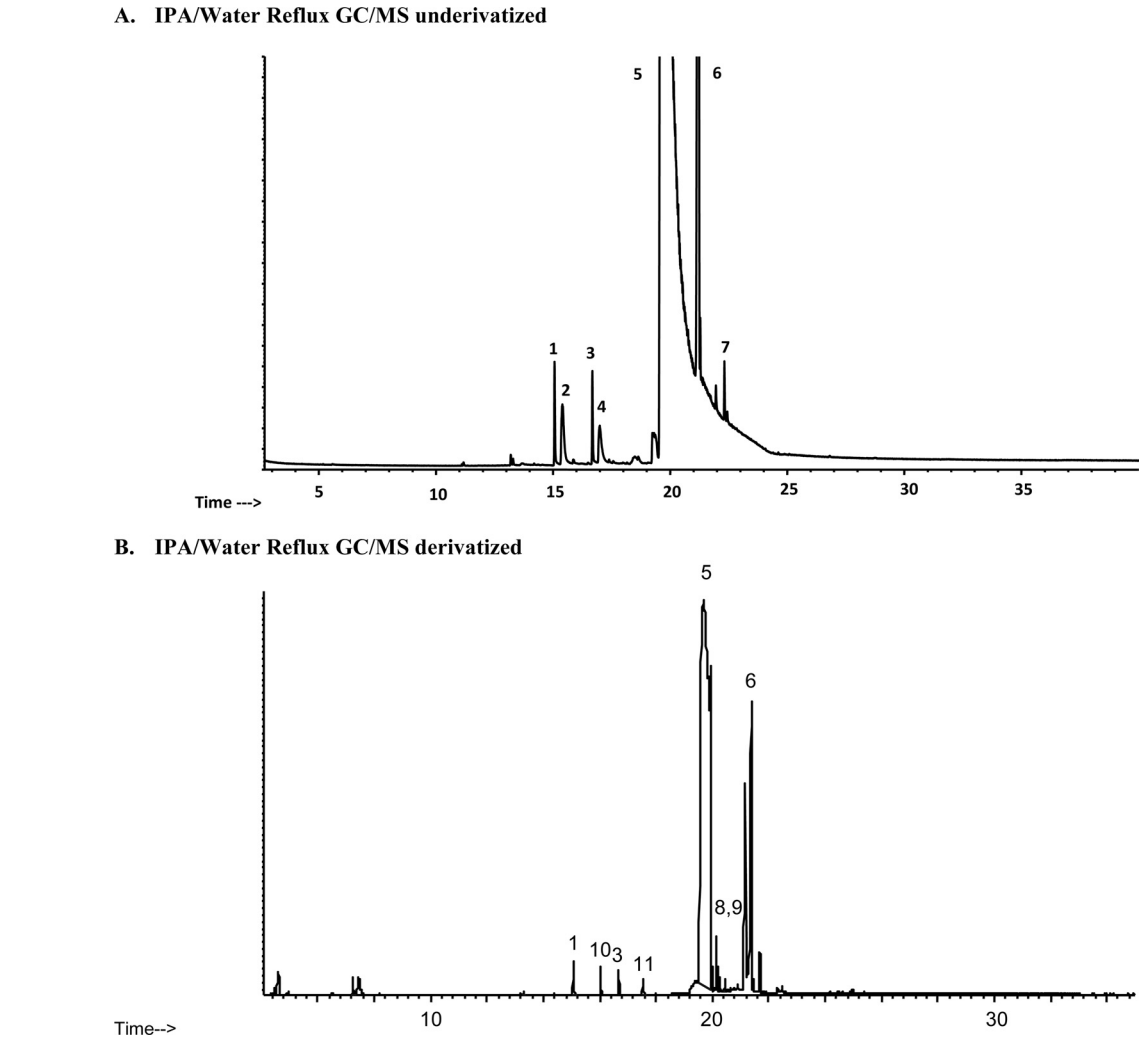

Figure 6

GC/MS Chromatograms for the IPA/Water Reflux Extracts for the PVC. The upper chromatogram is for the full scale chromatogram, the lower chromatogram is an expanded scale chromatogram showing the smaller peaks. The major peaks in the chromatograms are extracted DEHP (19.7 min) and Bisphenol M (internal standard, 21.7 min). The smaller peaks in the derivatized chromatogram in the elution region of 14 to 18 minutes are organic fatty acids such as myristic, palmitic and stearic acids. See Table VIII for information related to the extractables revealed by this testing.

anticipation that they stay in the material to perform their necessary function. Alternatively, it is reasonable to anticipate that certain additives (e.g., fatty acids and their salts) may partition favorably into an aqueous phase under certain circumstances (e.g., at high pH). Additionally, decomposition products of, and impurities in, the additives (and the base polymer) would tend to be more polar than the additive or base polymer itself and thus would have an increased aqueous solubility. It is therefore reasonable to anticipate that the aqueous, sealed vessel, or sonication extracts could contain extractables that differ significantly (in identity and concentration) from the extractables that are contained in the organic (i.e., reflux or Soxhlet) extracts. It is expected that the aqueous extracts would not contain large quantities of the additives themselves, due to solubility constraints, but rather would contain both the additives' more water-soluble and more polar impurities and hydrolysis products. Conversely, the organic extracts should predominantly contain the nonpolar additives themselves, as well as the additive's nonpolar impurities and reaction products. It is thus the combination of the information derived from the analysis of these diverse extracts that establishes the complete extractables profile of the test article.

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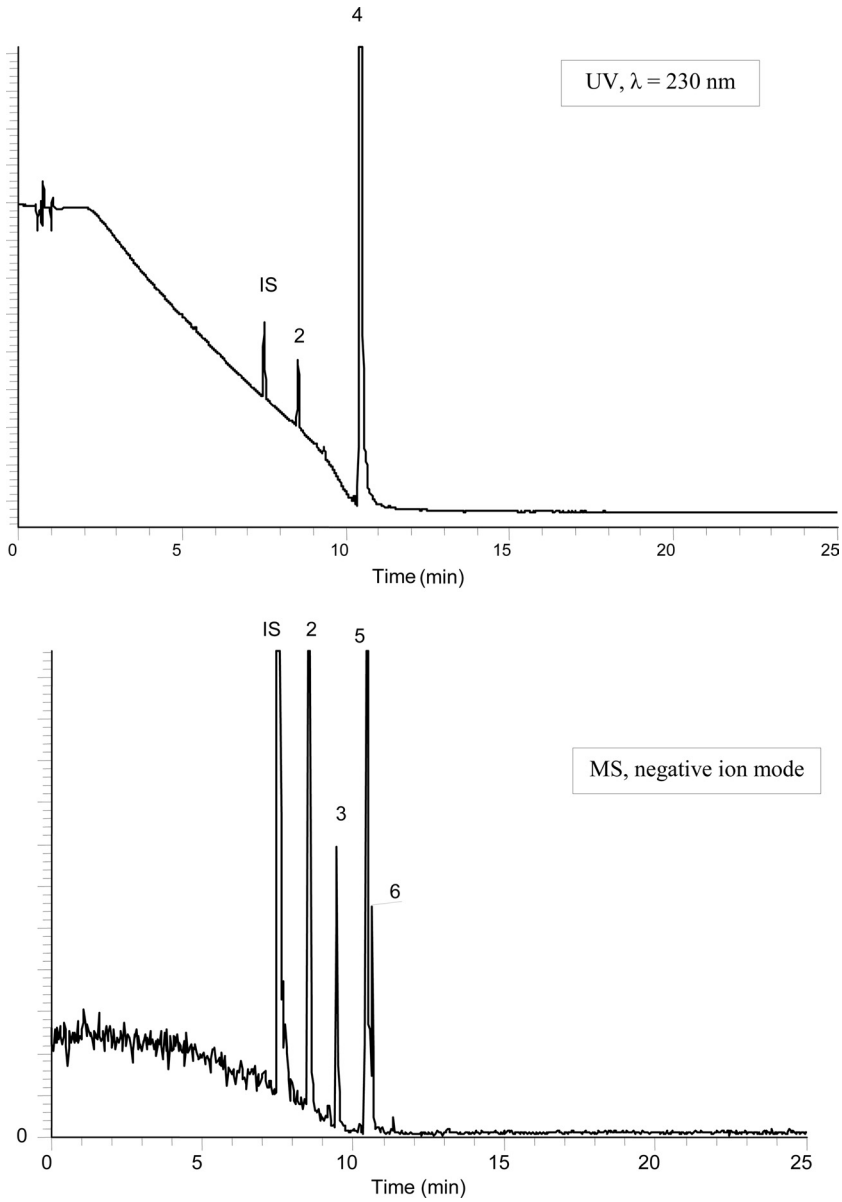

Figure 7

LC/UV (λ = 230 nm) and LC/MS (APCI ionization, negative ion mode) Chromatogram for the IPA/Water Reflux Extract for the PVC. See Table IX for information related to the extractables revealed by this testing (peaks labeled with numbers). The peak labeled IS is associated with one of the method's internal standards.

As it was generally the case that the extracts produced by sonication contained fewer organic extractables at lesser concentrations than did the extracts produced by sealed vessel extraction, only the results of the testing of the sealed vessel extracts will be reported and considered in greater detail.

Plasticized Poly(Vinyl Chloride), PVC

Introduction: Plasticized poly(vinyl chloride), PVC, is the primary material in numerous medical devices and pharmaceutical packaging systems, including intravenous (IV), blood, enteral, and parenteral nutrition and peritoneal dialysis bags and infusion tubing, nasogastric tubes, blister packaging and tubing used in devices for cardiopulmonary bypass, extracorporeal membrane oxygenation, and other applications. Its extensive use is due to its desirable properties; flexibility in a variety of physical forms, chemical stability, compatibility with typical sterilization processes, low cost, wide availability, and general lack of significant adverse consequences during pa-

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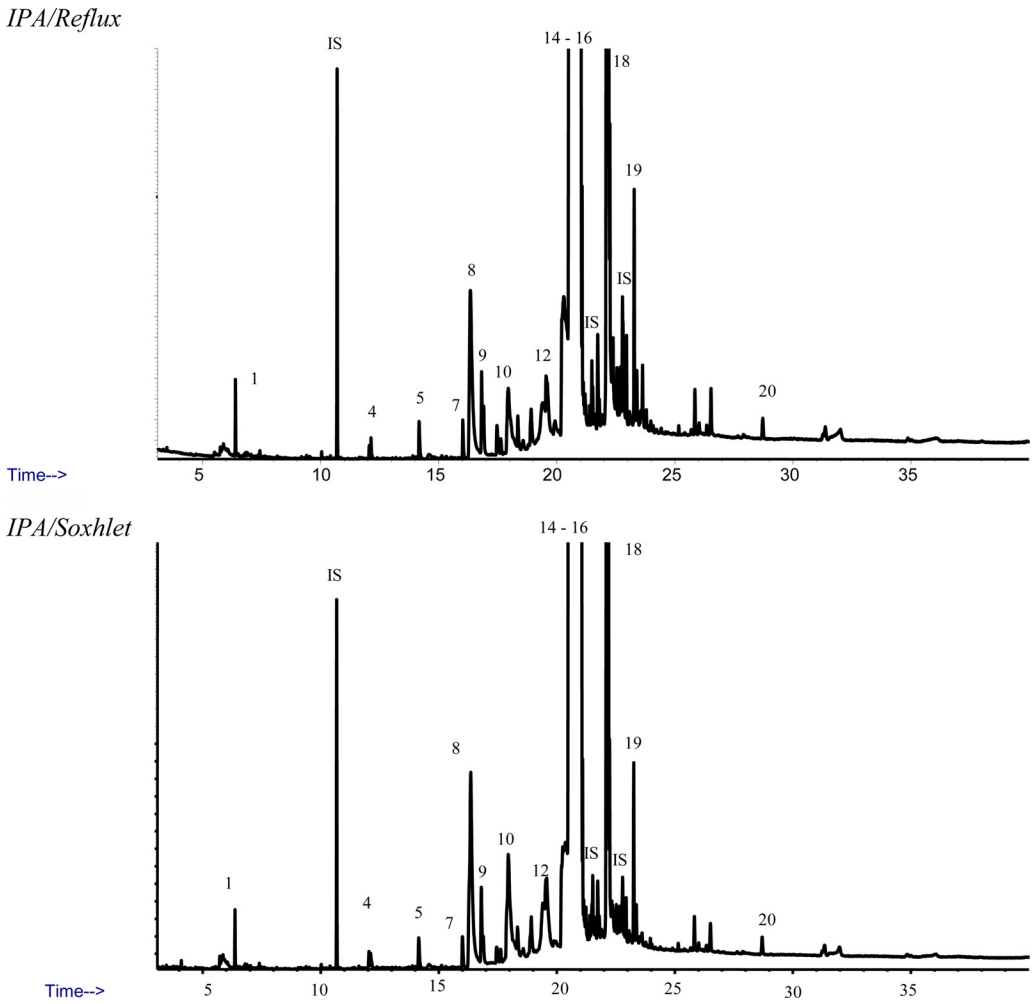

Figure 8

GC/MS Chromatograms (underivatized) for the IPA Extracts for the PVC. The upper chromatogram is for the reflux extraction and the lower chromatogram is for the Soxhlet extraction. Extractables associated with the chromatographic peaks are summarized in Table VIII. The major peaks in the chromatograms are extracted DEHP (≈ 21 min), fatty acids (17 – 20 min) and amides such as erucamide (≈ 23 min). The peaks labeled IS are due to the internal standards. The chromatograms for both extraction conditions are similar and these chromatograms for the IPA extracts are similar to those for the hexane extracts, Figure 9.

tient use. In its natural state, PVC is hard and brittle at room temperature, and a plasticizer is added to make it flexible, resilient, and easier to handle. While there are more than 300 different plasticizers described in the literature, only 50 to 100 are in commercial use and di-(2-ethylhexyl) phthalate (DEHP) has historically been the most widely used plasticizer in medical PVC plastics.

In addition to the primary plasticizer, commercial plasticized PVCs contain other additives that serve a particular purpose. Secondary plasticizers such as epoxidized oils are known as *extenders* and are commonly encountered in medical PVCs. In addition to promoting plasticity, these additives also serve as lubricants and acid scavengers. Additionally, medical PVCs will contain tertiary additives such as heat stabilizers (e.g., metal salts of stearic acid), tinting agents, and various processing aids.

Given its prominence as a medical plastic, plasticized PVC has been extensively characterized with respect to its extractables profile, and products contacting plasticized PVC materials have been characterized for leached substances (10–34). This information notwithstanding, it is the case that there are few studies that examine how

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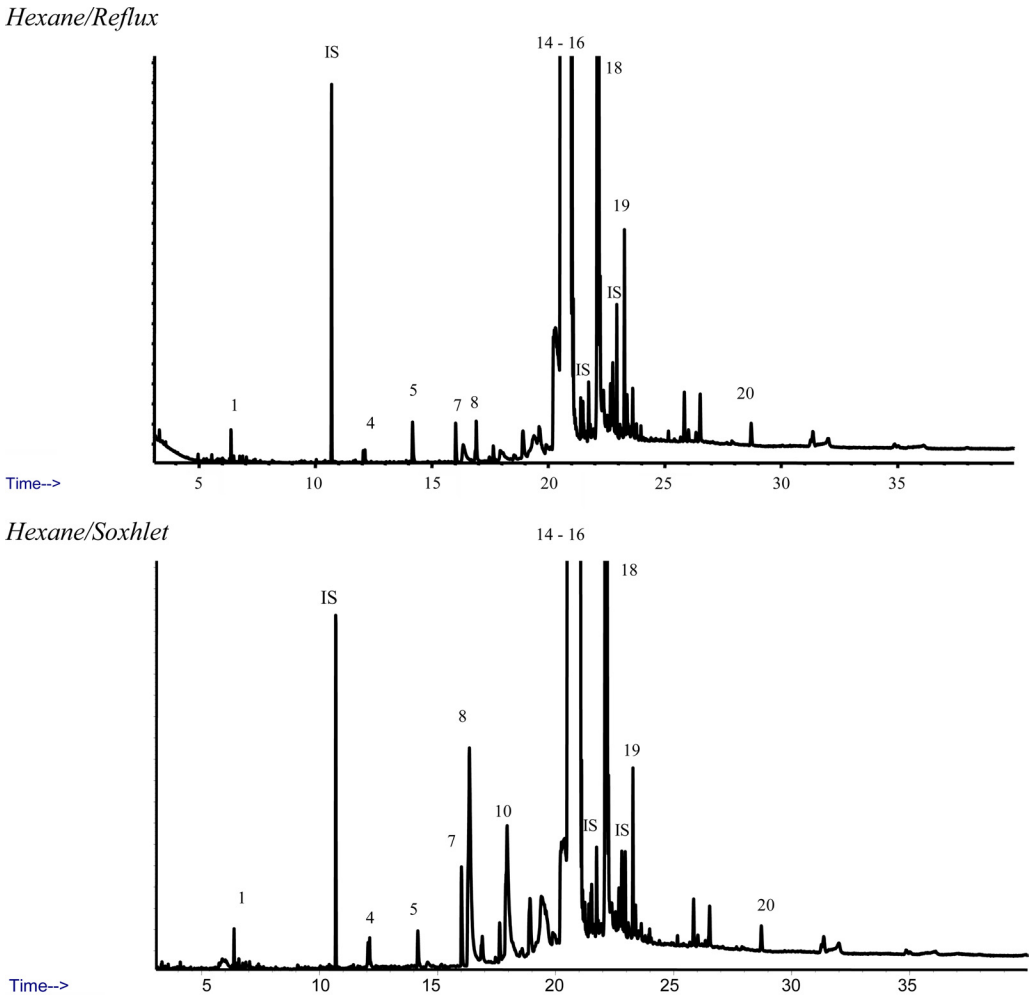

Figure 9

GC/MS Chromatograms (underivatized) for the Hexane Extracts for the PVC. The upper chromatogram is for the reflux extraction and the lower chromatogram is for the Soxhlet extraction. Extractables associated with the chromatographic peaks are summarized in Table VIII. The major peaks in the chromatograms are extracted DEHP (≈ 21 min), fatty acids (17 – 20 min) and amides such as erucamide (≈ 23 min). The peaks labeled IS are due to the internal standard. The chromatograms for both extraction conditions are similar and these chromatograms for the hexane extracts are similar to those for the IPA extracts, Figure 8.

the profile of plasticized PVC extractables varies as a function of the extraction conditions used.

Test Article: The test article was a representative DEHP-plasticized PVC material, supplied as pellets, as follows:

- PVC resin, ≈60% by weight
- Primary plasticizer, DEHP, ≈30% by weight
- Secondary plasticizer, epoxidized oil, ≈7% by weight
- Acid scavengers, calcium- and zinc-stearates, ≈0.5% each by weight
- Alkyl amide (e.g., Erucamide), ≈1% by weight

Although the test article's formulation is representative of plasticized PVCs used in pharmaceutical applications, this particular material is not used in commercial products.

Elemental Analysis: Elements extracted into the aqueous extracts from all test articles are summarized in Table VII. Many of the targeted elements were not

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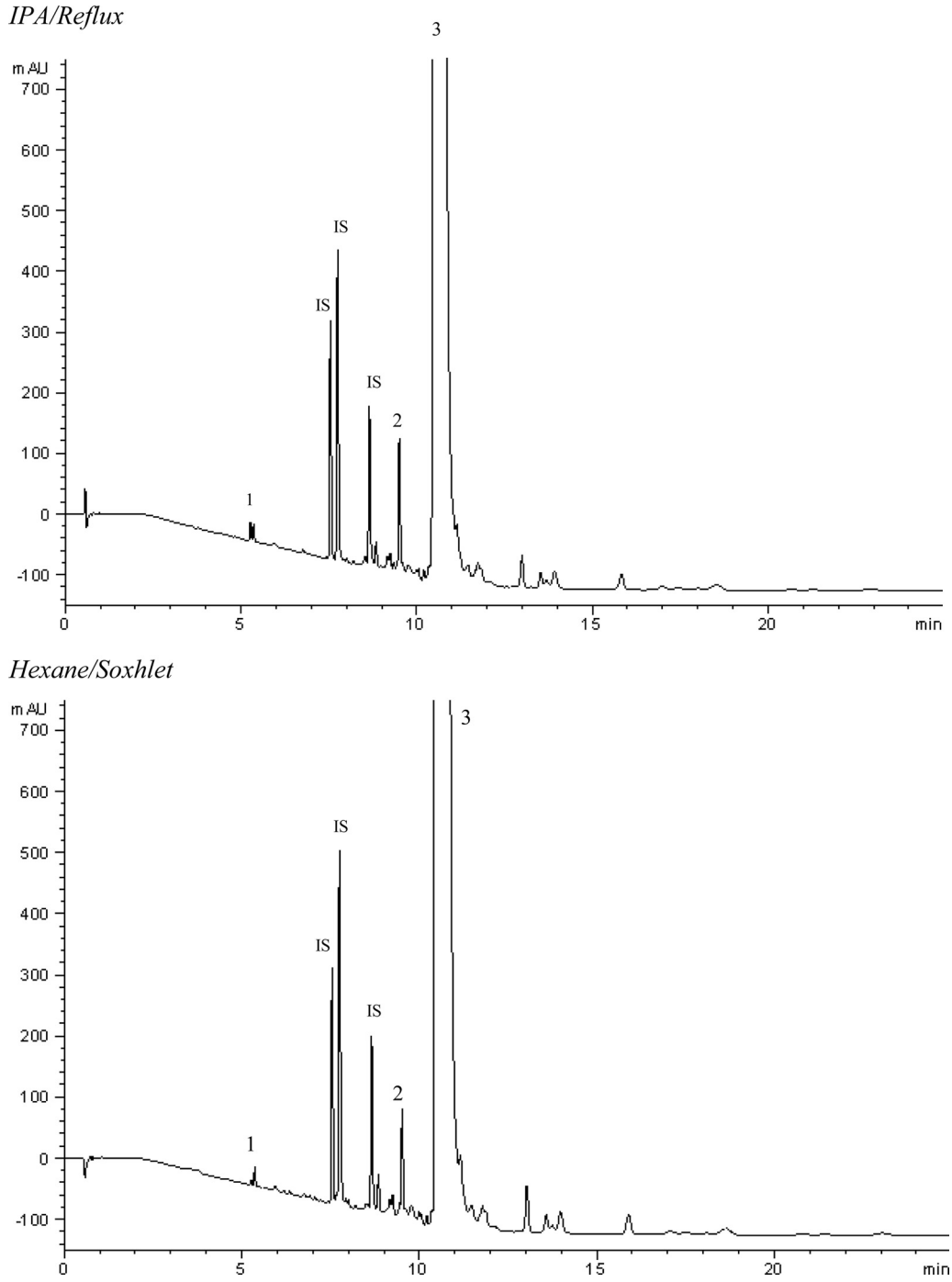

Figure 10

LC/UV (λ = 220 nm) Chromatograms of IPA Reflux and Hexane Soxhlet Extracts for the PVC. See Table IX for information related to the extractables revealed by this testing (numbered peaks). Peaks labeled as IS are associated with the method's internal standards. The LC/MS analysis was not able to establish the identities of several of the major chromatographic peaks.

reproducibly extracted from the plasticized PVC in reportable quantities (reporting threshold was approximately 0.01 μg/g). Major elements extracted from the plasticized PVC at levels of 0.1 μg/g or greater in one or more of the extracts included Ca, Zn, Br, Na, Fe, Mg, and Al. The highest levels of the extracted elements were in the pH 2.5 extract, suggesting that ion exchange could be a predominant extraction mechanism.

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TABLE X
Organic Extractables Profile of the PVC Material as Established by the Testing Performed in this Study; Identified Compounds Reproducibly Extracted from the Test Article at Levels of Approximately 1 μg/g or Greater

Identification	CAS RN	Chemical Formula	Molecular Weight	Concentration in Material, μg/g							
				Sealed Vessel			Reflux			Soxhlet	
				pH 2.5	pH 9.5	IPA/W	IPA/W	IPA	Hexane	IPA	Hexane
Di-(2-ethylhexyl) phthalate (DEHP)[a]	117-81-7	$C_{24}H_{38}O_4$	390.56	1–10	10–100	>1000	>10000	>10,000	>10,000	>10,000	>10,000
(z)-13-Docosenamide (Erucamide)[a]	112-84-5	$C_{22}H_{43}NO$	337.58	—	—	>1000	>1000	>10,000	>10,000	>1000	>1000
cis-11-Eicosenamide[b]	10436-08-5	$C_{20}H_{39}NO$	309.53	—	—	—	100–1000	>1000	>1000	>1000	>1000
Hexadecanamide (Palmitamide)[b]	629-54-9	$C_{16}H_{33}NO$	255.44	—	—	—	100–1000	>1000	>1000	>1000	>1000
Hexadecanoic acid, 1-methylethyl ester[a]	142-91-6	$C_{19}H_{38}O_2$	298.50	—	—	—	1–10	100–1000	10–100	100–1000	>1000
Hexadecanoic (Palmitic) acid[a]	57-10-3	$C_{16}H_{32}O_2$	256.42	—	10–100	100–1000	100–1000	100–1000	10–100	100–1000	100–1000
Octadecanoic (Stearic) acid[a]	57-11-4	$C_{18}H_{36}O_2$	284.47	—	—	100–1000	100–1000	100–1000	—	100–1000	100–1000
Tetradecanoic (Myristic) acid[a]	544-63-8	$C_{14}H_{28}O_2$	228.57	—	10–100	100–1000	—	—	—	—	—
Hexadecanoic acid, methyl ester[b]	112-39-0	$C_{17}H_{34}O_2$	270.45	—	1–10	—	100–1000	10–100	10–100	10–100	100–1000
Octadecanoic acid, methyl ester[b]	112-61-8	$C_{19}H_{38}O_2$	298.50	—	—	—	100–1000	—	—	—	—
(z)-9-Octadecenamide (Oleamide)[b]	301-02-0	$C_{18}H_{35}NO$	281.48	—	—	100–1000	10–100	10–100	100–1000	—	—
9-Hexadecenoic acid[c]	2091-29-1	$C_{16}H_{30}O_2$	259.22	—	—	—	—	100–1000	10–100	10–100	100–1000
Behenic Amide[b]	3061-75-4	$C_{22}H_{45}NO$	339.60	—	—	—	10–100	—	—	—	—
Benzoic acid, 2-ethylhexyl ester[b]	5444-75-7	$C_{15}H_{22}O_2$	234.33	—	—	10–100	10–100	—	—	—	—
2-Ethyl-1-hexanol[a]	104-76-7	$C_8H_{18}O$	130.23	1–10	1–10	1–10	10–100	10–100	10–100	10–100	10–100
Mono-(2-ethylhexyl) phthalate (MEHP)[a]	4376-20-9	$C_{16}H_{22}O_4$	278.34	—	1–10	—	—	—	—	—	—
Phthalic anhydride[a]	85-44-9	$C_8H_4O_3$	148.12	—	1–10	10–100	—	10–100	10–100	10–100	10–100
Tetradecanoic acid, methyl ester[a]	124-10-7	$C_{15}H_{30}O_2$	242.40	—	—	—	1–10	—	—	—	—

Notes:
[a]These identifications are classified as confirmed.
[b]These identifications are classified as confident.
[c]These identifications are classified as tentative.

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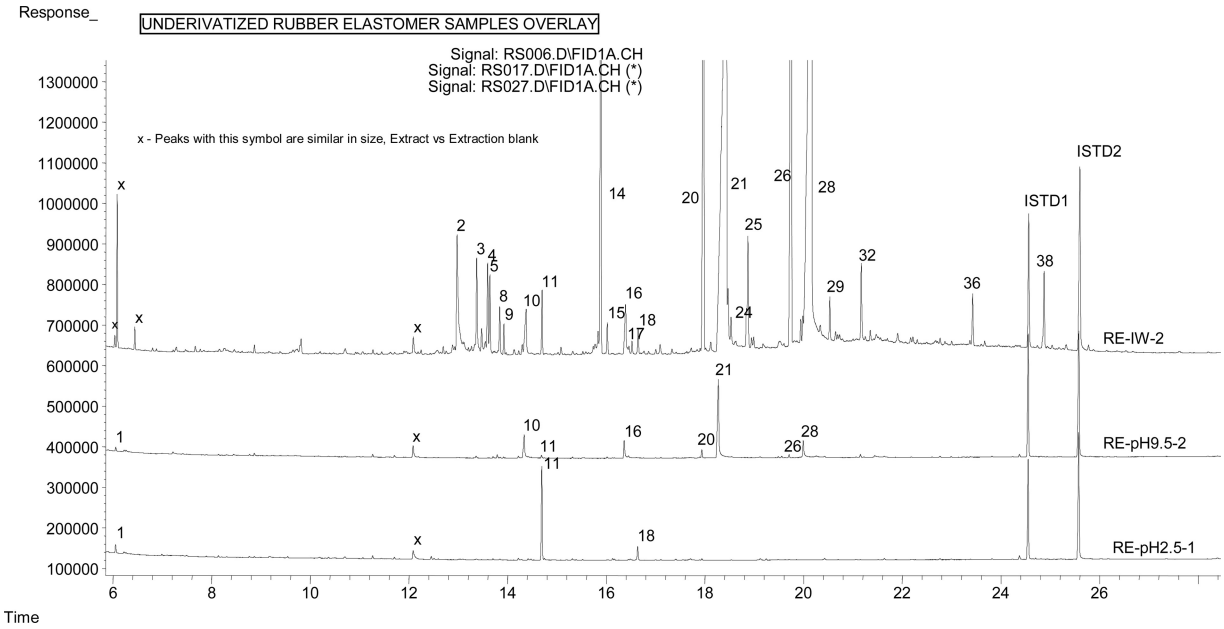

Figure 11

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts of the Elastomer (underivatized sample preparation). Peaks ISTD1 and ISTD2 are the two internal standards (1 = Irganox 415 and 2 = Bisphenol M), reflecting compounds present in the extract at a concentration of approximately 1 mg/L (ppm). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. See Table XI for a summary of information about the numbered peaks, all of which were ascribed to extracted substances.

Extraction of measurable quantities of Ca and Zn is expected, as the plastic includes calcium and zinc salts as intentional additives. Other elements, Cr, Mn, Sr, Cu, V, As, Pb, Sb, and Mo, were present in the extracts at levels near the detection limits and thus are trace level constituents of the test article.

Volatile Components: The headspace GC/MS chromatograms contained several peaks related to volatile hydrocarbons of unspecified identity, present at levels ranging from 0.5 to 4.6 μg/g. The identity of one volatile compound, 2-ethyl-1-hexanol, was confirmed; this compound was present in the test material at a level of 3.0 μg/g.

Organic Extractables:
Sealed Vessel Extracts: Typical GC/FID chromatograms obtained for the sealed vessel extracts are shown in Figures 2 and 3. Information for the extractables that were ascribed to the major chromatographic peaks is summarized in Table VIII. LC chromatograms obtained for the sealed vessel extracts are shown in Figures 4 and 5. Information related to the extractables peaks in these chromatograms is summarized in Table IX. As was anticipated, there are relatively few extracted substances at generally low levels in the aqueous pH 2.5 and pH 9.5 extracts. Most of the nonpolar additives were not detected in these extracts, with the exception of very low levels of DEHP. The aqueous extracts contained larger quantities of the more soluble 2-ethyl-1-hexanol, which is related to DEHP as an impurity or decomposition product. The higher-pH extract also contained small quantities of several fatty acids and mono-(2-ehtylhexyl) phthalate (MEHP), reflecting their increased solubility at a pH above the acid's pK_a.

The chromatographic analyses indicated that the IPA/water extracts contained more numerous extractables at higher concentrations than did the aqueous extracts. Figures 2 through 5 illustrate the effect that the extracting solvent had on the extractables profile. In general, the IPA/water extracts contained the nonpolar additives themselves as well as the additives' higher molecular weight constituents, specifically phthalates related to the DEHP plasticizer, organic acids associated with the stearate additive, and erucamide and related compounds.

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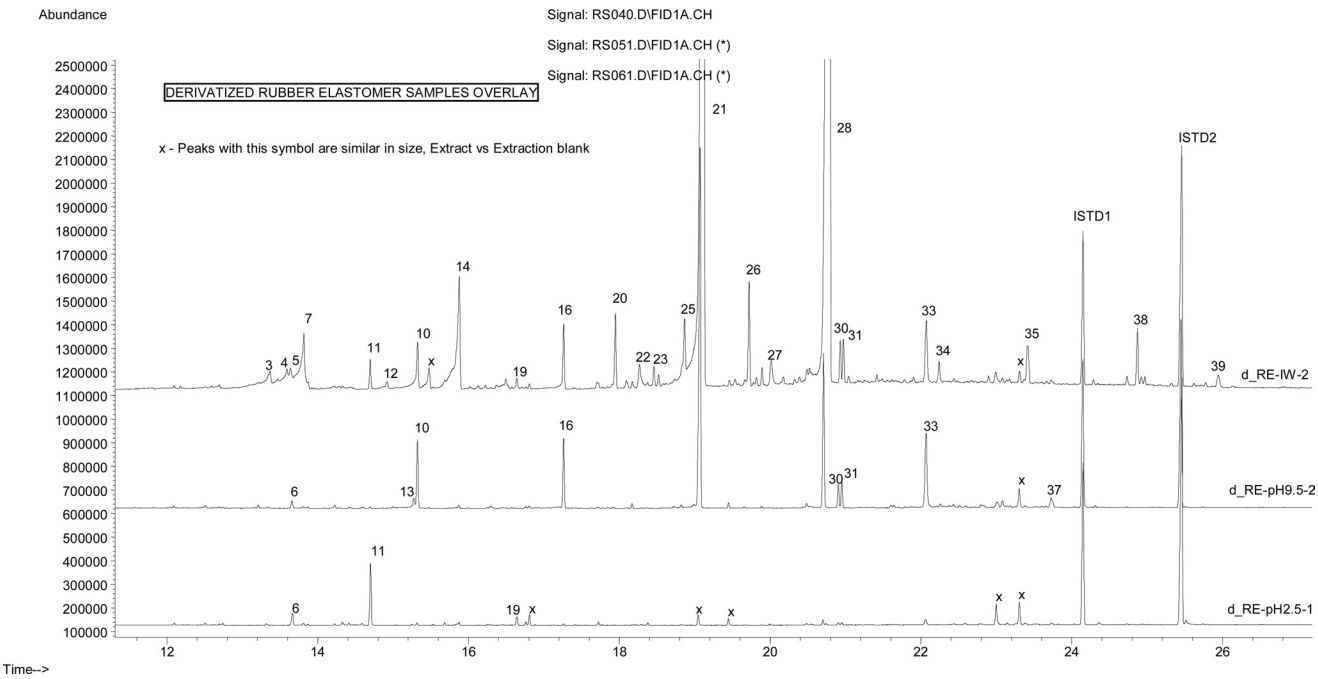

Figure 12

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts of the Elastomer (derivatized sample preparation). Peaks ISTD1 and ISTD2 are the two internal standards (1 = Irganox 415 and 2 = Bisphenol M), reflecting compounds present in the extract at a concentration of approximately 1 mg/L (ppm). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. See Table XI for a summary of information about the numbered peaks, all of which were ascribed to extracted substances.

Reflux and Soxhlet Extracts: Chromatograms obtained for the various reflux and Soxhlet extracts are illustrated in Figures 6 through 10. Chemical information related to the identified extractables present in these extracts is summarized in Tables VIII and IX. The nonpolar additives were the prevalent extractables discovered and account for the major peaks. In general, the extractables profile is not greatly affected, qualitatively, by either the extraction process (Soxhlet versus reflux) or the extraction solvent (IPA/water versus IPA versus hexane). As the levels of the extractables in these extracts were relatively high, it was difficult to ascertain whether there were meaningful quantitative differences in the extractables profile as a function of extraction method and extraction solvent.

In addition to the extractables listed in the relevant tables, the reflux and Soxhlet extracts contained numerous compounds whose specific identities could not be established but which could be attributed to a compound class, specifically epoxidized fatty acids. These substances, whose association with PVC extracts has been previously documented (16), were particularly prevalent in the LC/MS chromatograms and represent hydrolysis products and related substances of the secondary plasticizer (epoxidized linseed oil).

Summary: The extractables profile of a DEHP-plasticized PVC material was established via the use of multiple extraction processes, multiple extracting media, and multiple analytical tests. The predominant extracted metals (Ca and Zn) were attributed to the acid scavenger additive (calcium and zinc stearate salts). As the highest levels of these extracted elements were obtained in the pH 2.5 extract, ion exchange is a believed to be the predominant extraction mechanism. This material's profile of organic extractables is summarized in Table X. The organic extractables generally fell into four classes of compounds, roughly linked to the four major PVC additives. Thus, the organic extractables profile includes phthalate extractables associated with the primary plasticizer (DEHP); epoxidized fatty acids as impurities in or

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TABLE XI
Information Related to the GC Peaks Associated with Organic Extractables from the Rubber

Peak #				Highest Concentration In Extract	
Set A[a]	Set B[b]	Identification	CAS RN	Medium	Type
28	8	Octadecanoic (Stearic) acid[c]	57-11-4	Hexane	Soxhlet
21	5	Hexadecanoic (Palmitic) acid[c]	57-10-3	Hexane	Soxhlet
—	3	C-21 oligomer[d,f]	—	Hexane	Soxhlet
—	13	Oleamide[c]	301-02-0	IPA	Soxhlet
24	7	Isopropyl palmitate[c]	142-91-6	Hexane	Soxhlet
—	6[h]	Unsaturated aliphatic hydrocarbon	—	Hexane	Soxhlet
—	15	Octadecane[d]	593-45-3	IPA	Soxhlet
—	16	Octacosane[c]	630-02-4	IPA	Soxhlet
36	17	1-(4-Morpholinyl)-octanoic acid[d]	5299-54-7	IPA	Soxhlet
—	1	Morpholine[c]	110-91-8	IPA	Reflux
—	14	Tetracosane[c]	646-31-1	IPA	Soxhlet
—	19	Aliphatic hydrocarbon[e]	—	IPA	Soxhlet
—	12	10-Oxo-octadecanoic acid[d]	870-10-0	IPA	Reflux
—	18	4,4'-Dioctlydiphenylamine[c]	101-67-7	IPA	Reflux
—	2	C13-oligomer, brominated[d,g]	—	IPA	Reflux
—	10	Hexadecanamide[c]	629-54-9	IPA	Reflux
—	11	Docosane[d]	629-97-0	IPA	Reflux
20	4	Methyl-n-hexadecanoate[c]	112-39-0	IPA	Reflux
26	9	Octadecanoic acid, methyl ester[d]	112-61-8	Hexane	Soxhlet
33	—	Nonadecanoic acid[d]	646-30-0	pH 9.5	Sealed
11	—	Diethyl phthalate[d]	84-66-2	pH 2.5	Sealed
32	—	9-Oxo-octadecanoic acid, methyl ester[e]	1842-70-2	IPA/Water	Sealed
17	—	Tri-tert-butyl-di-hydroxy benzene[e]	24851-96-5	IPA/Water	Sealed
10	—	Dodecanoic acid[d]	143-07-7	pH 9.5	Sealed
38	—	n-Decanoyl morpholine[e]	5299-65-0	IPA/Water	Sealed

Notes:
[a]In the sealed vessel extracts, see Figures 11, 12. These extracts contained several extractables at levels less than 10 μg/g whose peaks are numbered in the chromatograms but whose associated compounds were not established, specifically peaks 1, 6, 8, 9, 12, 13, 15, 16, 18, 19, 22, 23, 24, 27, 29, 30, 31, 34, 35, 37, and 39. These extracts also contained extractables above 10 μg/g whose identities could not be established, specifically peaks 2–5, 7, 14, and 25.
[b]In the solvent extracts, Soxhlet and reflux, see Figures 15, 16.
[c]These identifications are classified as confirmed.
[d]These identifications are classified as confident.
[e]These identifications are classified as tentative.
[f]1-Isopropenyl-2,2,4,4-tetramethyl-6-(2,2,4-trimethyl-pentyl-1-)-cyclohexane, $C_{21}H_{40}$.
[g]1-(1-Bromoethylethenyl)-2,2,4,4-tetramethylcyclohexane, $C_{13}H_{23}Br$.
[h]This peak was present in the extract chromatogram but was not labeled in the relevant figure.

hydrolysis products of the secondary plasticizer (epoxidized linseed oil); aliphatic amides, associated with the erucamide present in the test article; and fatty acids, associated with either the secondary plasticizer or the acid scavenger additive (metal salts of stearic acid).

Rubber

Introduction: The use of rubber in the medical industry is nearly as old as the rubber industry itself, as the utility of rubber components of packaging and delivery devices was recognized shortly after the discovery of the vulcanization process. The unique properties of processed rubber, including elasticity, penetrability, resiliency, the ability to act as a gas/vapor barrier, and general chemical compatibility, were the driving forces behind its ready adoption in early 20th century pharmaceutical applications (primarily as closures for glass vials); these properties ensure rubber's continued use in modern pharmaceutical practice (closures, o-rings, plungers, seals, etc.).

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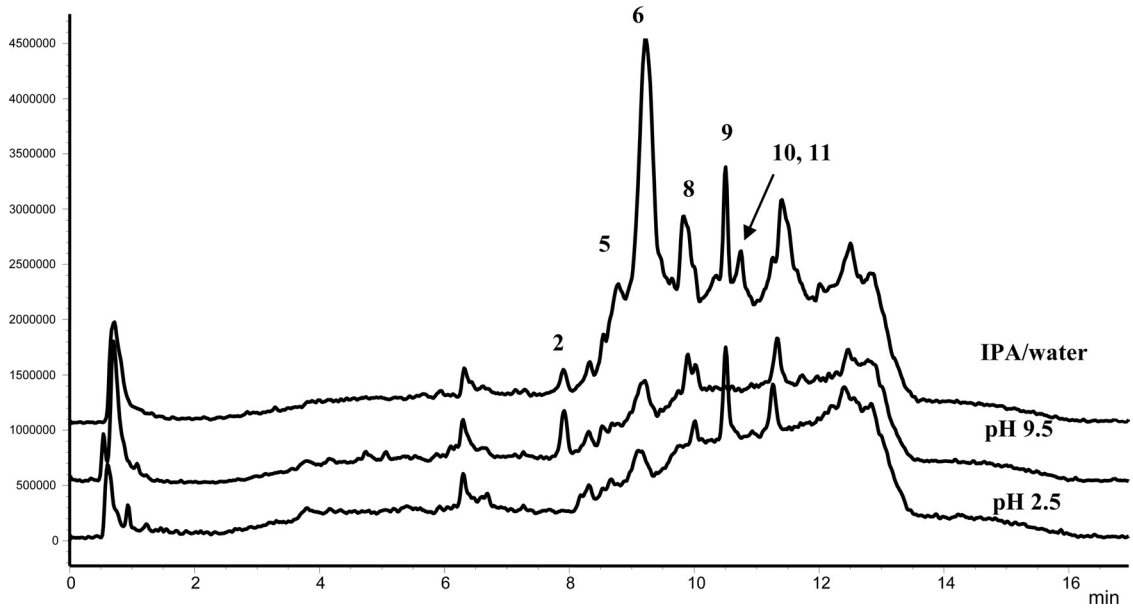

Figure 13

LC/MS TIC (Total Ion Current) Chromatograms, positive ion mode, of the Sealed Vessel Extracts for the Elastomer. See Table XII for the identities, as available, for the numbered extractables. Peaks that are not numbered were present in the extraction blanks and thus are not associated with extractables. The upper chromatogram is the IPA/water extract, the middle chromatogram is the pH 9.5 extract and the lower chromatogram is the pH 2.5 extract.

As the performance characteristics required for pharmaceutical applications are not intrinsic to the "base" elastomer, such materials are compounded and/or reacted with chemical additives (e.g., curing agents, vulcanizing agents, activators, accelerators, plasticizers, tackifiers, colorants, fillers, antioxidants, lubricants) at elevated temperature and pressure. These chemical additives, their impurities, and their processing-induced reaction or decomposition products are all probable extractables, and therefore potential leachables.

Given its long standing and prominent use in packaging, delivery, and manufacturing systems, numerous rubber materials and components has been extensively characterized with respect to their compatibility with drug products, including extractables and leachables characterizations. Compatibility investigations performed prior to 1970 were largely empirical in nature, as the analytical chemistry supporting such investigations was limited in scope and sensitivity (35–46). The development of "modern" chromatographic and spectroscopic methods facilitated the study of rubbers for organic extractables, and the time between the early 1970s and the present was one of active research in this area (47–59). For example, a widely documented incompatibility involved EPREX® (epoetinum alfa) and its pre-filled syringe packaging system (60–62). At some point in its market lifetime, EPREX, containing recombinant human erythropoietin, was reformulated with polysorbate 80, replacing human serum albumin as a stabilizer. Shortly thereafter, the incidence of antibody-mediated pure red cell aplasis (PCRA) in chronic renal failure patients using EPREX increased. The occurrence of PCRA was directly linked to the formation of neutralizing antibodies to both recombinant and endogenous erythropoietin in patients administered EPREX. One potential root cause of antibody formation involved leached substances. Previously unidentified leachables were suggested as new peaks in the tryptic map of EPREX, and leaching studies established that polysorbate 80 extracted low levels of vulcanizing agents (and related substances) from the uncoated rubber components of the pre-filled syringe. The leaching issue was addressed by coating the rubber components with a fluoropolymer, an effective barrier to migration, thereby reducing leaching of the rubber's components. After the conversion from the uncoated to the coated components, the incidence of PCRA returned to the

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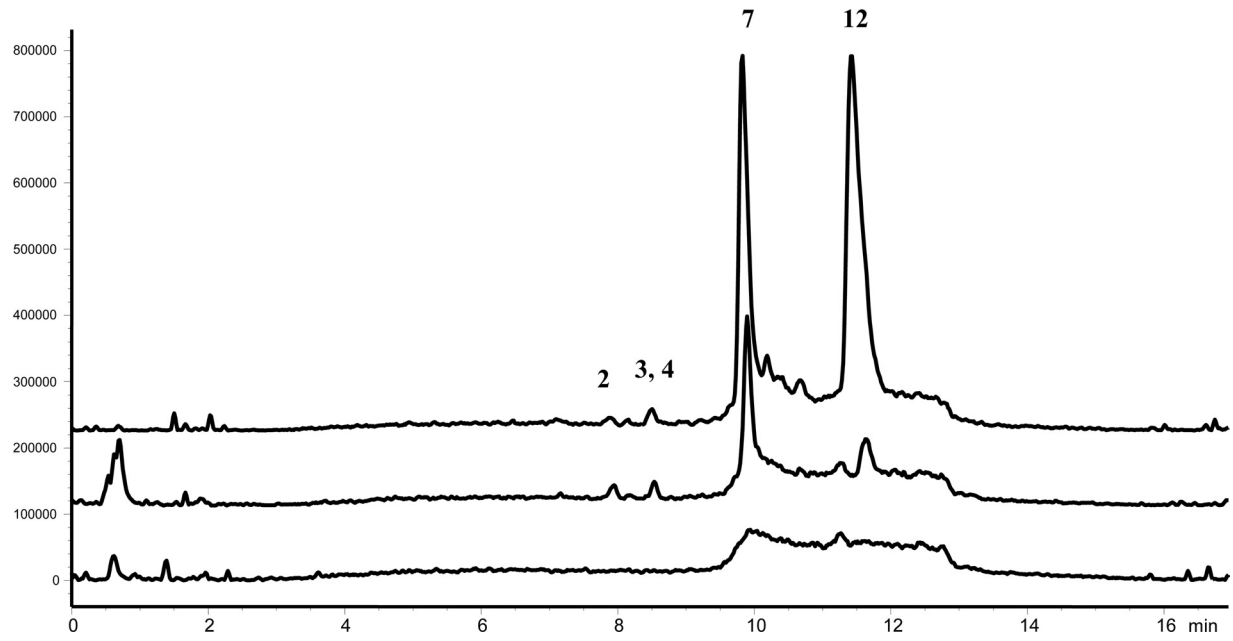

Figure 14

LC/MS TIC (Total Ion Current) Chromatograms, negative ion mode, of the Sealed Vessel Extracts for the Elastomer. See Table XII for the identities, as available, for the numbered extractables. Peaks that are not numbered were present in the extraction blanks and thus are not associated with extractables. The upper chromatogram is the IPA/water extract, the middle chromatogram is the pH 9.5 extract and the lower chromatogram is the pH 2.5 extract.

baseline rate seen for all marketed epoetin products. This was strong evidence that leaching of the vulcanizing agent was a root cause of the observed effect.

Additional extractables/leachables information for rubbers can be found in recent reviews of this subject (10, 63).

Test Article: The rubber test article consisted of a brominated isobutylene isoprene copolymer base rubber (57.3% by weight) and contained calcined aluminum silicate, 38.2%; titanium dioxide, 1.2%; paraffinic oil, 1.2%; zinc oxide, 0.6%; polyethylene, 0.6%; carbon black, 0.4%; calcined magnesium oxide, 0.3%; and 4,4'-dithiodimorpholine (in a polyisobutylene binder masterbatch), 0.3%. Additional unspecified additives may have been present in the test article. Although the test article's formulation is consistent with and representative of some rubbers used in pharmaceutical applications, it is not specifically used in commercial products.

Elemental Analysis: The elements that were present in the aqueous extracts are summarized in Table VII. Many of the targeted elements were not reproducibly extracted from the rubber in reportable quantities, where the reporting threshold was approximately 0.01 μg/g. As the test article is a brominated isobutylene isoprene copolymer, it is not unexpected that Br was extracted from the material in measurable quantities, approximately 20 μg/g. Other extracted elements include the alkali and alkaline earth metals such as K (6.8 μg/g), Ca (4.1 μg/g), Na (3.0 μg/g), and Mg (3.5 μg/g), and Si (0.25 μg/g). Among the metals, Al was present in the pH 9.5 extracts at levels of 3.6 μg/g or lower, while Zn was present in the pH 2.5 extracts at levels of 2.9 μg/g or lower. Additionally, Fe and Ti were present in the pH 2.5 extracts at levels near 0.3 μg/g, and several metals (including Ni, V, Cr, Mn, Sr) were detected in the extracts at levels near the reporting threshold.

Volatile Components: The headspace GC/MS chromatograms contained several peaks related to volatiles present in the test article at low levels, approximately 1 μg/g or less, including methylcyclopentane (1.2 μg/g), cyclohexane (0.5 μg/g), and unspecified butyl oligomers present at levels of 0.8 and 0.5 μg/g.

Organic Extractables:
Sealed Vessel Extracts: Typical GC/FID chromatograms obtained for the sealed vessel extracts are

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TABLE XII
Summary of Identified Organic Extractables from the Rubber, LC Analysis

Peak		Identification[c]	CAS RN
Set A[a]	Set B[b]		
—[f]	1[g]	Hexanoic acid morpholide	17598-10-6
—	2[g]	Dihydroxy stearic acid	858802-85-4[i]
—	3[g]	9,10-Epoxy stearic acid (cis/trans)	13980-07-9
—	4[g]	9,10-Epoxy stearic acid (cis/trans)	24560-98-3
—	5	3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzaldehyde[e]	1620-98-0
—	6[g]	2,6-Di-tert-butylbenzoquinone[d]	719-22-2
—	7	2,6-Bis-(1,1-dimethylethyl)-4-methyl-phenol, BHT[e]	128-37-0
7	8[g]	Hexadecanoic (Palmitic) acid[e]	57-10-3
—	9[g]	Oleamide[e]	301-02-0
—	10[g]	Palmitic acid morpholide[d]	5299-68-3
12	11[g]	Octadecanoic (Stearic) acid[e]	57-11-4
—	12[g]	Stearic acid morpholide[d]	5299-54-7
—	13	3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid, 1,1'-[2-[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxopropoxy]methyl]-2-(hydroxymethyl)-1,3-propanediyl] ester[e]	84633-54-5
—	14	Dioctyldiphenylamine[e]	101-67-7
—	15[g]	Diglyceride, epoxidized	N/A
—	16[g]	Diglyceride, epoxidized	N/A
—	17	3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid, 1,1'-[2,2-bis[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxopropoxy]methyl]-1,3-propanediyl] ester, Irganox 1010[e]	6683-19-8
1[h]	—	Morpholine[d]	110-91-8
3	—	Tetradecanoic (Myristic) acid[e]	544-63-8
5,6	—	Unspecified oligomers	—

Notes:
[a]In the sealed vessel aqueous extracts, see Figures 13, 14. The chromatograms contained additional peaks whose associated extractables could not be identified; for example, peaks 2, 4, and 8–11.
[b]In solvent extracts, Soxhlet and reflux, see Figure 17.
[c]These identifications are classified as tentative unless otherwise noted.
[d]These identifications are classified as confident.
[e]These identifications are classified as confirmed.
[f]— = not detected.
[g]Not shown in the LC/UV chromatograms, Figure 17, but present in the LC/MS chromatograms.
[h]This peak was present in the extract chromatogram but was not labeled in the relevant figure.
[i]The listed compound is an example of the possible isomers of this extractable and may not be the exact isomer that was encountered in this study.

shown in Figures 11 and 12. Information for the extractables that were ascribed to the major chromatographic peaks is summarized in Table XI. LC chromatograms obtained for the sealed vessel extracts are shown in Figures 13 and 14, which focus on the individual extracting media themselves. Information related to the extractables peaks in the LC chromatograms is summarized in Table XII. As was anticipated, there were a relatively few extracted substances at low levels in the aqueous pH 2.5 and pH 9.5 extracts. Most

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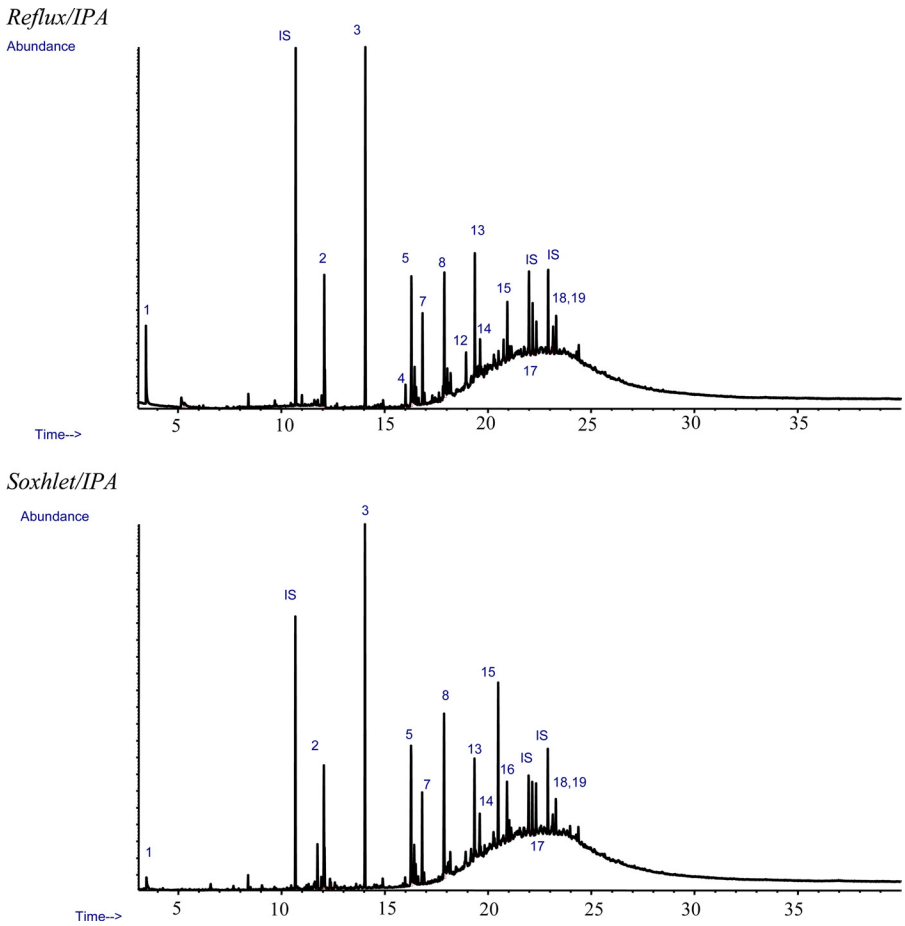

Figure 15

GC/MS Chromatograms (underivatized) for the IPA Extracts for the Elastomer. The upper chromatogram is for the reflux extraction and the lower chromatogram is for the Soxhlet extraction. Extractables associated with the chromatographic peaks are summarized in Table XI. Peaks labeled IS are the internal standards, including 2-Fluorobiphenyl at 10.7 min, Irganox 415 at 22.0 min and Bisphenol M at 23.0 min. The chromatograms for both extraction conditions are similar and these chromatograms for the IPA extracts are similar to those for the hexane extracts, Figure 16.

of the nonpolar ingredients were not detected in these extracts, with the exception of several fatty acids in the pH 9.5 extracts. The pH 2.5 extracts contained measurable quantities of morpholine, as this degradation product of the accelerator has an intrinsically high water solubility at low pH. The aqueous extracts contained trace quantities of lower molecular weight polymer oligomers and similarly low levels of degradation products that are typically associated with phenolic antioxidants.

The chromatographic analyses indicated that the IPA/water extracts contained more numerous extractables at higher concentrations than did the aqueous extracts. Figures 11 through 14 illustrate the effect that the extracting solvent had on the extractables profile. The IPA/water extracts contain the same fatty acids that were present in the aqueous extracts but at higher concentrations as well as fatty acids (and their methyl esters) that were not present in the aqueous extracts at detectable levels. The IPA/water extracts contained additional degradants/reaction products of the dithiodimorpholine accelerator and more numerous unidentifiable polymer oligomers than did the aqueous extracts. However, the IPA/water extracts contained few identifiable extractables other than those that were present in the aqueous extracts. Thus, both the aqueous and IPA/water extracts generally provided only limited insights into the composition of the test material.

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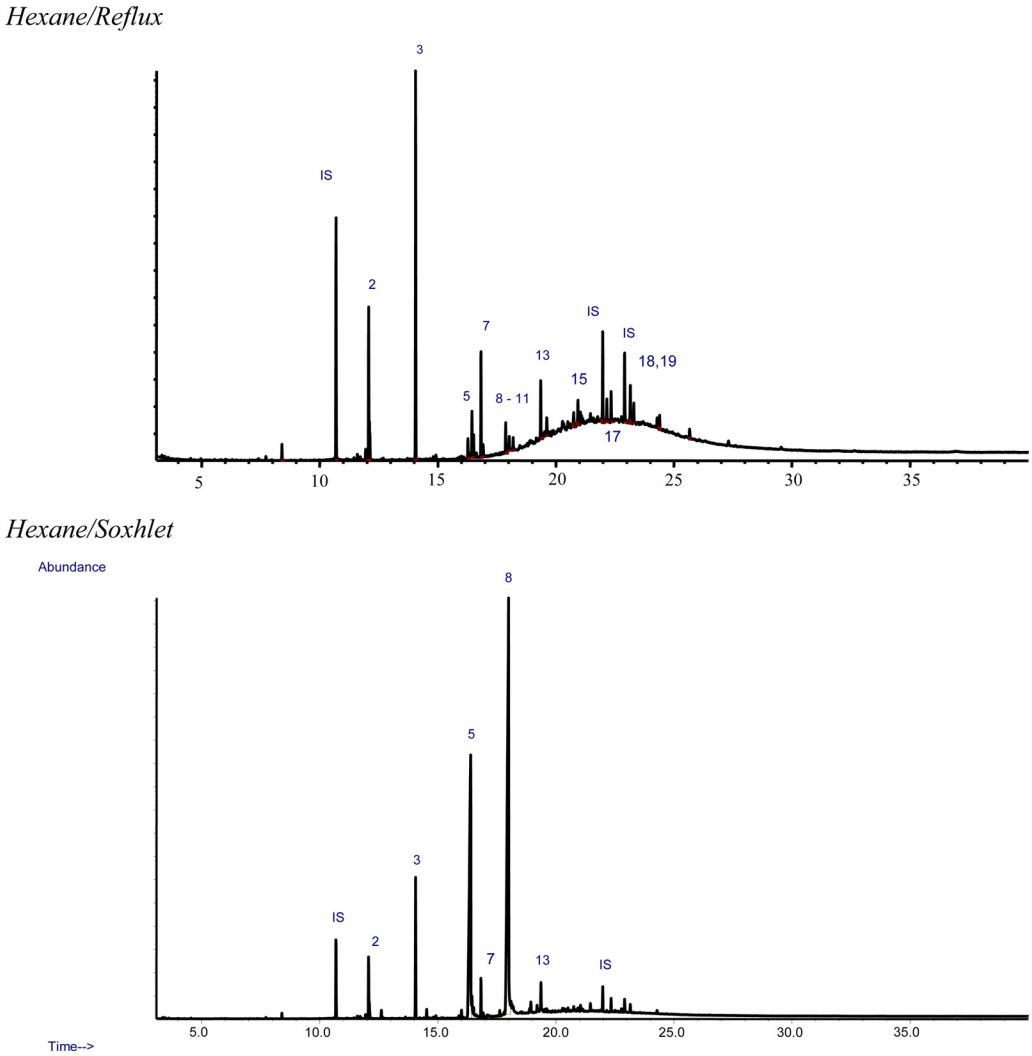

Figure 16

GC/MS Chromatograms (underivatized) for the Hexane Extracts for the Elastomer. The upper chromatogram is for the reflux extraction and the lower chromatogram is for the Soxhlet extraction. Extractables associated with the chromatographic peaks are summarized in Table XI. The major peaks in the chromatograms are. Peaks labeled IS are the internal standards, including 2-Fluorobiphenyl at 10.7 min, Irganox 415 at 22.0 min and Bisphenol M at 23.0 min. The chromatograms for both extraction conditions are similar and these chromatograms for the hexane extracts are similar to those for the IPA extracts, Figure 15.

Reflux and Soxhlet Extracts: Chromatograms for the various reflux and Soxhlet extracts are illustrated in Figures 15 through 17. Chemical information related to the identified extractables is summarized in Tables XI and XII. As was the case with the sealed vessel extracts, fatty acids such as stearic and palmitic acids were the predominant organic extractables in the reflux and Soxhlet extracts. Several specific oligomeric hydrocarbons, including brominated compounds, were present in these extracts at readily measurable levels. These extracts also contained readily measurable quantities of oleamide and related substances. As oleamide was not an intentional additive in the rubber, its source is unclear; it is possible that it is an unintentional additive, an impurity in either the base material or one of the intentional additives, or a contaminant in the test article arising from its handling. LC chromatograms revealed phenolic antioxidants in the test article such as butylated hydroxytoluene (BHT) and Irganox 1010. In general, the extractables profile was not greatly affected, qualitatively, by either the extraction process (Soxhlet versus reflux) or the extraction solvent (IPA/water versus IPA versus hexane). As the levels

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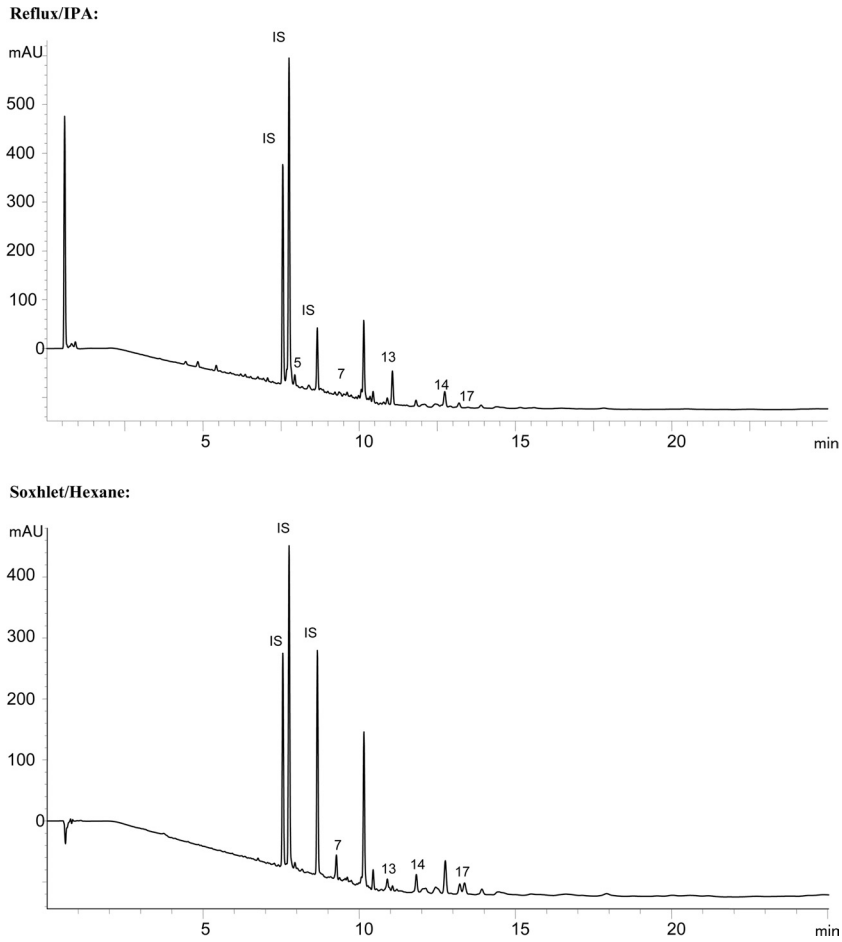

Figure 17

LC/UV (λ = 220 nm) Chromatograms of the IPA Reflux and Hexane Soxhlet Extracts for the Elastomer. The major peaks in the UV chromatogram are associated with the internal standards, Bisphenol M at 7.5 min, 2-Fluorobiphenyl at 7.7 min and Irgnaox 415 at 8.6 min. The major peaks associated with an extractable were antioxidant-related compounds, such as BHT and Irganox 1010 and a related degradation product (Table XII). The chromatograms also included several peaks whose associated substance could not be identified.

of the extractables in these extracts are relatively high, it is difficult to ascertain whether there are meaningful quantitative differences in the extractables profile as a function of extraction method and extraction solvent.

Summary: The extractables profile of the halobutyl elastomeric material has been established via the use of multiple extraction processes, multiple extracting media, and multiple analytical tests. This material's profile of organic extractables is summarized in Table XIII. These predominant organic extractables fall into several classes of compounds, readily linked to the specified major ingredients and/or additives in the test material. For example, the organic extractables profile included numerous hydrocarbons, which are typically associated with the materials' paraffinic oil and polyethylene additives, and brominated oligomers, which are well-known byproducts of the elastomer's polymerization and/or curing process (for example, reference 64). A second group of extractables are decomposition products of the material's accelerator (4,4'-dithiodimorpholine) and include morpholine itself and various related substances, such as fatty acid–morpholine reaction products. A third group of extractables consists of fatty acids and their associated methyl esters, which were extracted from the test material in relatively high quantities. Although these fatty acids cannot be readily linked to one of the specified additives in the test material, fatty acids and their metal salts are commonly used in the

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TABLE XIII

Organic Extractables Profile of the Rubber Material as Established by the Testing Performed in this Study; Identified Compounds Reproducibly Extracted from the Test Article at Levels of Approximately 1 μg/g or Greater

Identification	CAS RN	Chemical Formula	Molecular Weight	Concentration in Material, μg/g						
				Sealed Vessel			Reflux		Soxhlet	
				pH 2.5	pH 9.5	IPA/W	IPA	Hexane	IPA	Hexane
Octadecanoic (Stearic) acid[a]	57-11-4	$C_{18}H_{36}O_2$	284.47	—[d]	10–100	100–1000	10–100	100–1000	10–100	>1000
Hexadecanoic (Palmitic) acid[a]	57-10-3	$C_{16}H_{32}O_2$	256.42	—[d]	10–00	100–1000	10–100	>100	10–100	>1000
C-21 Oligomer[b,d]	—	$C_{21}H_{40}$	292.34	—[d]	—[d]	—[d]	100–1000	100–1000	100–1000	100–1000
Oxctadecanoic acid, methyl ester[b]	112-39-0	$C_{19}H_{38}O_2$	298.50	—[d]	1–10	>100	—[d]	—[d]	—[d]	—[d]
Hexadecanoic acid, methyl ester[b]	112-61-8	$C_{17}H_{34}O_2$	270.45	—[d]	1–10	>100	—[d]	—[d]	—[d]	—[d]
Dimethylterephthalate[a]	120-61-6	$C_{10}H_{10}O_4$	194.06	—[d]	—[d]	—[d]	100–1000	10–100	100–1000	10–100
Oleamide[a]	301-02-0	$C_{18}H_{35}NO$	281.27	—[d]	—[d]	—[d]	10–100	100–1000	10–100	10–100
Hexadecanoic acid, isopropyl ester[a]	142-91-6	$C_{19}H_{38}O_2$	298.50	—[d]	—[d]	6	10–100	10–100	10–100	10–100
Octadecane[b]	593-45-3	$C_{18}H_{38}$	254.49	—[d]	—[d]	—[d]	10–100	10–100	100–1000	10–100
Octacosane[a]	630-02-4	$C_{28}H_{58}$	394.45	—[d]	—[d]	—[d]	10–100	10–100	10–100	1–10
1-(4-Morpholinyl)-octanoic acid[b]	5299-54-7	$C_{22}H_{43}NO_2$	353.58	—[d]	—[d]	—[d]	10–100	10–100	10–100	10–100
Morpholine[a]	110-91-8	C_4H_9NO	87.07	P[e]	—[d]	—[d]	10–100	10–100	1–10	1–10
Tetracosane[a]	646-31-1	$C_{24}H_{50}$	338.39	—[d]	—[d]	—[d]	10–100	10–100	10–100	1–10
10-Oxo-octadecanoic acid[b]	870-10-0	$C_{19}H_{35}O_3$	312.27	—[d]	—[d]	10–100	10–100	10–100	1–10	10–100
4,4'-Dioctyldiphenylamine[a]	101-67-7	$C_{28}H_{43}N$	393.34	—[d]	—[d]	—[d]	10–100	10–100	10–100	10–100
Hexadecanamide[a]	629-54-9	$C_{15}H_{33}NO$	256.26	—[d]	—[d]	—[d]	10–100	1–10	1–10	—[d]
Docosane[b]	629-97-0	$C_{22}H_{46}$	310.36	—[d]	—[d]	—[d]	10–100	1–10	1–10	—[d]
Nonadecanoic acid[c]	646-30-0	$C_{19}H_{38}O_2$	298.50	—[d]	10–100	10–100	—[d]	—[d]	—[d]	—[d]

Notes:

[a]These identifications are classified as confirmed.

[b]These identifications are classified as confident.

[c]These identifications are classified as tentative.

[d]1-Isopropenyl-2,2,4,4-tetramethyl-6-(2,2,4-trimethyl-pentyl-1-)-cyclohexane.

[d]— = not present in this extract at detectable levels.

[e]P = present in this extract but not quantified.

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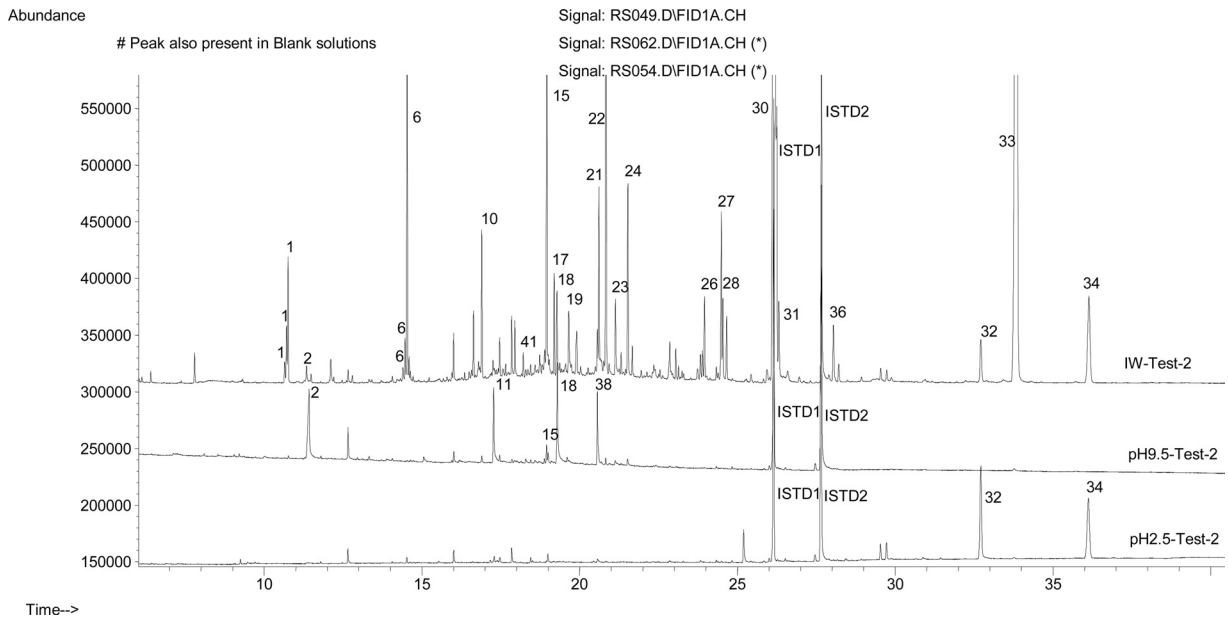

Figure 18

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts of the LDPE (underivatized sample preparation). Peaks ISTD1 and ISTD2 are the two internal standards (1 = Irganox 415 and 2 = Bisphenol M), reflecting compounds present in the extract at a concentration of approximately 1 mg/L (ppm). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. See Table XIV for a summary of information about the numbered peaks, all of which were ascribed to extracted substances.

manufacturing of halobutyl rubbers as process aids. The fatty acids might also be derived as impurities in, or hydrolysis products of, the materials' paraffinic oil, although this is most likely a secondary source of the fatty acid extractables. While oleamide was a major extractable in the organic extracts, it was not a specified additive in the rubber, and its source is unknown. It is possible that it is an unintentional additive, an impurity in either the base material or one of the intentional additives, or a contaminant in the test article arising from materials used in its handling. Finally, the organic extracts contained readily measurable quantities of Irganox 1010 and BHT, antioxidants that are commonly employed in halobutyl rubbers (for example, reference 64).

Extracted metals were directly associated with either the base material or its additives; for example, Br, the predominant elemental extractable, is derived from the brominated isobutylene isoprene copolymer. Other significant extracted elements, including Ca, Na, Al, and Si, are derived from the material's calcined aluminum silicate. Extractable metals associated with the calcined magnesium oxide included Mg and Ca. Metals that were present in the test article as their respective oxides, including Zn and Ti, were extracted from the test article in relatively lower amounts.

Low-Density Polyethylene, LDPE

Introduction: Various grades of polyethylene are used in a wide variety of pharmaceutical applications, including packaging films, tubing, bottles and caps, IV set components, and others. Polyethylene is a generic material description that refers to several functionally distinct materials that share a similar composition. LDPE contains many long-chain branches along the polymer backbone, preventing the alignment and packing of the chains and thus forming a low-density material. LDPE generally has a good balance of flexibility, strength, barrier properties, clarity, tear and crack resistance, and cost. It is resistant to low-dose radiation, and this radiation resistance can be enhanced with appropriate additives (both stabilizers and colorants). Given these properties, LDPE is widely used in pharmaceutical packaging (flexible bags, fluid bottles, single dose ampoules, caps and luers, blister packs).

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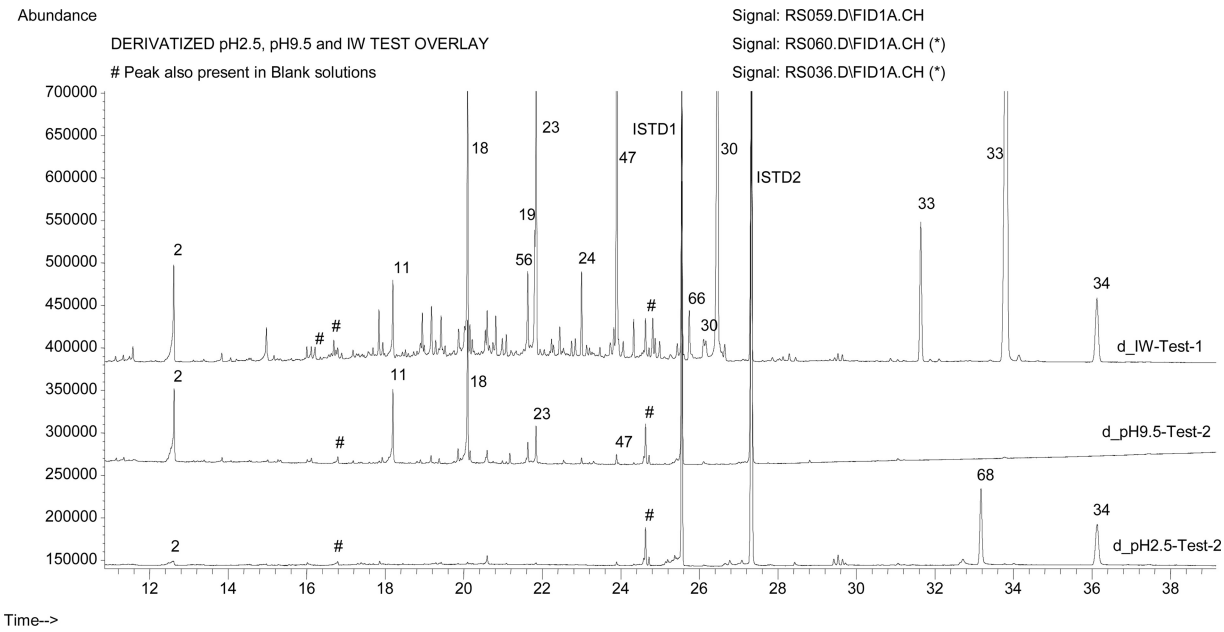

Figure 19

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts of the LDPE (derivatized sample preparation). Peaks ISTD1 and ISTD2 are the two internal standards (1 = Irganox 415 and 2 = Bisphenol M), reflecting compounds present in the extract at a concentration of approximately 1 mg/L (ppm). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. See Table XIV for a summary of information about the numbered peaks, all of which were ascribed to extracted substances.

PE materials used in packaging contain additives to provide it with the desired functionality, stability, and appearance-related properties. The European Pharmacopeia (Ph. Eur.), section 3.1.5, specifies additives limits for materials used in polyethylene containers for parenteral and ophthalmic preparations, based on compliance with stated formulations (65). Furthermore, the Ph. Eur. indicates that materials with formulations other than those described in the monograph would be subject to additional testing and approval. Given their wide use as pharmaceutical polymers, polyethylene materials have been extensively characterized for their extractables and leachables characteristics in numerous applications (66–76).

Test Article: The test article film was a representative LDPE formulation. The base resin was Dow 640-1-LDPE, supplied as a barefoot resin with no additives. Additives including Irganox B 215 (2:1 blend of Irgafos 168 and Irganox 1010), 1000 ppm (μg/g); BHT (2,6-Bis(1,1-dimethylethyl)-4-methyl-phenol), 200 ppm; calcium stearate, 500 ppm; erucamide ((z)-13-Docosenamide), 500 ppm; and Chimassorb 944 (Poly[[6-[(1,1,3,3-tetramethylbutyl)amino]-1,3,5-triazine-2,4-diyl][(2,2,6,6-tetramethyl-4-piperidinyl)imino]-1,6-hexanediyl[(2,2,6,6-tetramethyl-4-piperidinyl)imino]]), 2000 ppm were added to the barefoot resin. This test article was formulated to facilitate this study and it was not intended to be compliant with the Ph. Eur. The test article is not used in commercial products, but is representative of LDPE materials used in pharmaceutical applications.

Elemental Analysis: The results of the analysis of the aqueous extracts for extracted elements are summarized in Table VII. Most of the targeted elements were not reproducibly extracted from the LDPE test article in reportable quantities, where the reporting threshold was approximately 0.01 μg/g, and none of the targeted elements was extracted at levels higher than 1 μg/g. The predominant acid-extracted elements included the alkali and alkaline earth metals such as Na (1.0 μg/g) and Mg (0.2 μg/g). Individual metals, such as Fe, Al, Zn, Mn, and Co, were present in the acid extracts at levels of 0.1 μg/g or lower. Fewer elements were present at lower levels in the high pH extracts. This suggests that the trace elements and metals are extracted out of the LDPE

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TABLE XIV
Information Related to the GC Peaks Associated with Organic Extractables from the LDPE

Peak #		Identification	CAS RN	Highest Conc In Extract	
Set A[a]	Set B[b]			Medium	Type
33[h]	1	Irgafos 168[e]	31570-04-4	Hexane	Soxhlet
33[h]	2	Irgafos 168 Oxide[e]	95906-11-9	IPA	Reflux
30	3	Erucamide[e]	112-84-5	IPA	Reflux
—	4	Irganox PS800[f]	123-28-4	IPA	Soxhlet
—	5	Oleamide[e]	301-02-0	IPA	Reflux
23	6	Octadecanoic (Stearic) acid[e]	57-11-4	IPA	Soxhlet
—	7	Aliphatic amide[g]	—	Hexane	Reflux
43	8	Stearamide[e]	124-26-5	IPA	Reflux
—	9	Hexadecanamide[e]	629-54-9	IPA	Reflux
—	10	Di-(2-ethyhexyl) phthalate (DEHP)[e]	117-81-7	Hexane	Soxhlet
—	11	Unknown[g], Empirical formula = $C_{26}H_{24}O_{13}$	—	IPA	Soxhlet
18	12	Hexadecanoic (Palmitic) acid[e]	57-10-3	IPA	Soxhlet
—	13	Aliphatic hydrocarbon[g], Empirical formula = $C_{10}H_{20}$	—	Hexane	Soxhlet
—	14	Butylated hydroxytoluene (BHT)[e]	128-37-0	IPA	Reflux
—	15	C21-oligomer[g], Empirical formula = $C_{21}H_{40}$	—	IPA	Reflux
—	16	Unspecified Amide[g]; Empirical formula = $C_5H_{11}NO$	—	Hexane	Soxhlet
—	17	Aliphatic hydrocarbon[g]; Empirical formula = $C_{12}H_{24}$	—	Hexane	Soxhlet
22	—	Octadecanoic acid, methyl ester[f]	112-61-8	IPA/Water	Sealed
15	—	Hexadecanoic acid, methyl ester[f]	112-39-0	IPA/Water	Sealed
1	—	Nonanoic acid, methyl ester[f]	1731-84-6	IPA/Water	Sealed
10	—	Tetradecanoic acid, methyl ester[f]	124-10-7	IPA/Water	Sealed
21	—	9-Octadecenoic acid, methyl ester[f]	1937-62-8	IPA/Water	Sealed
6	—	2,4-Di-t-butylphenol[e]	96-76-4	IPA/Water	Sealed
Various[c]	—	Erucamide-related compounds[g]	—	IPA/Water	Sealed
2	—	Nonanoic acid[e]	112-05-0	pH 9.5	Sealed
11	—	Tetradecanoic (Myristic) acid[f]	544-63-8	pH 9.5	Sealed
34	—	Chimassorb 944 Monomer[f]	71878-19-8	IPA/Water	Sealed
Various[d]	—	Chimassorb 944-related compound[g]	—	pH 2.5	Sealed
31	—	Docosanamide[f]	3061-75-4	IPA/Water	Sealed

Notes:
[a]In the sealed vessel extracts, see Figures 18, 19. These extracts also contained extractables whose identities could not be established, specifically peaks 17, 19, 41, 56, 66, 68.
[b]In the solvent extracts, Soxhlet and Reflux, see Figures 22 and 23.
[c]Although the compounds associated with some peaks could not be identified, it was established that they were erucamide-related. Such peaks included 24, 26, 27, 28, and 36.
[d]Although the compounds associated with some peaks could not be identified, it was established that such peaks were related to Chimassorb 944. Such peaks included 32, 37 and 47.
[e]These identifications are classified as confirmed.
[f]These identifications are classified as confident.
[g]These identifications are classified as tentative.
[h]The oxide is the earlier eluting peak in the IPA/Water chromatogram shown in Figure 19.

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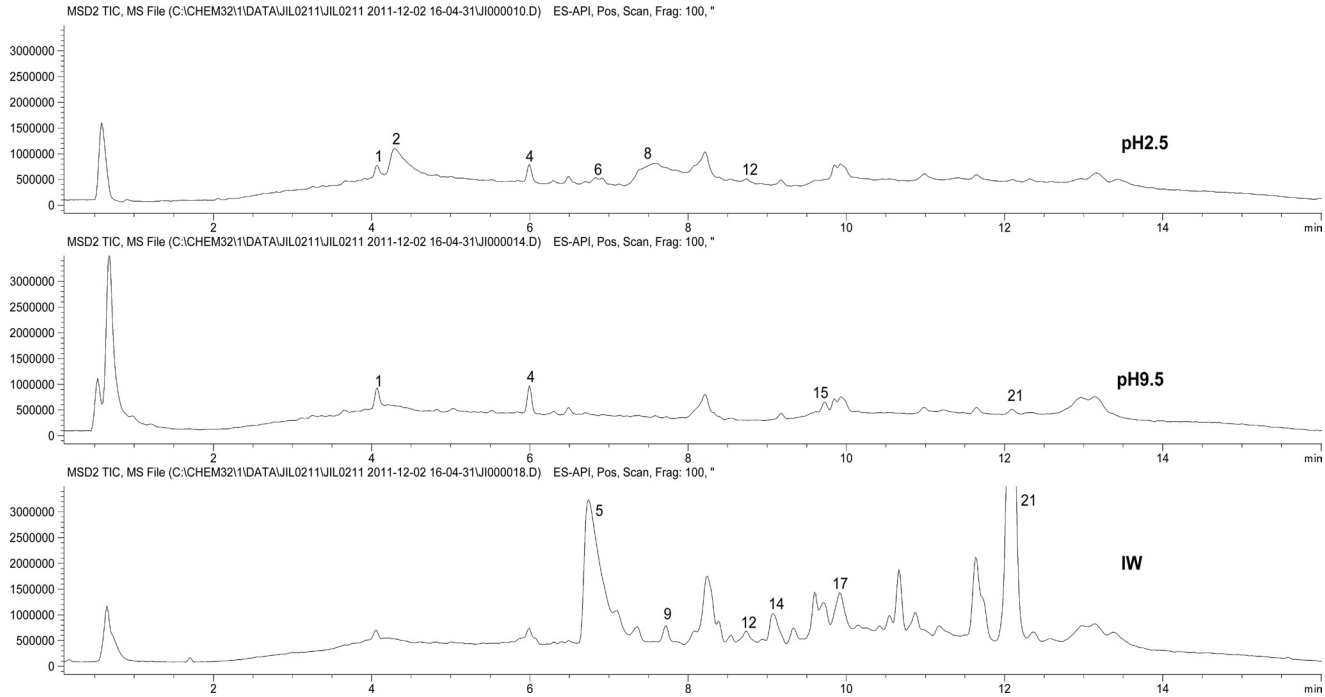

Figure 20

LC/MS TIC (Total Ion Current) Chromatograms, positive ion mode, of the Sealed Vessel Extracts for the LPDE. See Table XV for the identities, as available, for the numbered extractables. Peaks that are not numbered were present in the extraction blanks and thus are not associated with extractables. The lower chromatogram is the IPA/water extract, the middle chromatogram is the pH 9.5 extract and the upper chromatogram is the pH 2.5 extract.

from undetermined sources. As the extracts did not contain measureable quantities of Ca, even though the material contained calcium stearate, it is likely that the major extraction process is not ion exchange with constituent salts.

Volatile Components: A headspace GC/MS chromatograms contained several peaks generally associated with hydrocarbons, including butylated oligomers, at low levels, approximately 1 μg/g or less.

Organic Extractables:

Sealed Vessel Extracts: Typical GC/FID chromatograms obtained for the sealed vessel extracts are shown in Figures 18 and 19. Information for the extractables that were ascribed to the major chromatographic peaks is summarized in Table XIV. LC chromatograms obtained for the sealed glass vessel extracts are shown in Figures 20 and 21. Information related to the extractables peaks in the LC chromatograms is summarized in Table XV. The extractables profiles of the aqueous extracts reflect the pH of the extracts and the varying nature of the LDPE ingredients. For example, the low-pH extracts were dominated by amine-type compounds associated with the Chimasorb 944 additive. Alternatively, the high-pH extracts were dominated by extracted fatty acids that are most likely associated with the calcium stearate. Few other substances were detected in these extracts, with the exception of very low levels of relatively polar degradation products of the antioxidants.

The chromatographic analyses indicated that the IPA/water extracts contained more numerous extractables at higher concentrations than did the aqueous extracts. Figures 18 through 21 clearly illustrate the effect that the extracting solvent had on the extractables profile. The IPA/water extracts contain the same fatty acids that were present in the aqueous extracts but at higher concentrations, as well as additional fatty acids (and their methyl esters) which were not present in the aqueous extracts at detectable levels. The IPA/water extracts contained the same Chimassorb 944–related substances that were present in the low-pH aqueous extracts. More significantly, however, the IPA/water extracts contained relatively large quantities of several

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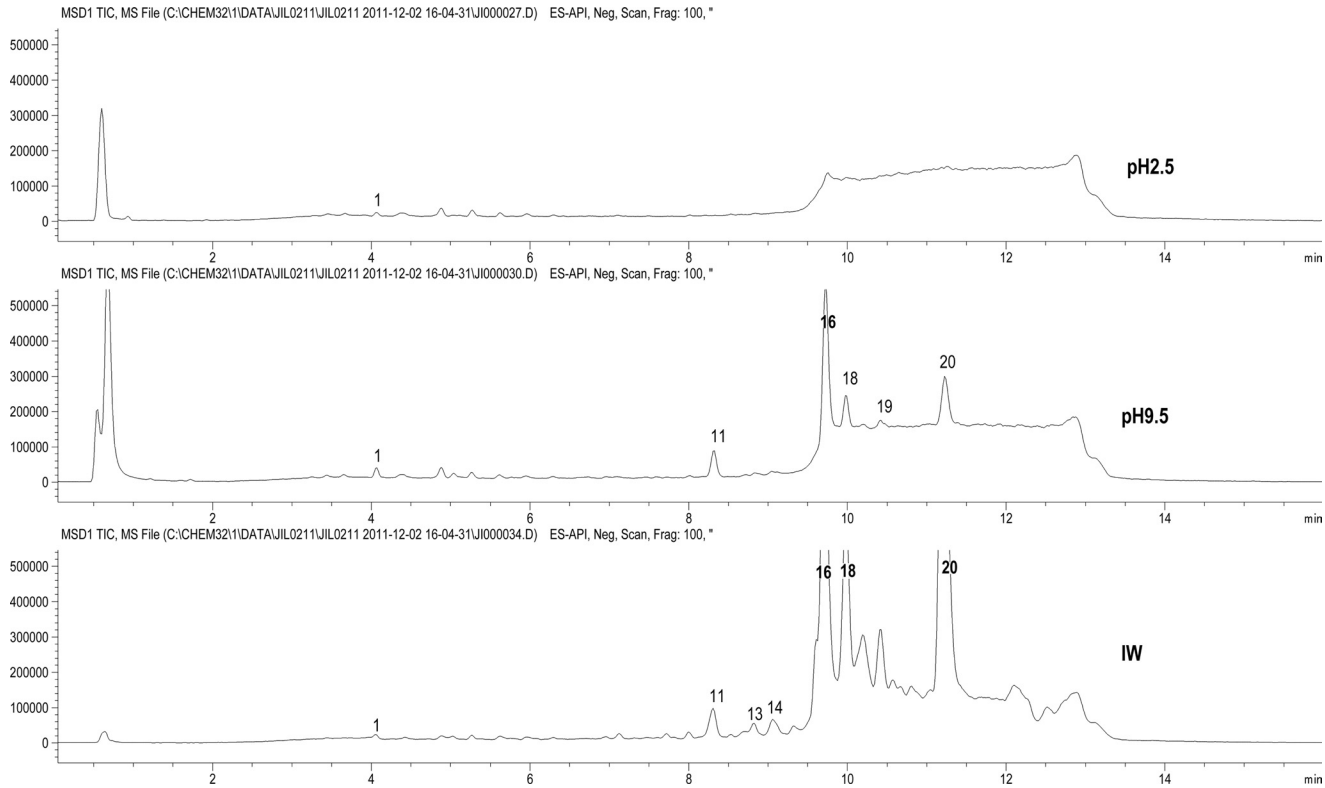

Figure 21

LC/MS TIC (Total Ion Current) Chromatograms, negative ion mode, of the Sealed Vessel Extracts for the LPDE. See Table XV for the identities, as available, for the numbered extractables. Peaks that are not numbered were present in the extraction blanks and thus are not associated with extractables. The lower chromatogram is the IPA/water extract, the middle chromatogram is the pH 9.5 extract and the upper chromatogram is the pH 2.5 extract.

of the LDPE's additives and their associated related substances. For example, erucamide was a predominant extractable in the IPA/water sealed vessel extracts, which also contained lower quantities of other fatty acid amides. Irgafos 168 and its related oxidation products were also present in the IPA/water extracts at relatively larger levels. Additionally, the IPA/water extracts contained numerous other additive-derived substances, such as decomposition products or impurities.

Reflux and Soxhlet Extracts: Chromatograms obtained for the reflux and Soxhlet extracts are illustrated in Figures 22 through 24. Chemical information for the identified extractables is summarized in Tables XIV and XV. The reflux and Soxhlet extracts generally contained the same extractables as did the IPA/water sealed vessel extracts but at higher levels. The Irgafos 168 additive and erucamide were almost completely extracted from the LDPE, as their levels in the extracts are nearly equal to their levels in the LDPE itself. While the other additives were present in the extracts in measurable quantities, their level in the extracts were lower than their total pool in the test article. For example, LC chromatograms revealed phenolic antioxidants in the extracts, specifically BHT and Irganox 1010. The chromatograms obtained for the solvent-based extracts clearly establish how extractables profiles can become complex due to impurities in, and degradation products of, the intended additives. For example, the extracts contained measurable quantities of oleamide and other amide-related substances in addition to extracted erucamide, a known additive. Finally, chromatographic analysis of the organic solvent extracts revealed an additive, Irganox PS800 (3,3'-Thiobis-propanoic acid, 1,1'-didodecyl ester), which was not specified in the test article's composition list.

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TABLE XV
Summary of Identified Organic Extractables from the LDPE, LC Analysis

Peak #		Identification	CAS RN
Set A[a]	Set B[b]		
12	5	Irgafos 168[c]	31570-04-4
—[e]	4	Irgafos 168 oxide[c]	95906-11-9
—	3	Irganox 1010[c]	6683-19-8
5	1	Chimassorb 944 monomer[d]	—
—[e]	2	Butylated hydroxytoluene (BHT)	128-37-0
4	—	Tetradecanamide	638-58-4
11	—	Tetradecanoic (myristic) acid[c]	544-63-8
16	—	Hexadecanoic (palmitic) acid[c]	57-10-3
20	—	Octadecanoic (stearic) acid[c]	57-11-4
21	—	Erucamide[c]	112-84-5
18	—	Oleic acid[c]	112-80-1
13	—	Palmitoleic acid[d]	373-49-9
1, 17	—	Erucamide-related substances [d]	—
2	—	Chimassorb degradation product[d]	—

Notes:
[a]In the sealed vessel extracts, see Figures 20 and 21. These extracts also contained extractables whose identities could not be established, specifically peaks 3, 6, 8, 9, 14, 15, and 19.
[b]In the solvent extracts, Soxhlet and reflux, see Figure 24. The chromatogram also contained peaks whose associated substance could not be identified.
[c]These identifications are classified as either confident or confirmed.
[d]Tentative identification.
[e]This peak was present in the extract chromatogram but was not labeled in the relevant figure.

Summary: The extractables profile of the LDPE material was established via multiple extraction processes, multiple extracting media, and multiple analytical tests. This material's profile of organic extractables is summarized in Table XVI. These predominant organic extractables generally fall into classes of compounds readily linked to the specified major ingredients and/or additives in the test material. For example, the organic extractables profile includes erucamide (and other related amides), Irgafos 168, Irganox 1010, and BHT (and their related oxidation products), fatty acids (associated with stearate salts), and substances related to the material's light stabilizer, Chimassorb 944.

The few metals that were extracted from the test article were present in the acid extract at very low levels; while Na and Mg were extracted at levels between 0.1 and 1 μg/g, metals, such as Fe, Al, Zn, Mn, and Co, were extracted in amounts less than 0.1 μg/g. The source and extraction mechanism for these metals were not established.

Polycarbonate, PC

Introduction: Polycarbonate based on Bisphenol A (BPA) has been commercially available since the 1960s and has been utilized in packaging and device applications since that time. Polycarbonate possesses several properties that make it a suitable replacement for glass or metal, including strength, rigidity, toughness, clarity, and general biocompatibility. Medical applications of polycarbonates include their use as components in injection systems, packaging systems, devices (as connectors and housings), and in surgical instruments. Despite its use in or as packaging components, polycarbonate is rarely used as a primary material in pharmaceutical packaging.

Polycarbonates are produced by polymerization of a monomer containing hydroxyl end groups (aliphatic diols or aromatic phenols) and phosgene. The most common and well-known PC is produced by the

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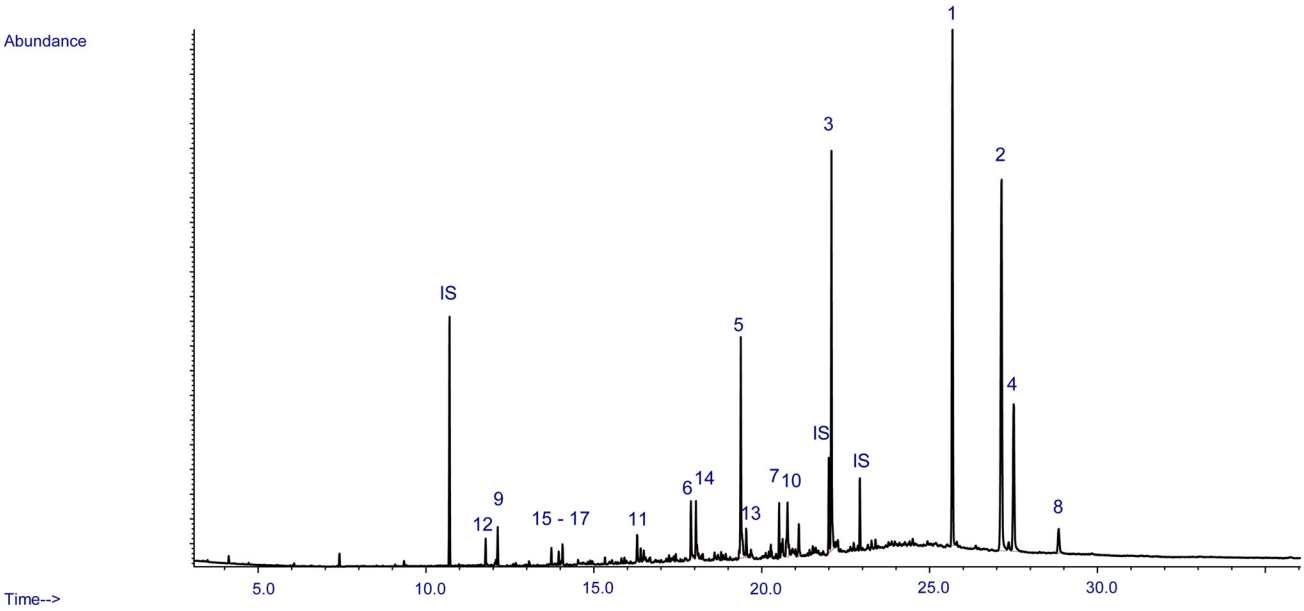
Reflux/IPA



Soxhlet/IPA

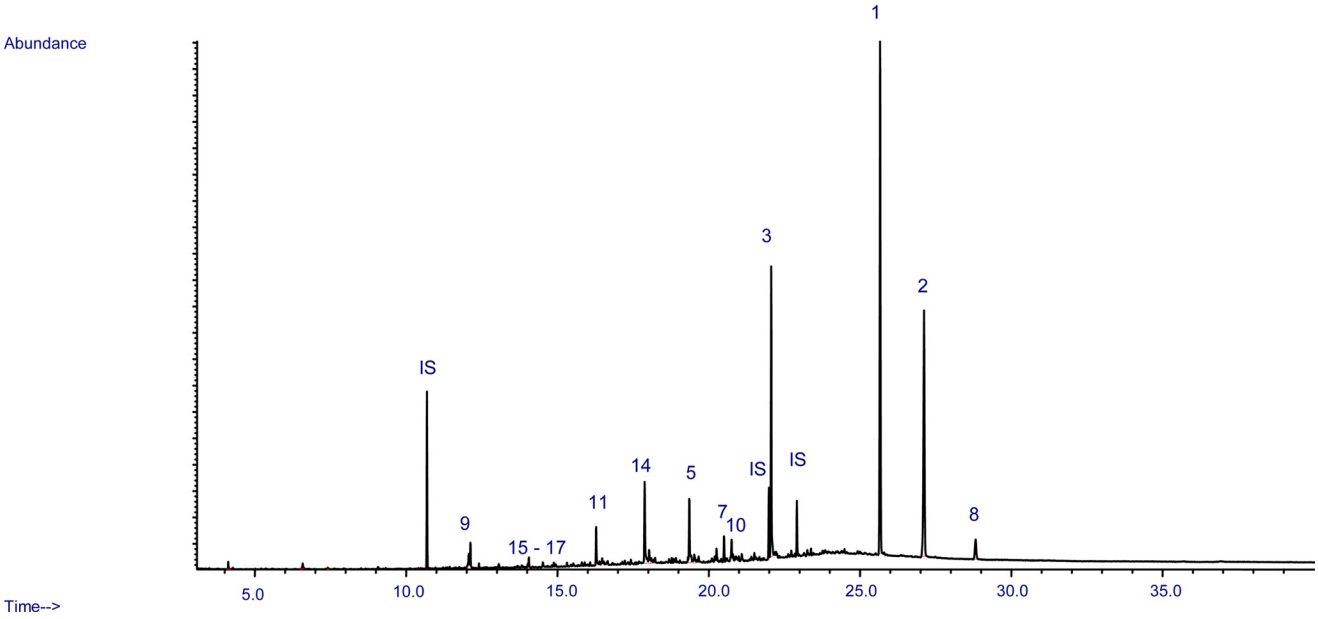


Figure 22

GC/MS Chromatograms (underivatized) for the IPA Extracts for the LDPE. The upper chromatogram is for the reflux extraction and the lower chromatogram is for the Soxhlet extraction. Extractables associated with the chromatographic peaks are summarized in Table XIV. The peaks labeled IS are the internal standards. Internal standards producing peaks in these chromatograms include 2-Fluorobiphenyl at 10.7 min, Irganox 415 at 22.0 min and Bisphenol M at 23.0 min. The chromatograms for both extraction conditions are similar and these chromatograms for the IPA extracts are similar to those for the hexane extracts, Figure 23.

reaction of BPA and phosgene. More recently, commercialized PCs are produced using other monomers from the bisphenol family. Polycarbonates typically contain one or more additives for stabilization and property enhancement. While polycarbonates are relatively resistant, they degrade and discolor under certain conditions, especially exposure to radiation; thus the PC polymer is stabilized

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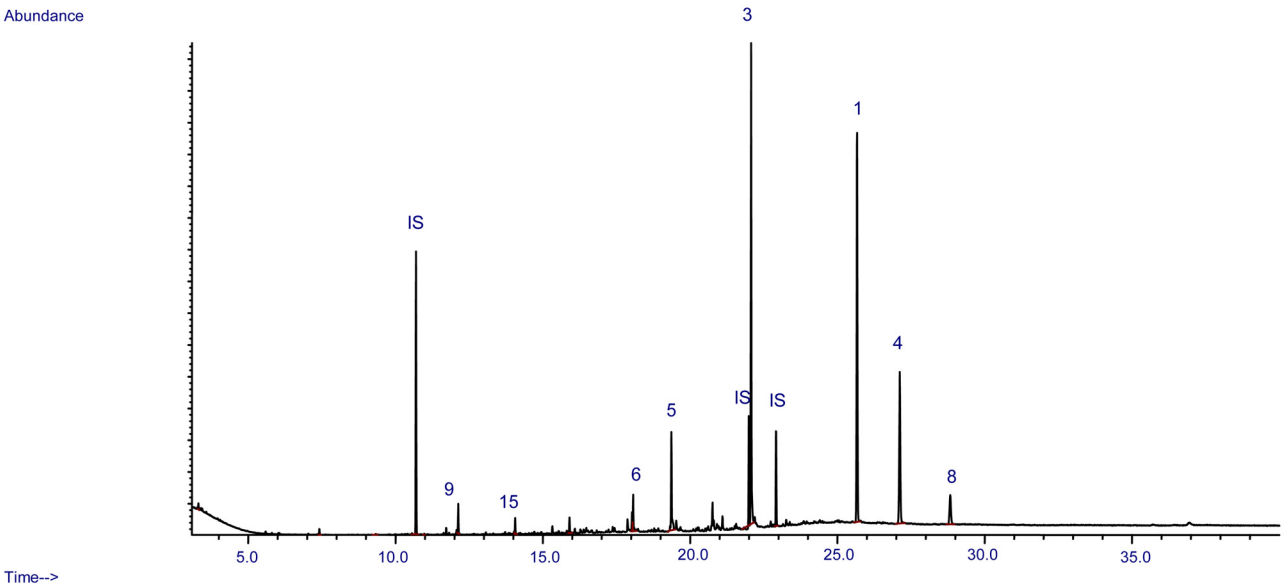
Hexane/Reflux



Hexane/Soxhlet

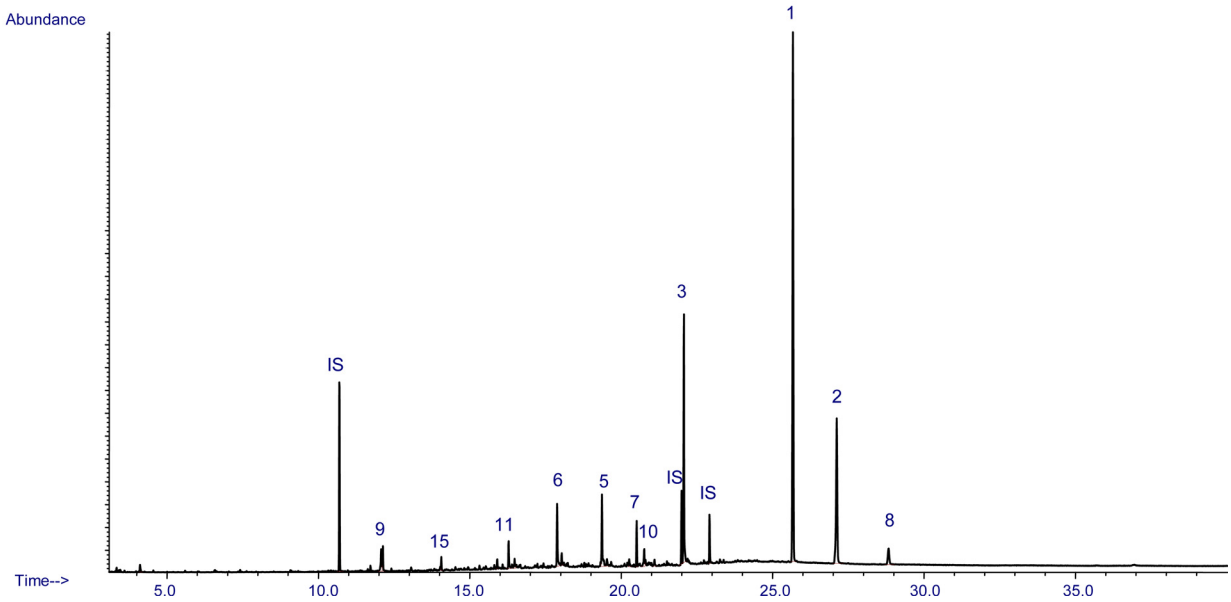


Figure 23

GC/MS Chromatograms (underivatized) for the Hexane Extracts for the LDPE. The upper chromatogram is for the reflux extraction and the lower chromatogram is for the Soxhlet extraction. Extractables associated with the chromatographic peaks are summarized in Table XIV. The peaks labeled IS are the internal standards. Internal standards producing peaks in these chromatograms include 2-Fluorobiphenyl at 10.7 min, Irganox 415 at 22.0 min and Bisphenol M at 23.0 min. The chromatograms for both extraction conditions are similar and these chromatograms for the hexane extracts are similar to those for the IPA extracts, Figure 22.

by the addition of free radical and/or acid scavengers. Additionally, discoloration caused by degradation may be masked by colorants. As PC is molded into parts for medical and pharmaceutical applications, it may contain process residuals such as mold release agents. Additional extractables from PC includes its monomers and shorter chain oligomers. Polycarbonate has been extensively character-

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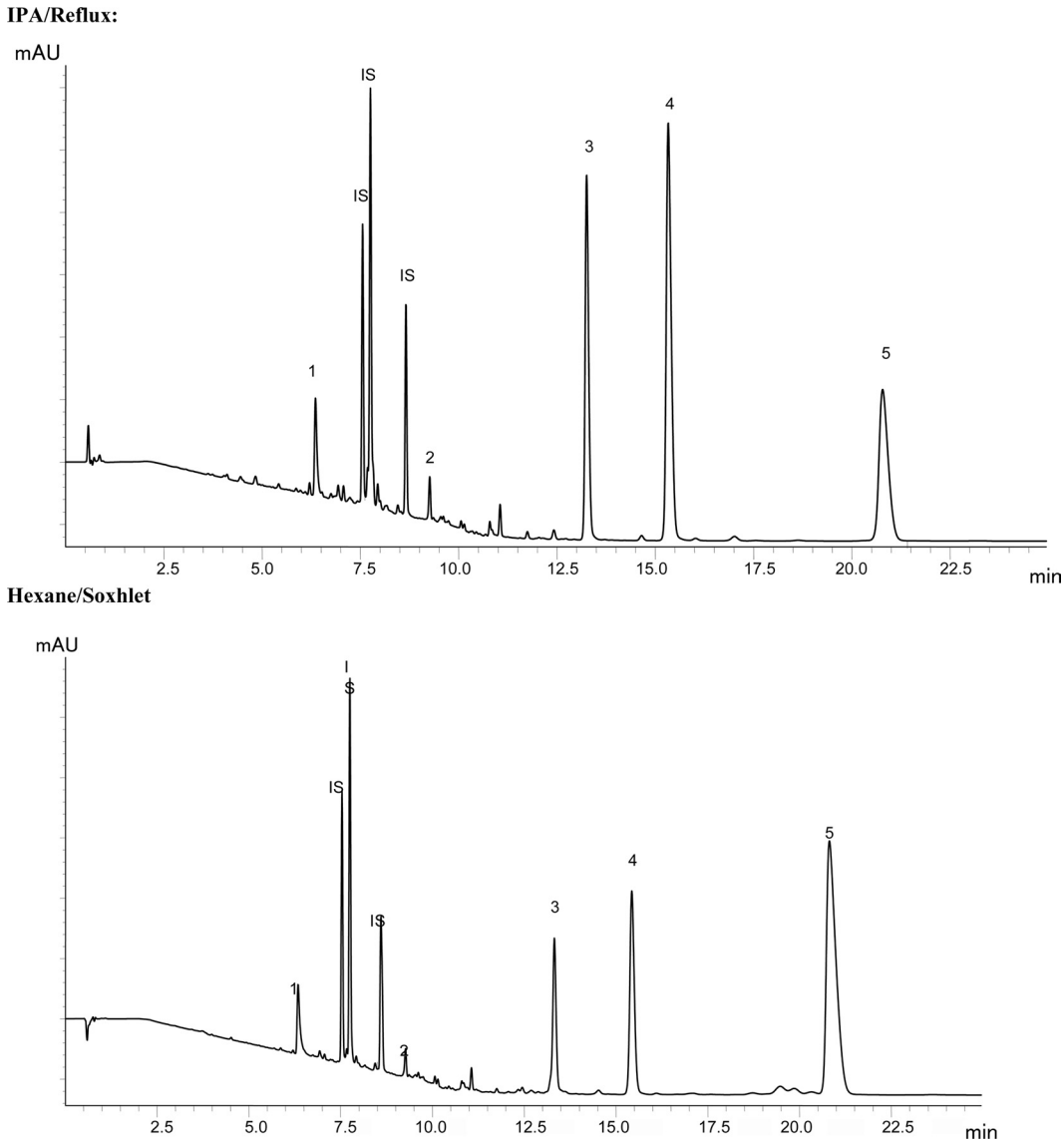

Figure 24

LC/UV (λ = 220 nm) Chromatograms of Reflux Extracts for the LDPE. The peaks associated with the internal standards, Bisphenol M at 7.5 min, 2-Fluorobiphenyl at 7.7 min and Irganox 415 at 8.6 min, are labeled as IS. The major peaks associated with an extractables were antioxidants, such as Irganox 1010 and Irgafos 168, and their associated decomposition products (Table XV). The chromatograms also included several peaks whose associated substance could not be identified.

ized in terms of its leaching characteristics in non-pharmaceutical applications, given its extensive use in, for example, the food industry. References 10, 11, 63, and 77–82 are more specifically focused on polycarbonate used in pharmaceutical applications.

Test Article: The PC test material was BPA-based and was supplied as injection molded plaques. This material contained 0.05 phr (parts per hundred) Irganox 1076 (3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid, octadecyl ester) and 0.1 phr Irgafos 168 and could also have contained molding residuals. Although this test article is representative of materials used in pharmaceutical applications, it is not specifically used in commercial products.

Elemental Analysis: The levels of extracted elements in the aqueous extracts are summarized in Table VII. Most of the targeted elements were not reproducibly extracted from

TABLE XVI

Organic Extractables Profile of the LDPE Material as Established by the Testing Performed in this Study; Identified Compounds Reproducibly Extracted from the Test Article at Levels of Approximately 1 μg/g or Greater

Identification	CAS RN	Chemical Formula	Molecular Weight	Concentration in Material, μg/g						
				Sealed Vessel			Reflux		Soxhlet	
				pH 2.5	pH 9.5	IPA/W	IPA	Hexane	IPA	Hexane
Irgafos 168[a]	31570-04-4	$C_{42}H_{63}O_3P$	646.92	—[d]	—[d]	10–100	100–1000	100–1000	100–1000	100–1000
Irgafos 168 Oxide[a]	95906-11-9	$C_{42}H_{63}O_4P$	662.92	—[d]	—[d]	100–1000	100–1000	100–1000	100–1000	100–1000
Erucamide[a]	112-84-5	$C_{22}H_{43}NO$	337.58	—[d]	—[d]	100–1000	100–1000	100–1000	100–1000	100–1000
Irganox PS800[b]	123-28-4	$C_{30}H_{58}O_4S$	514.41	—[d]	—[d]	—[d]	100–1000	100–1000	100–1000	100–1000
Oleamide[a]	301-02-0	$C_{18}H_{35}NO$	281.48	—[d]	—[d]	—[d]	100–1000	10–100	10–100	10–100
Octadecanoic (Stearic) acid[a]	57-11-4	$C_{16}H_{36}O_2$	284.48	—[d]	1–10	10–100	10–100	10–100	10–100	10–100
Octadecanoic acid, methyl ester[b]	112-61-8	$C_{19}H_{38}O_2$	298.50	—[d]	—[d]	10–100	—[d]	—[d]	—[d]	—[d]
Hexadecanoic acid, methyl ester[b]	112-39-0	$C_{17}H_{34}O_2$	270.45	—[d]	1–10	10–100	—[d]	—[d]	—[d]	—[d]
Stearamide[a]	124-26-5	$C_{18}H_{37}NO$	283.49	—[d]	—[d]	—[d]	10–100	10–100	—[d]	10–100
Chimassorb 944-related substance[c]	—	—	—	10–100	—[d]	10–100	10–100	10–100	—[d]	10–100
Di-(2-ethyhexyl) phthalate (DEHP)[a]	117-81-7	$C_{24}H_{38}O_4$	390.28	—[d]	—[d]	—[d]	10–100	10–100	—[d]	10–100
Unknown[c]	—	$C_{26}H_{24}O_{13}$	—	—[d]	—[d]	—[d]	10–100	10–100	10–100	10–100
2,4-Di-t-butyl phenol[a]	96-76-4	$C_{14}H_{22}O$	206.32	—[d]	—[d]	10–100	—[d]	—[d]	—[d]	—[d]
Butylated hydroxytoluene (BHT)[a]	128-37-0	$C_{15}H_{24}O$	220.35	—[d]	—[d]	—[d]	10–100	10–100	10–100	10–100
Hexadecanoic (Palmitic) acid[a]	57-10-3	$C_{16}H_{32}O_2$	256.42	—[d]	10–100	10–100	10–100	10–100	—[d]	10–100
Aliphatic hydrocarbon[c]	—	$C_{10}H_{20}$	—	—[d]	—[d]	—[d]	10–100	10–100	10–100	10–100
Aliphatic amide[c]	—	—	—	—[d]	—[d]	—[d]	10–100	10–100	10–100	10–100
Hexadecanamide[a]	629-54-9	$C_{16}H_{33}NO$	255.45	—[d]	—[d]	—[d]	10–100	10–100	1–10	10–100
C21-oligomer[c]	—	$C_{21}H_{40}$	292.60	—[d]	—[d]	—[d]	10–100	1–10	1–10	10–100
Unspecified Amide[c]	—	$C_5H_{11}NO$	—	—[d]	—[d]	—[d]	10–100	1–10	10–100	10–100
Nonanoic acid, methyl ester[b]	1731-84-6	$C_{10}H_{20}O_2$	172.26	—[d]	—[d]	10–100	—[d]	—[d]	—[d]	—[d]
9-Octadecenoic acid, methyl ester[b]	1937-62-8	$C_{19}H_{36}O_2$	296.49	1–10	1–10	10–100	—[d]	—[d]	—[d]	—[d]
Nonanoic acid[a]	112-05-0	$C_9H_{18}O_2$	158.13	1–10	10–100	10–100	1–10	1–10	—[d]	1–10
Aliphatic hydrocarbon[c]	—	$C_{12}H_{24}$	—	—[d]	—[d]	—[d]	1–10	1–10	1–10	>10
Docosanamide[b]	3061-75-4	$C_{22}H_{45}NO$	339.60	—[d]	—[d]	10–100	—[d]	—[d]	—[d]	—[d]
Tetradecanoic (Myristic) acid[b]	544-63-8	$C_{14}H_{28}O_2$	228.37	—[d]	10–100	10–100	—[d]	—[d]	—[d]	—[d]

Notes:

[a]These identifications are classified as confirmed.

[b]These identifications are classified as confident.

[c]These identifications are classified as tentative.

[d]— = not present in this extract at detectable levels.

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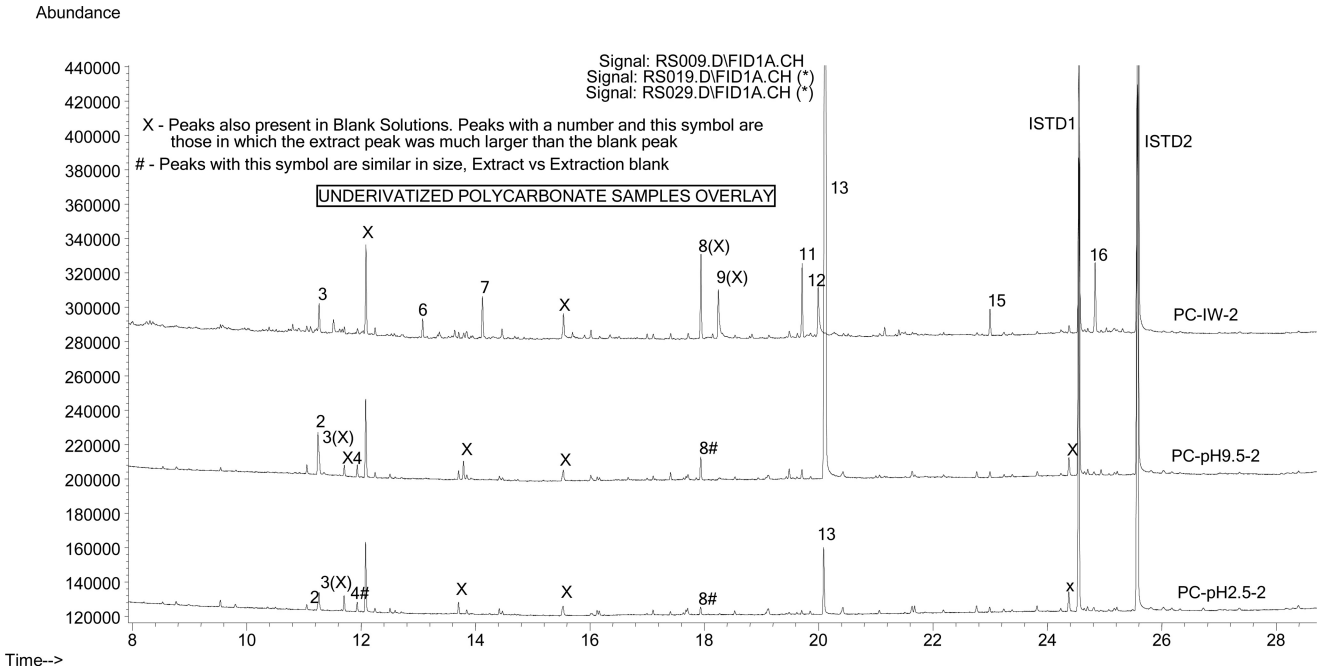

Figure 25

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts of the Polycarbonate, PC (underivatized sample preparation). Peaks ISTD1 and ISTD2 are the two internal standards (1 = Irganox 415 and 2 = Bisphenol M), reflecting compounds present in the extract at a concentration of approximately 1 mg/L (ppm). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. See Table XVII for a summary of information about the numbered peaks, all of which were ascribed to extracted substances.

the PC in reportable quantities, where the reporting threshold was approximately 0.01 μg/g. The levels of extracted metals are greatest in the low pH extracts, suggesting that the extraction mechanism could be ion exchange. The predominant extracted elements include the alkali and alkaline earth metals such as Ca (6.6 μg/g), Na (1.0 μg/g), and Mg (0.2 μg/g). Bromine (Br) was present in the pH 2.5 extracts at a level of approximately 1 μg/g. Among the metals, iron was present in the pH 2.5 extracts at levels of 0.7 μg/g or less, while Zn and Cr were present in the pH 2.5 extracts at levels of 0.1 μg/g or less.

Volatile Components: The headspace GC/MS chromatograms contained a few peaks related to volatiles present in the test article at low levels, including nonanal (0.12 μg/g), acetone (0.09 μg/g), and methyl isocyanide (0.08 μg/g).

Organic Extractables:

Sealed Vessel Extracts: Typical GC/FID chromatograms obtained for the sealed vessel extracts are shown in Figures 25 and 26. Information for the extractables that were ascribed to the major chromatographic peaks is summarized in Table XVII. LC chromatograms obtained for the sealed vessel extracts are shown in Figure 27. As was anticipated, there were relatively few extracted substances at relatively low levels in either the aqueous pH 2.5 and pH 9.5 extracts or the IPA/water extract. While BPA was extracted at high pH at readily measurable levels (approximately 70 μg/g), all other extractables, including several fatty acids and their methyl esters, were present in primarily the IPA/water extract at very low levels, less than 5 μg/g. The sealed vessels extracts contained trace levels of extractables that could be linked to the PC's antioxidant additives, such as 4-*tert*-butyl phenol and 2-*tert*-butyl-6-methylphenol.

Reflux and Soxhlet Extracts: Chromatograms obtained for the reflux and Soxhlet extracts are illustrated in Figures 28 through 30. Chemical information related to the identified extractables present in these extracts is summarized in Tables XVII and XVIII. The predominant organic extractables in the reflux and Soxhlet extracts were the antioxidant additives themselves (Irganox 1076

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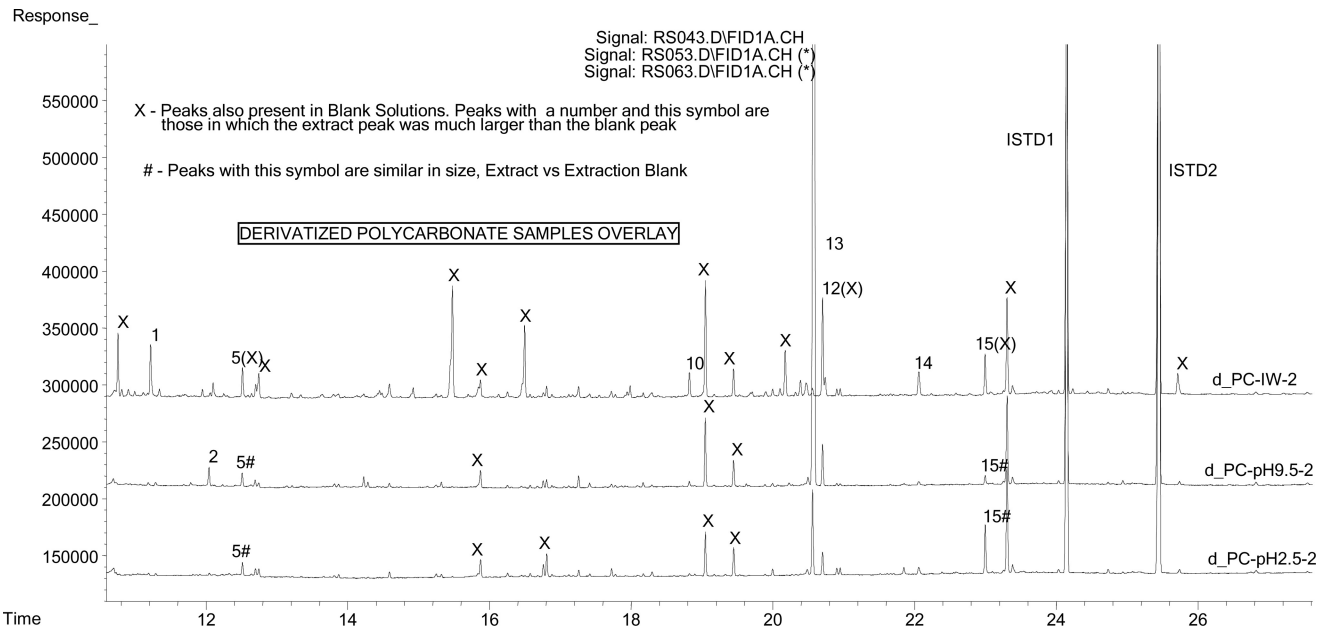

Figure 26

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts of the Polycarbonate, PC (derivatized sample preparation). Peaks ISTD1 and ISTD2 are the two internal standards (1 = Irganox 415 and 2 = Bisphenol M), reflecting compounds present in the extract at a concentration of approximately 1 mg/L (ppm). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. See Table XVII for a summary of information about the numbered peaks, all of which were ascribed to extracted substances.

and Irgafos 168) and their associated related substances (decomposition products). Several fatty acids were present in these extracts at readily measurable levels. These extracts contained small but measurable quantities of BPA and dimethylterephthalate.

Summary: The extractables profile of the polycarbonate material has been established via multiple extraction processes and multiple extracting media. The polycarbonate's profile of organic extractables is summarized in Table XIX. The qualitative and quantitative nature of the extractables profile differed greatly as a function of extraction solvent polarity. Except in the case of BPA, the highest amounts of these extractables were present in the organic extracts; BPA was present at the highest level in the aqueous pH 9.5 extract. This suggests that the BPA does not arise from extraction of residual monomer but rather that the PC depolymerizes at the higher pH. The differences in extractables profiles, polar versus nonpolar extracting media, are consistent with both the nature of the extracting media and the nature of the extractables, as reflected in their octanol/water partition coefficients ($P_{o/w}$). Thus, the relatively nonpolar PC additives are only extracted, to an appreciable extent, by the nonpolar organic solvents.

The polycarbonate's extracted trace elements and metals consist primarily of alkali and alkaline earth metals such as Ca, Na, and Mg. Among the metals, Fe and Zn were extracted in measurable quantities while Al was detected at levels near the reporting threshold. These species were extracted at low pH, suggesting that the extraction mechanism could be ion exchange.

Cyclic Olefin Copolymer, COC

Introduction: COCs are recent additions to medical plastics. These amorphous, transparent copolymers of cycloolefins and linear olefins are manufactured by the polymerization of a cyclic olefin (for example, cyclopentene, norborene) with an olefin such as ethylene or propylene. The catalyzed ring opening polymerization of a COC results in a material that is highly transparent, impact-resistant, shatter-resistant, and a good moisture barrier. Although COCs generally have few additives, they can be com-

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TABLE XVII
Information Related to the GC Peaks Associated with Organic Extractables from the PC

Peak #				Highest Concentration In Extract	
Set A[a]	Set B[b]	Identification[c]	CAS RN	Medium	Type
13	4	Bisphenol A	80-05-7	IPA	Reflux
2	1	4-Tert-butylphenol	98-54-4	IPA	Reflux
—	3	2,4-Di-t-butylphenol	96-76-4	IPA	Reflux
—	6	Irgafos 168	31570-04-4	IPA	Reflux
—	5	Unknown[d]	—	IPA	Soxhlet
—	2	Dimethylterephthalate	120-61-6	Hexane	Soxhlet
—	7	Irgafos 168 oxide	95906-11-9	IPA	Reflux
—	8	Irganox 1076	2082-79-3	IPA	Reflux
8, 9, 11, 12	—	Fatty acids and their methyl esters	—	IPA/Water	Sealed

Notes:
[a]In the sealed vessel extracts, see Figures 25, 26. These extracts also contained extractables whose identities could not be confidently established based on their low concentration, specifically peaks 1, 3–7, 10, 14, 15, and 16.
[b]In the solvent extracts, Soxhlet and reflux, see Figures 28, 29.
[c]These identifications are classified as confirmed.
[d]Unknowns are compounds whose identities could not be established by the methods used in this study.

pounded with pigments, lubricants, flame retardants, fillers, and the like. Nevertheless, COCs are often described as having very low levels of extractables (for example, references 83–86). As a class, COCs are used in pharmaceutical applications that have traditionally been dominated by glass, such as vials, syringes, and others. Because it can be extruded as a film, COC may be used in flexible packaging (e.g., bags) and blister packs.

Test Article: The COC test article plaques contained Irganox 1010 and Ultramarine Blue in unspecified quantities and could also contain molding residuals. Although the test article can be considered to be representative of materials used in pharmaceutical applications, it is not specifically used in commercial products.

Elemental Analysis: The results for the aqueous extracts for extracted elements are summarized in Table VII. Most of the targeted elements were not reproducibly extracted from the COC in reportable quantities, where the reporting threshold was approximately 0.01 μg/g. The levels of extracted metals are greatest in the low pH extracts, suggesting that the extraction mechanism is ion exchange. The predominant extracted elements include the alkali and alkaline earth metals such as Ca (1.7 μg/g), Na (1.0 μg/g), and Mg (0.2 μg/g). Bromine (Br) was present in the pH 2.5 extracts at a level of approximately 0.5 μg/g. Among the other metals, Fe was present in the pH 2.5 extracts at levels of 0.3 μg/g, while Zn and Al were detected in the pH 2.5 extracts at levels near the reporting threshold.

Volatile Components: The headspace GC/MS chromatograms contained several small peaks related to unidentified volatiles at low levels, approximately 0.1 μg/g or less. The only identifiable volatile compound was *cis*-decahydronapthalene, which was present in the COC at approximately 0.03 μg/g.

Organic Extractables:
Sealed Vessel Extracts: Typical GC/FID chromatograms obtained for the sealed vessel extracts are shown in Figures 31 and 32. LC chromatograms obtained for the sealed vessel extracts did not reveal any identifiable organic extractables in the COC, as all extractables-related peaks were very small. As was anticipated earlier, there were few identifiable organic extractables in the aqueous pH 2.5 and pH 9.5 extracts. Even the IPA/water extracts contained only very low levels of organic extractables; while several extractables were revealed by the chromato-

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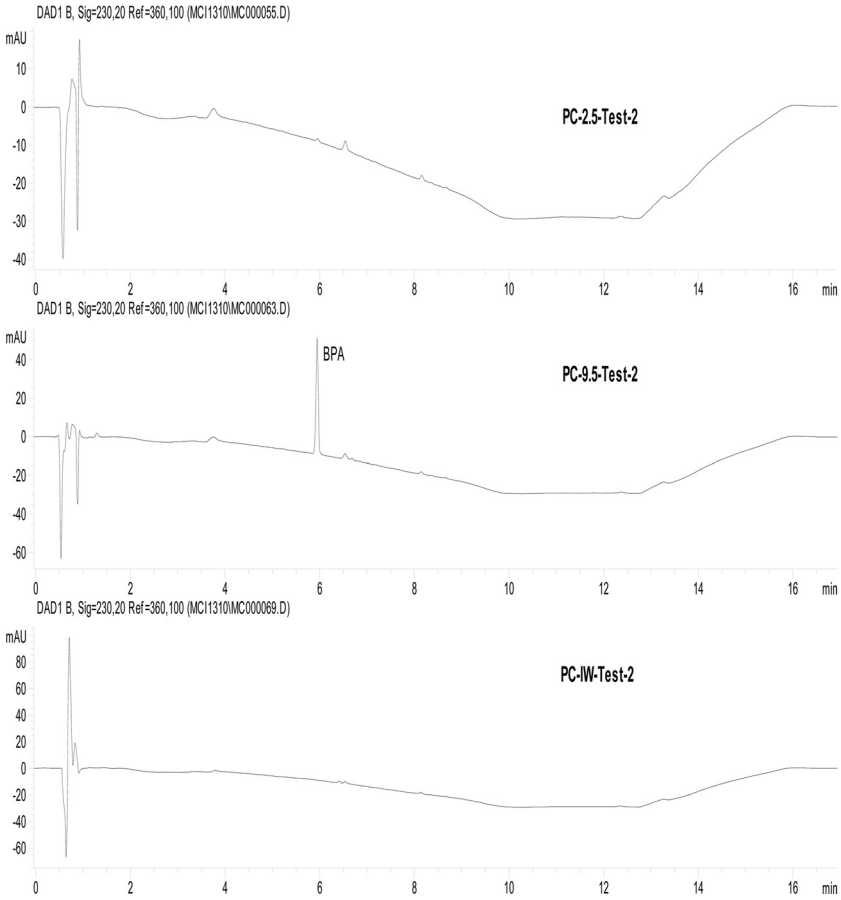

Figure 27

LC/UV Chromatograms (λ = 230 nm) for the Sealed Vessel Polycarbonate Extracts. Bisphenol A (BPA) was present in the pH 9.5 extracts at an estimated concentration of 0.83 mg/L. The lower chromatogram is the IPA/water extract, the middle chromatogram is the pH 9.5 extract and the upper chromatogram is the pH 2.5 extract.

graphic analyses, in most cases the chromatographic responses were too small to allow for their identification. In aggregate, the total amount of such unknown extractables was low, less than 35 μg/g. Although the exact identity of these extractables could not be established, the mass spectral data suggested that several of the extractables contained silicon. While the IPA/water extracts did contain identifiable organic extractables, the amount of each individual extractable was low, less than 5 μg/g, and the aggregate concentration of the identified extractables was less than 20 μg/g. Tentatively identified organic extractables included fatty acids and several cyclic organosiloxanes. Thus, both the aqueous and IPA/water extracts generally provided only limited insights into the composition of the test material.

Reflux and Soxhlet Extracts: GC and LC chromatograms obtained for the various reflux and Soxhlet extracts are illustrated in Figures 33 through 35. Chemical information related to the identified extractables present in these extracts is summarized in Table XX (GC). Two features of the chromatographic data for the organic extracts are noteworthy. First, while the COC may be low in extractables it is not without extractables, as several extractables were present in the reflux and Soxhlet organic extracts. These extractables included isomers of decahydronaphthalene, phthalates (both mono- and di-(2-ethylhexyl)phthalate were detected), oleamide, and either Irganox 1010 or its related degradation products. The discovery of extracted phthalates is unique to this test article, as extractable phthalates are not typically associated with COC materials.

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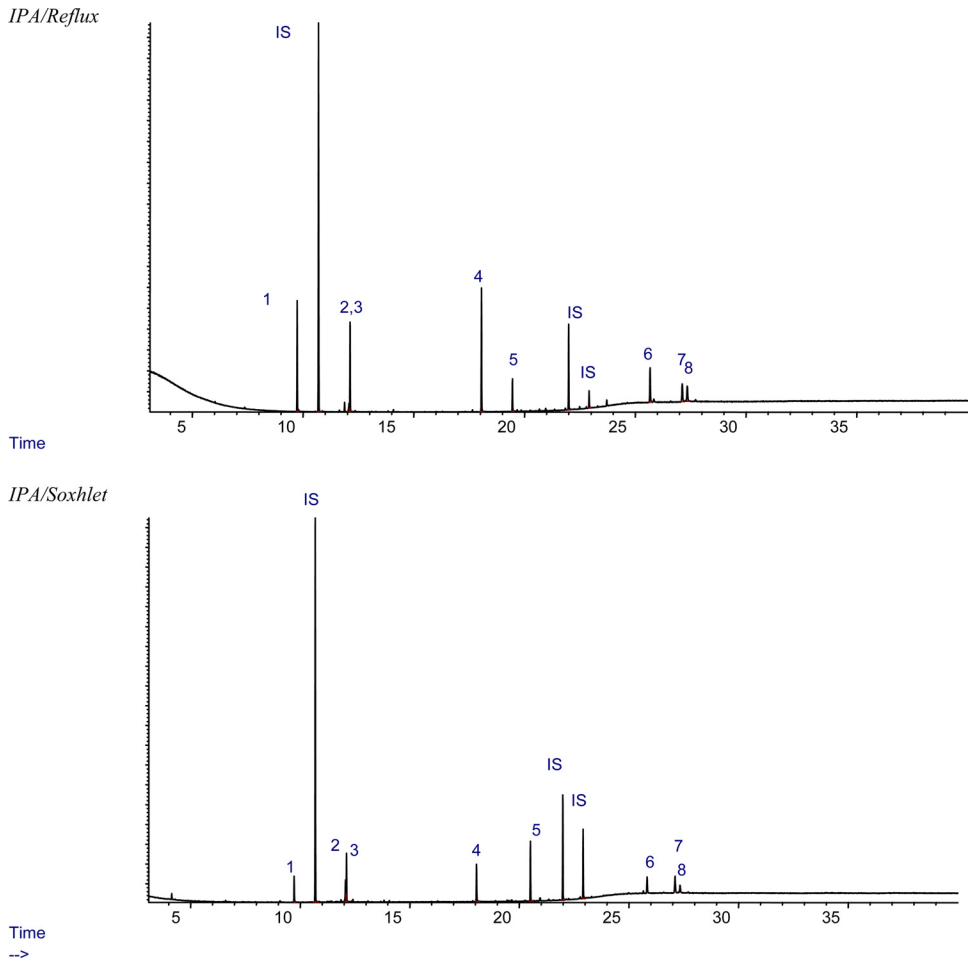

Figure 28

GC/MS Chromatograms (underivatized) for the IPA Extracts for the Polycarbonate. The upper chromatogram is for the Reflux extraction and the lower chromatogram is for the Soxhlet extraction. Internal standards (IS) producing peaks in these chromatograms include 2-Fluorobiphenyl at 10.7 min, Irganox 415 at 22.0 min and Bisphenol M at 23.0 min. Extractables associated with the chromatographic peaks are summarized in Table XVII. The major peaks in the chromatograms include the PC's monomer and either its antioxidants or their degradation products. The extractables profile revealed by GC analysis is much more extensive with IPA, versus hexane, as the extracting solvent (for example, comparing Figures 28 and 29).

Second, the extractables profiles were different as a function of the extracting solvent. Specifically, the IPA extract essentially contained only one extractable in readily measurable quantities, mono-(2-ethylhexyl) phthalate. Alternatively, the hexane extracts contained all the other reported extractables, such as the napthalenes, oleamide, and Irganox 1010 (and related substances). In general, the extractables profile was not qualitatively affected by the extraction process (Soxhlet versus reflux).

Summary: The cyclic olefin's profile of organic extractables is summarized in Table XXI. These predominant organic extractables included isomers of decahydronapthalene, phthalates, oleamide, and the material's known antioxidant, Irganox 1010. The qualitative and quantitative nature of the extractables profile differed greatly as a function of the polarity of the extracting solvent. The aqueous extracts contained no organic extractables at readily measurable levels. Sealed vessel extracts using a mixed organic/water extracting solvent contained only small amounts of fatty acids and organosiloxanes. The major extractables were only present in the organic solvent extracts. This difference in extractables profiles, polar versus nonpolar extracting

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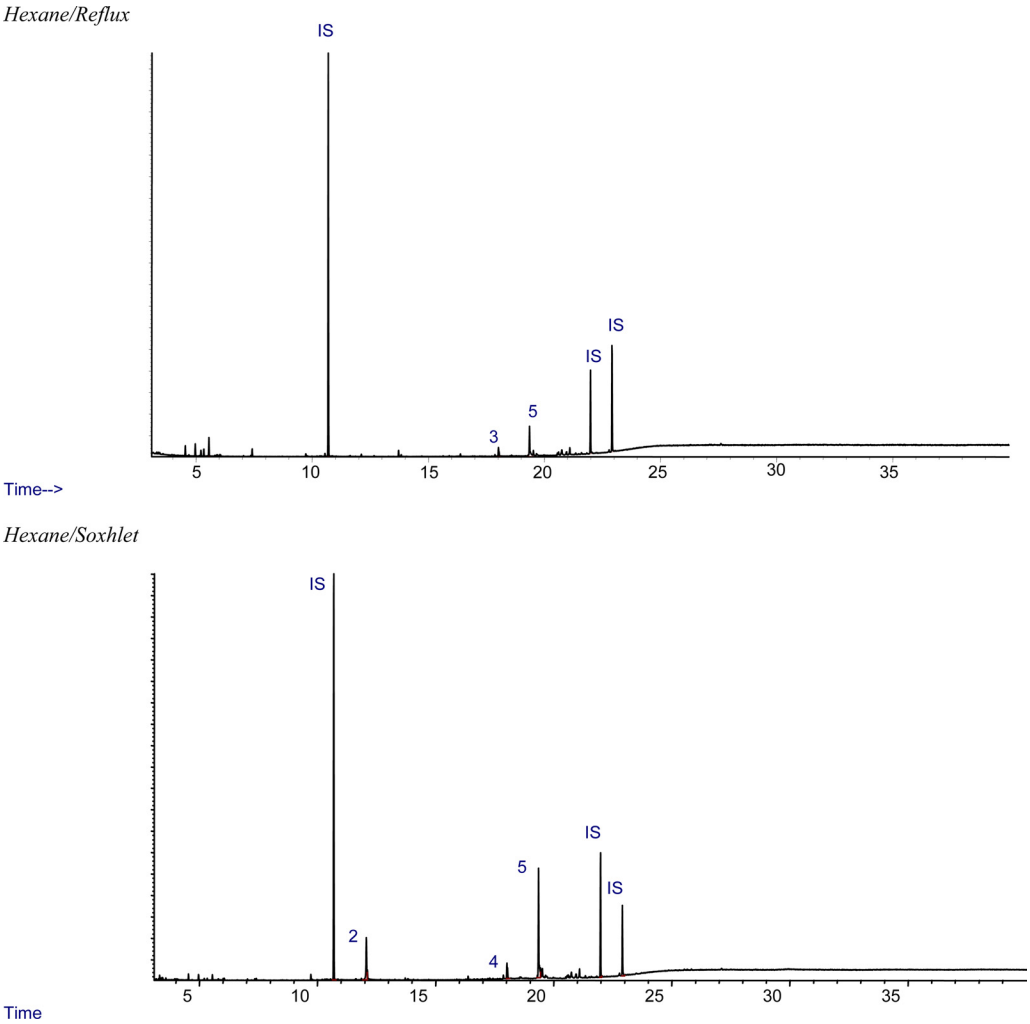

Figure 29

GC/MS Chromatograms (underivatized) for the Hexane Extracts for the Polycarbonate. The upper chromatogram is for the Reflux extraction and the lower chromatogram is for the Soxhlet extraction. Internal standards (IS) producing peaks in these chromatograms include 2-Fluorobiphenyl at 10.7 min, Irganox 415 at 22.0 min and Bisphenol M at 23.0 min. Extractables associated with the chromatographic peaks are summarized in Table XVII. The extractables profile revealed by GC analysis is much more extensive with IPA, versus hexane, as the extracting solvent (e.g., comparing Figures 28 and 29).

media, is consistent with not only the nature of the extracting media but also the nature of the extractables, as reflected in their octanol/water partition coefficients ($P_{o/w}$).

The COC's extracted trace elements and metals consist primarily of alkali and alkaline earth metals such as Ca, Na, and Mg. Among the metals, Fe was extracted in measurable quantities, while Al and Zn were detected at levels near the reporting threshold. These species were extracted in the low-pH extracting medium, suggesting that the extraction mechanism could be ion exchange.

Discussion

Studies designed to assess recovery (i.e., mass balance) for individual extractables relative to the known chemical additives in the various test articles, or to assess the reproducibility of extractables profiles for multiple "batches" of any particular test article were not within the scope of this study. Nevertheless, the resulting extractables profiles were qualitatively reconciled with the known composition of the test articles, suggesting that these extractables studies provide useful information for both materials characterization and forecasting potential leachables for various PODPs.

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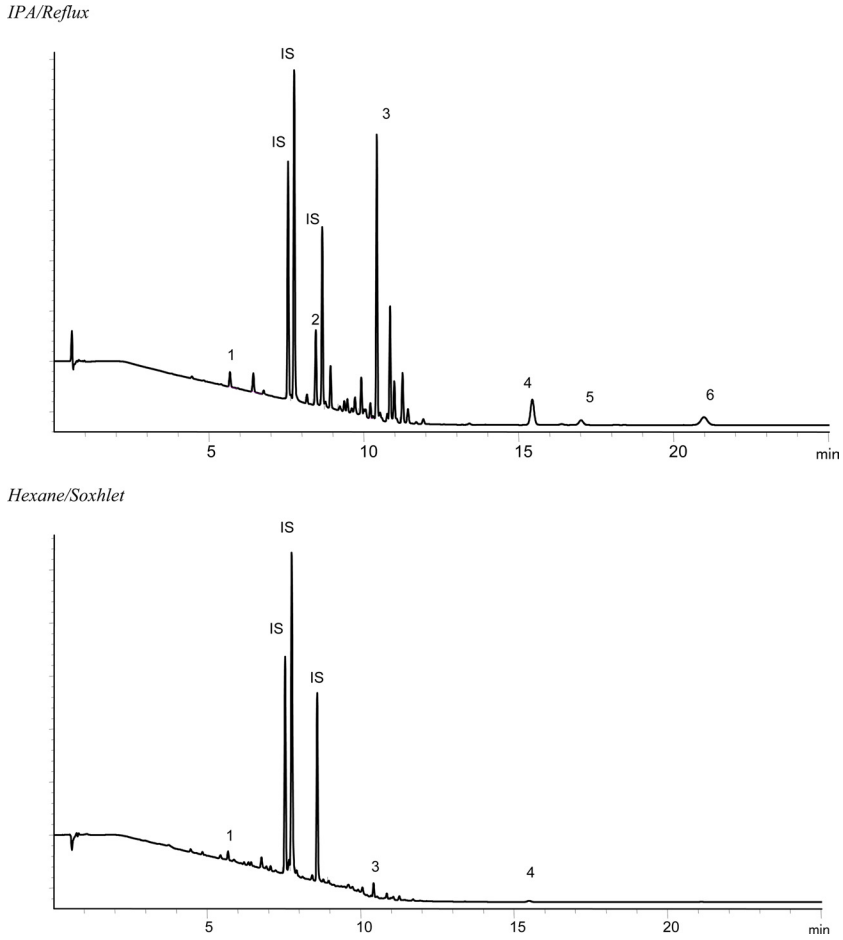

Figure 30

LC/UV Chromatograms (λ = 220 nm) of Selected Extracts for the Polycarbonate. The major peaks in the UV chromatogram are associated with the internal standards (IS), Bisphenol M at 7.5 min, 2-Fluorobiphenyl at 7.7 min and Irganox 415 at 8.6 min. The major peaks associated with extractables were antioxidant-related compounds and Bisphenol A (Table XVIII). The chromatograms also included several peaks whose associated substance could not be identified.

The organic extractables profiles for all the test materials differed significantly as a function of the nature (polarity and pH) of the extracting solvent in terms of both the number of extractables and their concentrations. As the test materials' additives were primarily nonpolar substances, the extractables profile revealed by aqueous extraction media did not generally include the additives themselves but rather consisted of the additives' more polar impurities and related substances and/or the additive's associated hydrolysis or oxidation products. Conversely, the extractables profile revealed by the organic extracting solvents effectively reflected the materials' additive packages and, for some materials, included oligomeric by-products of the test material's polymerization process. The differences in extractables profiles, polar versus nonpolar extracting media, are consistent with not only the nature of the extracting media but also the nature of the extractables, as reflected in their octanol/water partition coefficients ($P_{o/w}$). Examples of this trend in extractables profile versus the nature of the extracting solution are as follows:

- Plasticized PVC: Relatively large quantities of the primary additives, including the primary and secondary plasticizers (DEHP and epoxidized oil, respectively) and the slip agent (erucamide), were extracted by the organic solvents. The aqueous extracts contained only relatively minor amounts of these substances. Alternatively, the high-pH aqueous extracts contained levels of soluble fatty acids that were comparable to the levels of the

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TABLE XVIII
Summary of Identified Organic Extractables, Polycarbonate, LC Analysis, IPA, and Hexane Extracts via Reflux and Soxhlet. See Figure 30[a]

Peak #	Identification[b]	CAS RN
1	Bisphenol A[c]	80-05-7
2	2,4-Di-t-butylphenol	96-76-4
3	Di-(2-ethylhexyl) phthalate	84633-54-5
4	Irgafos 168 oxide	95906-11-9
5	Irganox 1076	2082-79-3
6	Irgafos 168	31570-04-4

Notes:
[a]The various LC chromatograms also contained several peaks whose associated substance could not be identified.
[b]These identifications are classified as either confident or confirmed.
[c]Bisphenol A was also present in the pH 9.5 extracts, see Figure 27.

acids measured in the organic solvents. Additionally, MEHP, a base-catalyzed hydrolysis product of DEHP, was present in the highest quantities in the high-pH aqueous extract. Finally, the levels of 2-ethly-1-hexanol, a highly water-soluble degradation product of DEHP, were highest in the aqueous extracts.

- Rubber: The organic extracts contained numerous nonpolar extractables at relatively high levels, including fatty acids, hydrocarbon oligomers, amides, antioxidants, and substances related to the accelerator. With the exception of the fatty acids, which were present in the high-pH aqueous extracts in readily measurable amounts and morpholine, which is an acid-catalyzed decomposition product of the accelerator that has an increased solubility at low pH, none of the compounds present in the organic extracts were present in the aqueous extractables in quantities consistently above the reporting threshold.

- Polyethylene (PE): Those substances that were extracted by the organic solvents were a clear reflection of this material's additive package, as the additives themselves were the major substances present in the organic extracts. With the exception of the fatty acids, which were present in the high-pH aqueous extracts in readily measurable amounts and an acid hydrolysis product of Chimassorb 944, present in the low-pH extracts, none of the compounds

TABLE XIX
Organic Extractables Profile of the Polycarbonate Material as Established by the Testing Performed in this Study; Identified Compounds Reproducibly Extracted from the Test Article at Levels of Approximately 1 µg/g or Greater

Identification[b]	CAS RN	Chemical Formula	Molecular Weight	Concentration in Material, µg/g						
				Sealed Vessel			Reflux		Soxhlet	
				pH 2.5	pH 9.5	IPA/W	IPA	Hexane	IPA	Hexane
Bisphenol A (4,4'-(1-methylethylidene)bis-phenol)	80-05-7	$C_{15}H_{16}O_2$	228.29	1–10	10–100	—[b]	10–100	10–100	1–10	10–100
4-Tert-butylphenol	98-54-4	$C_{10}H_{14}O$	150.22	1–10	1–10	—	10–100	10–100	1–10	1–10
2,4-Di-tert-butylphenol	96-76-4	$C_{14}H_{22}O$	206.32	—	—	—	10–100	10–100	1–10	10–100
Irgafos 168	31570-04-4	$C_{42}H_{63}O_3P$	646.92	—	—	—	10–100	10–100	1–10	1–10
Irgafos 168 oxide	95906-11-9	$C_{42}H_{63}O_4P$	662.69	—	—	—	10–100	10–100	1–10	1–10
Irganox 1076	2082-79-3	$C_{35}H_{62}O_3$	530.86	—	—	—	10–100	1–10	1–10	1–10
Dimethylterephthalate	120-61-6	$C_{10}H_{10}O$	194.18	—	—	—	10–100	10–100	1–10	10–100

Notes:
[a]These identifications are classified as confirmed.
[b]— = not present in this extract at detectable levels.

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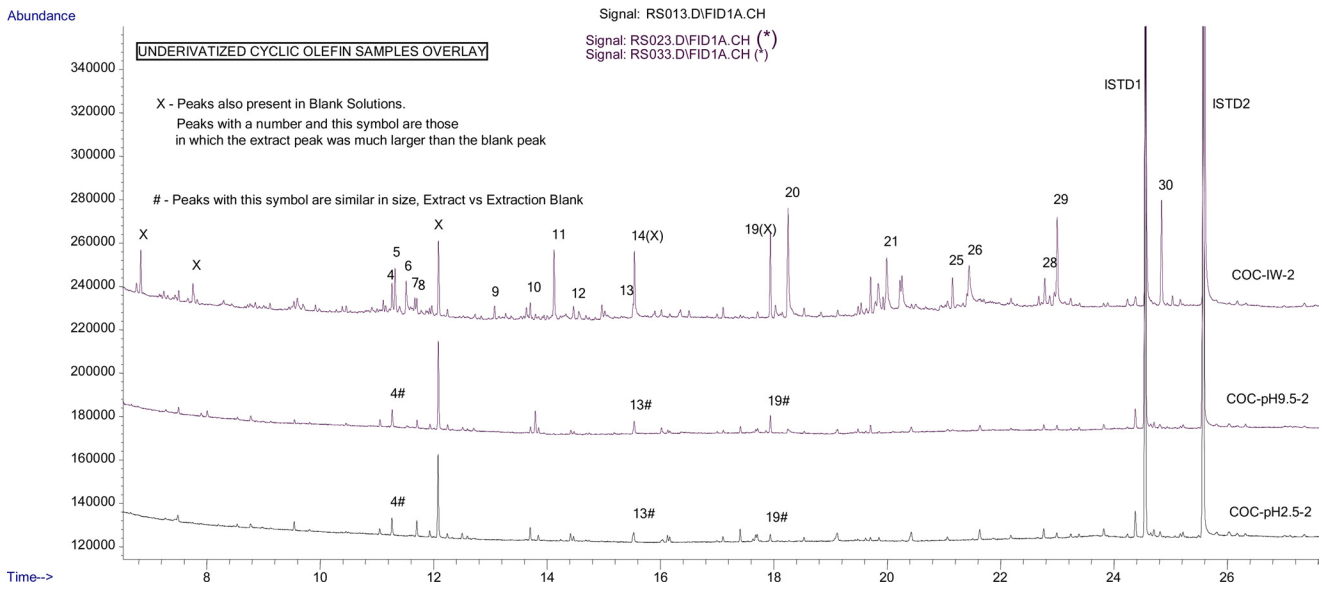

Figure 31

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts of the Cyclic Olefin Copolymer (COC), underivatized sample preparation. Peaks ISTD1 and ISTD2 are the two internal standards (1 = Irganox 415 ≈ 25 mg/L and 2 = Bisphenol M ≈ 1 mg/L). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. While the numbered peaks in the chromatograms could be ascribed to extractables, the peaks were lower than the reporting threshold. Thus, in many cases, the identitity of the extractables associated with apeak could not be ascertained and in those cases where an identity could be proposed, the identity was considered to be speculative and is not reported herein.

present in the organic extracts were present in the aqueous extractables in quantities consistently above the reporting threshold.

- Polycarbonate (PC): The organic extracts of the PC material contained readily measureable quantities of its two phenolic antioxidants, which were not present in the aqueous extracts in quantities consistently above the reporting threshold. Alternatively, BPA was the predominant organic extractable in the high-pH aqueous extracts, as it is produced by essentially depolymerizing the PC via base-catalyzed hydrolysis.

- Cyclic Olefin Copolymer (COC): The nonpolar extractables that were present in the organic extracts were not present in the aqueous extracts in quantities consistently above the reporting threshold.

In general, the organic extractables profiles obtained with the organic solvents were not qualitatively affected by the extraction solvent itself (IPA versus hexane versus IPA/water) or the extraction process (sealed vessel, reflux, or Soxhlet). Although quantitative differences might exist in the profiles revealed by the various organic extracting solvents and/or the extraction methods, such differences could not reproducibly be discerned in this study. However, there were two notable exceptions to this generalization:

- Although the COC's organic extractables profiles obtained with the organic solvents were not qualitatively affected by the extraction process (for example, reflux or Soxhlet), the extractables profiles were greatly different when comparing IPA versus hexane as the extraction solvent. While all the major organic extractables were present in the hexane extracts, the IPA extracts essentially contained only phthalates.

- The PC's organic extractables profile obtained with the organic solvents was discernibly affected by the extraction solvent itself (IPA versus hexane versus IPA/water) and, to a lesser extent, the extraction process (sealed vessel, reflux, or Soxhlet). In general, IPA as an extracting solvent and reflux as an extraction method produced the most extensive extractables profiles for the PC material.

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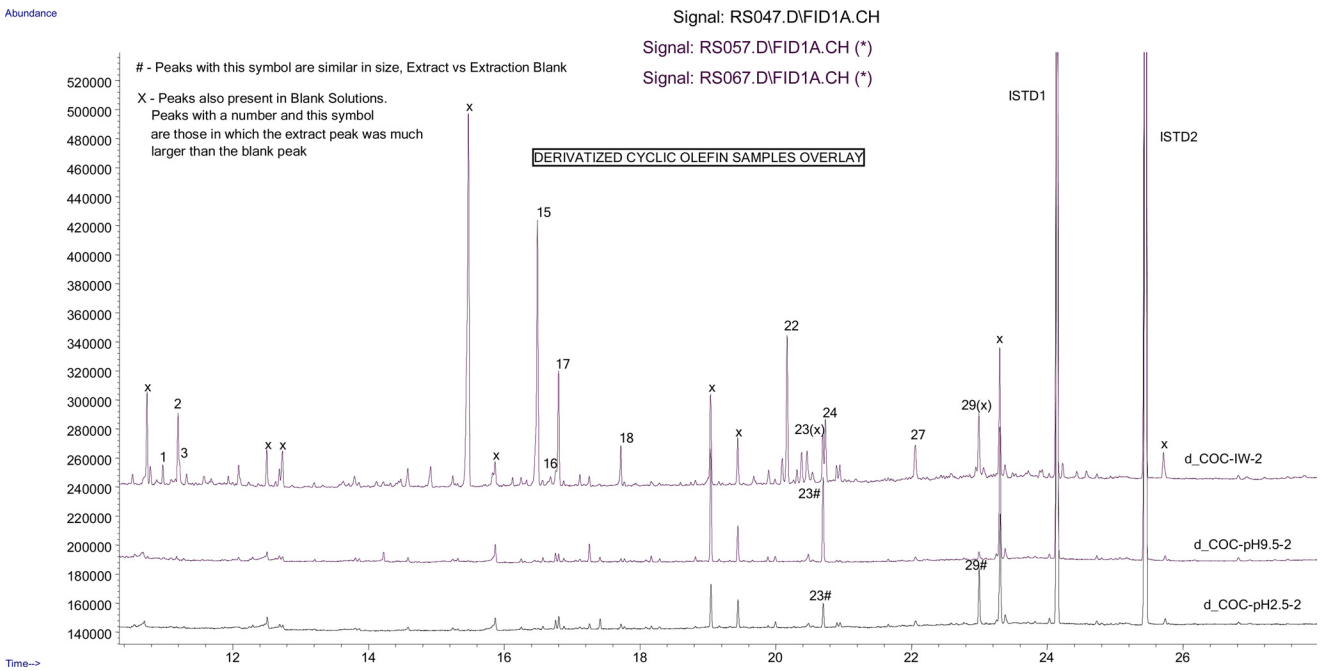

Figure 32

GC/FID Chromatograms Comparing the Various Extracting Solutions, Sealed Vessel Extracts of the Cyclic Olefin Copolymer (COC), derivatized sample preparation. Peaks ISTD1 and ISTD2 are the two internal standards (1 = Irganox 415 ≈ 25 mg/L and 2 = Bisphenol M ≈ 1 mg/L). The chromatograms reflect, from top to bottom, the IPA/water, pH 9.5 and pH 2.5 extracts respectively. While the numbered peaks in the chromatograms could be ascribed to extractables, the peaks were lower than the reporting threshold. Thus, in many cases, the identitity of the extractables associated with a peak could not be ascertained and in those cases where an identity could be proposed, the identity was considered to be speculative and is not reported herein.

The observed effect that extraction solvent had on the organic extractables profile is significant to the process of characterizing the test article in two respects. First, if the sole and exclusive intent of an extraction study is to characterize a test article by establishing its composition (e.g., additives), specifically for the purpose of establishing the material's suitability for use, then it is clear that the extracting medium should mirror the additives in terms of their essential chemical properties, such as polarity, consistent with the adage "likes dissolve likes". In the case of a material that contains primarily nonpolar additives, nonpolar extracting solvents should be used to reveal the additives, although in the case of fatty acid additives a high-pH extracting medium might be more effective. Analysis of the nonpolar extracts will certainly facilitate the identification of the additives and will provide an estimate of their relative abundance in the test article. However, if the amount of the additive in a material is high enough that it exceeds the additive's solubility in the extracting medium, then multiple extractions will be necessary to establish the test article's additives level. For example, while the levels of DEHP in the organic extracts of the PVC material were relatively high (up to approximately 0.04 g/g), this is actually a small portion of the total DEHP in the test article (approximately 0.3 g/g). While the use of multiple extractions to achieve complete or asymptotic extraction was not a design feature of this study, such a strategy might be necessary to establish the total amount of an additive in a test material, if so doing is necessary to establish the material's suitability for its intended use.

Alternatively, if the intent of the controlled extraction study is to make inferences about drug product leachables (for example, considering extractables as probable leachables), then the inferences are most relevant, accurate, and useful if the controlled extraction study uses extraction conditions, including the composition of the extracting solvent, that are comparable to the clinical use conditions for the drug product. For example, using an extractables profile based on aqueous extracts to assess the leachables profile of a drug

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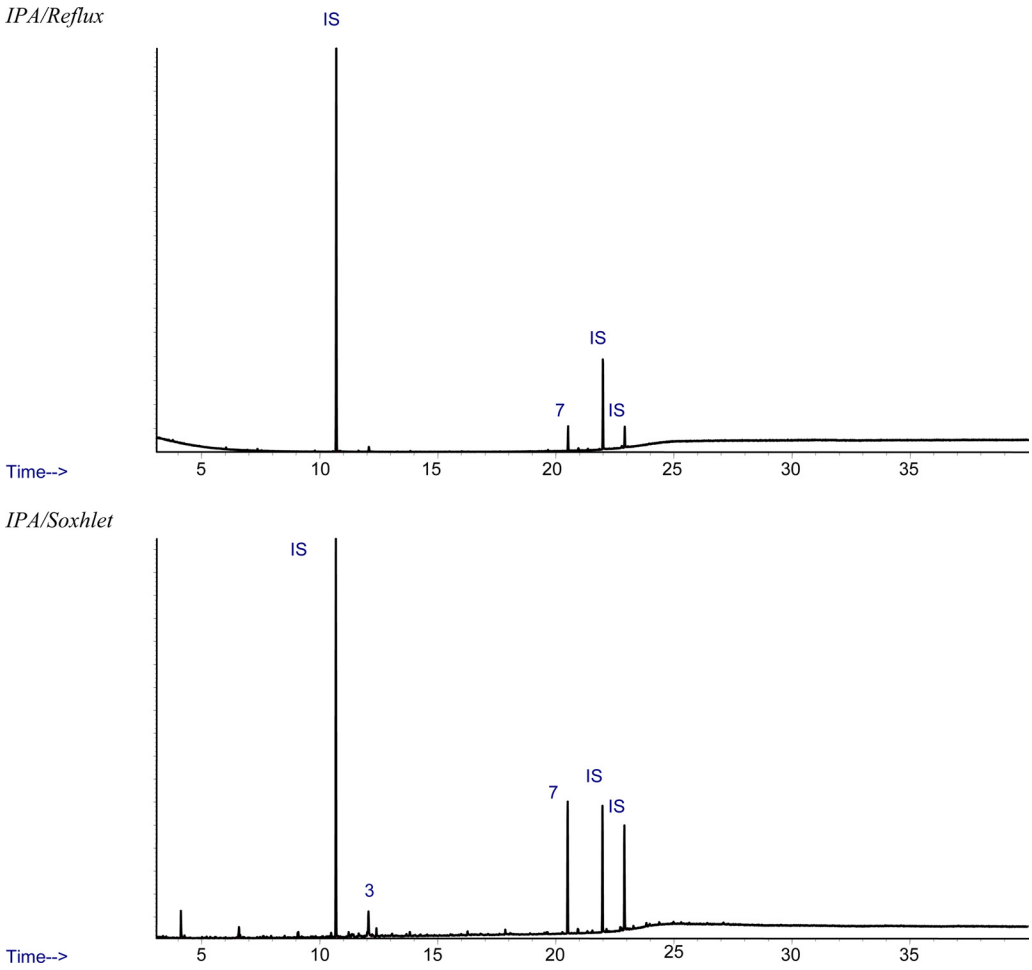

Figure 33

GC/MS Chromatograms (underivatized) for the IPA Extracts for the Cyclic Olefin Copolymer. The upper chromatogram is for the reflux extraction and the lower chromatogram is for the Soxhlet extraction. Internal standards (IS) producing peaks in these chromatograms include 2-Fluorobiphenyl at 10.7 min, Irganox 415 at 22.0 min and Bisphenol M at 23.0 min. Extractables associated with the chromatographic peaks are summarized in Table XX. While the chromatograms for both extraction conditions are similar, the extractables profile revealed by GC analysis is much more extensive with hexane, versus IPA, as the extracting solvent (e.g., comparing Figures 33 and 34).

product formulated in a solvent medium could produce a flawed assessment by both failing to reveal relevant leachables and potentially underestimating the concentration of those leachables that were revealed as extractables. As an example, the aqueous extracts of the elastomer did not reveal several of the more predominant nonpolar extractables. If the aqueous extractables data were used to establish target leachables to be measured in a nonpolar drug product, it is clear that the most potentially significant leachables would be missed. Conversely, using an extractables profile based on organic solvent extracts to assess the leachables profile for an aqueous drug product would produce a flawed assessment by considering extractables that could not possibly accumulate in the aqueous product as leachables and by potentially overestimating the concentration of the leachables in the drug product. Thus the most appropriate extraction solvent for an extractables study intended to make inferences about leachables is one that closely matches the chemical properties (e.g., polarity and pH) of the drug product for which the assessment is being performed.

Because the process of developing and qualifying a packaging system is a multifaceted endeavor, it is logical to expect that multiple types of controlled

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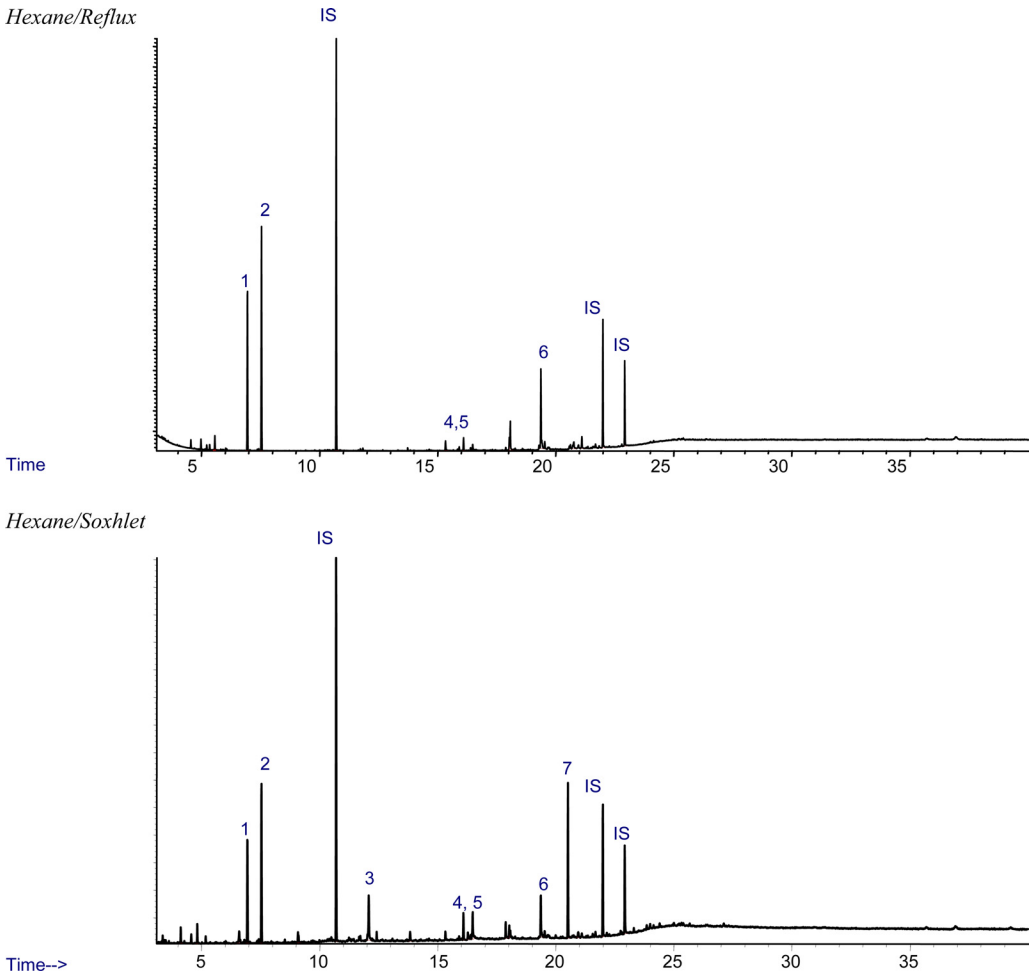

Figure 34

GC/MS Chromatograms (underivatized) for the Hexane Extracts for the Cyclic Olefin Copolymer. The upper chromatogram is for the reflux extraction and the lower chromatogram is for the Soxhlet extraction. Internal standards (IS) producing peaks in these chromatograms include 2-Fluorobiphenyl at 10.7 min, Irganox 415 at 22.0 min and Bisphenol M at 23.0 min. Extractables associated with the chromatographic peaks are summarized in Table XX. While the chromatograms for both extraction conditions are similar, the GC extractables profile is more extensive with hexane, versus IPA, as the extracting solvent (for example, comparing Figures 33 and 34).

extractions might be performed to support the development, qualification, and registration process. Considering the two previous examples, one can envision a packaging system development and commercialization process that includes both controlled extraction studies that characterize candidate materials so that appropriate candidates can be identified (screening and selection) and controlled extraction studies designed to assess extractables as probable leachables, facilitating the process of safety qualification.

It is expected that a material's extractables profile can establish the proper use of that material in pharmaceutical applications if the extractables profile is based on extractions that encompass an appropriately wide range of experimental conditions, such as identity of the extraction medium and nature of the extraction process. Thus this study, which included both polar and nonpolar extracting media and several extraction processes, could establish the test materials' compatibility with certain drug products. Although compatibility in specific product applications is most appropriately addressed on a case-by-case basis and would strongly depend on the conditions of contact between the drug product and the material in question, certain generalizations about compatibility can be made from

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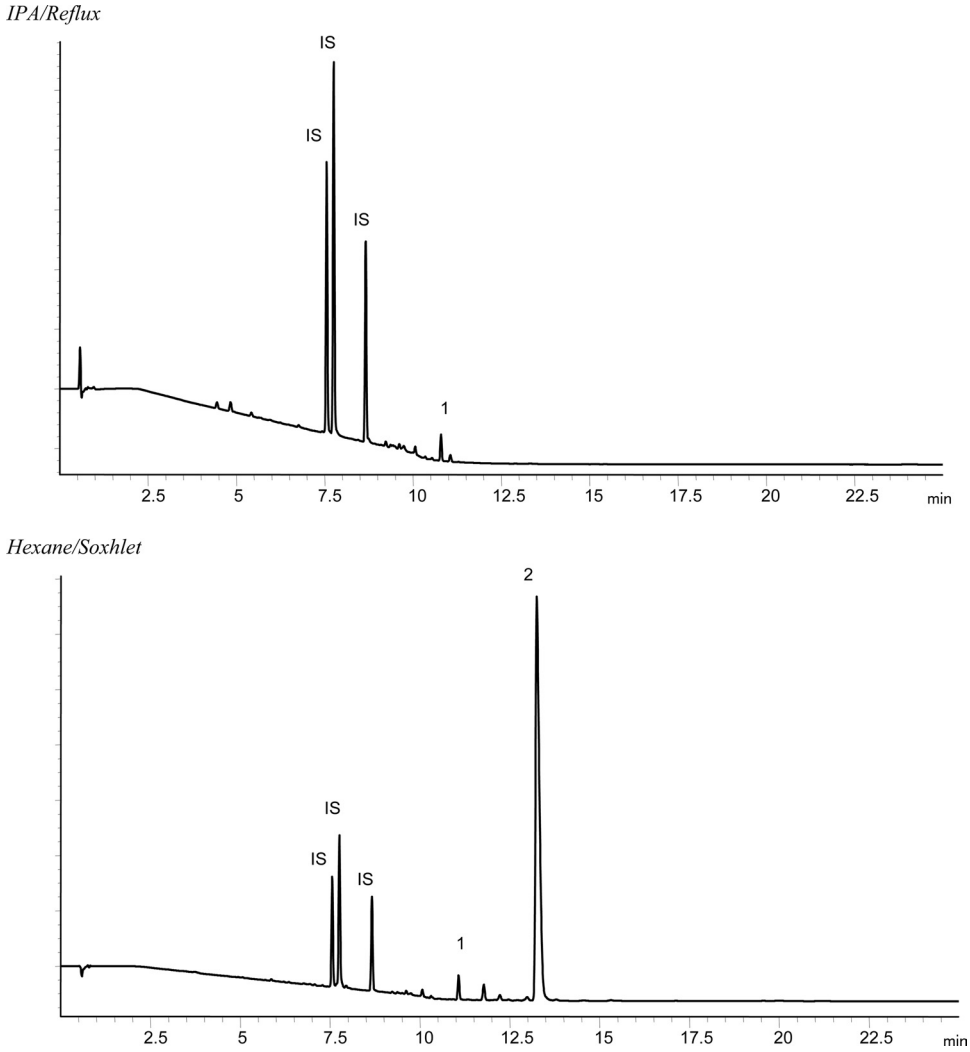

Figure 35

LC/UV Chromatograms (λ = 220 nm) of Selected Extracts for the Cyclic Olefin Copolymer. The major peaks in the UV chromatogram are associated with the internal standards (IS), Bisphenol M at 7.6 min, 2-Fluorobiphenyl at 7.8 min and Irganox 415 at 8.7 min. A small amount of DEHP (peak 1, CAS RN 117-81-7) was present in both extracts. The major difference in the chromatograms for the two extracting solvents is the presence of an Irganox 1010 (peak #2, CAS RN 6683-19-8) in the hexane extracts which was not present in the IPA extracts. The various LC chromatograms also included several peaks whose associated substance could not be identified.

this study. For example, the aqueous extractables profiles suggest that the levels of leachables in aqueous drug products could be sufficiently low that the risk of the leachables adversely affecting patient safety would be low. Exceptions to this statement might include aqueous drug products formulated at high pH, which could, for example, leach potentially meaningful amounts of extractables from PVC (MEHP), PC (BPA), and all the materials except the COC (fatty acids). Additionally, the more extensive solvent extractables profiles suggest that several of the materials examined in this study could be incompatible with drug products formulated in organic solvents or formulated to contain organic solubilizing agents. Additional studies, outside the scope of this article, would logically be required to establish whether such incompatibilities would be encountered with a specific drug product.

In their recommendations, the PQRI OINDP Extractables and Leachables Working Group enumerated certain best demonstrated practices for conducting

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TABLE XX
Information Related to the GC Peaks Associated with Organic Extractables from the COC

Peak #		Identification[c]	CAS RN	Highest Conc In Extract	
Set A[a]	Set B[b]			Medium	Type
—	2	cis-Decahydronaphthalene	493-01-6	Hexane	Reflux
—	1	trans-Decahydronaphthalene	493-02-7	Hexane	Reflux
—	7	Mono-(2-ethyhexyl) phthalate	4376-20-9	IPA	Soxhlet
—	6	Oleamide	301-02-0	Hexane	Reflux
—	3	Dimethylterephthalate	120-61-6	IPA	Soxhlet
—	4	3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid, methyl ester	6386-38-5	Hexane	Soxhlet
—	5	3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid	20170-32-5	Hexane	Soxhlet

Notes:
[a]In the sealed vessel extracts, see Figures 31 and 32. While these chromatograms included peaks that could be assigned to specific compounds, the levels of all these compounds were less than the reporting threshold of 10 μg/g and thus the identities were speculative and not reported herein. Thus, none of the peaks numbered in Figures 31 and 32 were identified.
[b]In the solvent extracts, Soxhlet and reflux, see Figures 33, 34.
[c]These identifications are classified as confirmed.

controlled extraction studies, where a controlled extraction study was defined as a laboratory investigation into the qualitative and quantitative nature of extractables profiles of critical components of an OINDP container/closure system (5). It was a reasonable supposition of the PQRI PODP Extractables and Leachables Working Group that the science-based best demonstrated practices established for the OINDP drug products could be extrapolated to PODP container closure systems. The work summarized in this paper is one vehicle for making and justifying such an extrapolation of certain of the OINDP recommendations. For example, it was recommended that controlled extraction studies for OINDP should

- Employ vigorous extraction with multiple solvents of varying polarity
- Incorporate multiple extraction techniques
- Include careful sample preparation based on a knowledge of the analytical techniques used
- Employ multiple analytical techniques
- Include a defined and systematic process for the identification of individual extractables
- Include a re-examination of supplier information describing component formulation

It is relevant and appropriate to note that the data generated and experiences gained in this study, which was performed on materials relevant for PODP products and with methods appropriate for PODP dosage forms, support the spirit, if not the exact letter, of all these recommendations as they are applied to the PODP situation. For example, the recommendation to re-examine supplier information is borne out in the several materials that had extractables which could not be correlated with the material's reported additives. While this activity was beyond the scope of this study, a complete and rigorous extractables assessment would include an investigation as to the source and genesis of these uncorrelated extractables. Furthermore, it is implied in the OINDP recommendations and further enumerated in the OINDP document that supplier information be consulted during the design and implementation of the controlled extraction study, as such information can influence study design and facilitate data interpretation. The wisdom of this aspect of the OINDP recommendation was borne out in this study, as reflected in the strong correlation that could be established between the major extractables and the materials' specified additives.

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TABLE XXI

Organic Extractables Profile of the Cyclic Olefin Copolymer Material as Established by the Testing Performed in This Study; Identified Compounds Reproducibly Extracted from the Test Article at Levels of Approximately 1 μg/g or Greater

Identification[a]	CAS RN	Chemical Formula	Molecular Weight	Concentration in Material, μg/g						
				Sealed Vessel			Reflux		Soxhlet	
				pH 2.5	pH 9.5	IPA/W	IPA	Hexane	IPA	Hexane
cis-Decahydronaphthalene	493-01-6	$C_{10}H_{18}$	138.25	—[b]	—	—	1–10	10–100	1–10	10–100
trans-Decahydronaphthalene	493-02-7	$C_{10}H_{18}$	138.25	—	—	—	1–10	10–100	1–10	10–100
Di-(2-ethyhexyl) phthalate related[d]	117-81-7	$C_{24}H_{38}O_4$	390.56	—	—	1–10	10–100	1–10	10–100	10–100
Oleamide	301-02-0	$C_{18}H_{35}NO$	281.48	—	—	—	1–10	10–100	1–10	10–100
Dimethylterephthalate	120-61-6	$C_{10}H_{10}O_4$	194.18	—	—	—	1–10	1–10	1–10	10–100
3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid	20170-32-5	$C_{17}H_{26}O_3$	278.39	—	—	—	1–10	1–10	1–10	10–100
3,5-Bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid, methyl ester	6386-38-5	$C_{18}H_{28}O_3$	292.41	—	—	—	1–10	1–10	1–10	10–100
Hexadecanoic (palmitic) acid	57-10-3	$C_{16}H_{32}O_2$	256.42	—	—	1–10	—	—	—	—
Irganox 1010	6683-19-8	$C_{73}H_{108}O_{12}$	1177.63	—	—	—	P[c]	P[c]	P[c]	P[c]

Notes:

[a]These identifications are classified as confirmed.

[b]— = not present in this extract at detectable levels.

[c]Present in the extracts based on the LC analyses but not quantitated.

[d]Total including both DEHP and MEHP.

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Considering the analytical aspects, the OINDP recommendation to employ multiple analytical techniques is supported by the difference in organic extractables revealed by the two chromatographic procedures used in this study (LC and GC). It is clear that neither methodology has the intrinsic capability to reveal, identify, and quantify all the potential extractables relevant for PODP applications. It is equally clear that both these approaches have their place in effective extractables characterizations, and it is logical to expect that the relative importance of the two methods will vary from situation to situation, depending on the specifics of each situation. Considering the OINDP recommendation that careful sample preparation based on knowledge of the analytical technique be used, the experience gained with respect to derivatized and underivatized GC analysis is relevant. Specifically, it was clear from the vendor information that several test materials contained extractable fatty acids. Knowledge of the chemical properties of the fatty acids (specifically the relationship between their solubility and the pH of an aqueous extraction solvent) suggests that they could be extracted in measurable quantities by the high-pH aqueous extracting medium. This would mean that the analytical strategy employed would need to be responsive to fatty acids. As the shape of fatty acids peaks in GC chromatograms is generally poor, GC's effectiveness for fatty acids is limited unless the fatty acids are converted (derivatized) into a form that is more conducive to GC analysis. Finally, considering the recommendation that there be a defined and systematic process for the identification of individual extractables, it is noted that many of the identifications reported in this study were termed tentative. While such a level of identification (or lack of identification) may be appropriate for some extractables (particularly those present in the extracts below the analytical evaluation threshold, AET), more rigorous identifications could be required to toxicologically assess the extractables. Such firmer identifications should be obtained via a defined and systematic process. As this study was not driven by an AET and the results were not to be toxicologically assessed, no significant attempts were made to improve the quality of all the identifications contained in this document.

The two remaining OINDP recommendations deal with generating the extract. In the case of these recommendations, it is appropriate to consider their spirit as opposed to their specific language. The spirit of the OINDP recommendations is that the extractables profile one obtains can be a function of the extraction solvent and conditions used. Thus in order to produce a complete extractables profile, one would need to use a combination of multiple solvents and/or extraction techniques. As this study clearly established that the extraction solvent significantly affected the nature of the extractables profile, the essential spirit of the recommendation is corroborated. However, the language of the OINDP recommendation is modified for PODP applications in recognition of the wide variety of dosage forms and packaging systems that fall within the category and in recognition of the fact that controlled extraction studies may be performed for different purposes. Specifically, a recommendation for PODP might be worded as follows: *Controlled extractions studies should use a combination of multiple extraction solvents and extraction techniques as appropriate for, and consistent with, the intent and purpose of the controlled extraction study.*

To understand the reasons for this language, consider three of the several potential applications of a controlled extraction study:

1. Material characterization (i.e., identify and quantify the additives and ingredients in a material, as ingredients and additives may be used to forecast extractables)

2. Clinical product assessment (i.e., identify extractables as a means of forecasting leachables in a specific dosage form)

3. Quality control (QC) (i.e., exercise control over the quality of incoming materials of construction for a packaging system)

Clearly these three controlled extraction studies differ in scope and intent and therefore could differ in terms of their key design parameters (extraction solvent and extraction conditions). For application 1, the ideal extraction could be one which liberates the total pool of all additives from the test material. One envisions that a successful extraction in this case might include a vigorous, multi-step process that uses strong extracting solvents to fully solubilize the additives without dissolving the bulk polymer. In order to effectively utilize extractables information to screen for probable leachables (application 2), the extraction conditions would model (and accelerate) the product contact conditions and would use extracting solvent(s) that have a similar propensity to leach as the drug product. Given

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the diversity in PODP drug products and their clinical use contact conditions, one envisions that controlled extraction studies designed to forecast leachables would vary greatly in design between various drug products. Finally, extraction methods that support ongoing QC control of extractables via the testing of incoming materials have dimensions of performance (e.g., precision, ruggedness, longevity) that are not typically relevant for other types of controlled extraction studies and which may dictate the nature of the extraction process utilized.

The significant point at the foundation of both the PODP recommendation and the OINDP recommendations for generating the extract is that the conditions for extract generation must be consistent with, and driven by, the intent of the study in which the controlled extractions is being performed. In the case of OINDPs, recommendations such as vigorous extraction, multiple solvents, and multiple extractions techniques were consistent with the chemical nature of those dosage forms, the chemical and physical properties of the polymers involved with this dosage form, and the conditions of contact. Such recommendations are not necessarily directly transferable to PODP, depending on the purpose of the controlled extraction study. Thus the PODP language offers the means of vigorous extractions, use of multiple solvents, and use of multiple methods as a way to accomplish the objective of customizing controlled extraction studies to meet the purposes and circumstances that the studies intend to address. Such language is consistent with the observation that the extraction conditions for a controlled extraction study designed to establish a material's composition can appropriately and necessarily be different from the extraction conditions used in a controlled extraction study designed to establish a packaging system's extractables as probable leachables. Additionally, such language properly indicates that while the general concepts of multiple and relevant extraction solvents and extraction procedures are applicable to all dosage forms and all situations, the exaction solvents and techniques that are most appropriate for a specific circumstance will depend on that circumstance and logically will vary somewhat from circumstance to circumstance.

It is noted that the PQRI OINDP document contained other best demonstrated practice recommendations. These recommendations are not discussed in this article, as the data generated and experiences gained in this study are not directly relevant to those recommendations.

In closing, it is appropriate to review what the present study did and did not accomplish. As noted previously, the present study established the test articles' semi-quantitative extractables profiles and revealed how those profiles varied as a function of the chemical nature of the extracting solution, the physical nature of the extracting process, and the method of analysis. While such information is useful in designing and justifying an extraction study that could, for example, be used to facilitate material selection, this present study did not produce information that could be used to definitively assess the potential impact of using the test articles in actual drug product packaging systems. This present study was not designed to be sufficiently quantitative for that purpose, did not definitively establish the identities of all observed extractables, did not extensively investigate perceived anomalies in the data, and did not include a consideration of factors such as lot-to-lot compositional variation. Thus the methodology used in the present study is not meant to be prescriptive or universally applied but rather to reflect a credible, rigorous, and science-based effort to establish a test article's extractables profile and to produce information that can suggest and support best demonstrated practice recommendations.

References

1. Guidance for Industry. Container Closure Systems for Packaging Human Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration: Rockville, MD, May, 1999.

2. Guideline on Plastic Immediate Packaging Materials. European Medicines Agency. CPMP/QWWP/4359/03. EMEA/CVMP/205/04. 5/19/05.

3. Guidance for Industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products. Chemistry, Manufacturing, and Controls Documentation. U.S. Department of Health and Human Services, Food and Drug Administration: Rockville, MD, October, 1998.

4. Guidance for Industry. Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation. U.S. Department of Health and Human Services, Food and Drug Administration: Rockville, MD, July, 2002.

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5. Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. PQRI Leachables and Extractables Working Group, September 9, 2006, available at http://www.pqri.org/pdfs/LE-Recommendations-to-FDA-09-29-06.pdf.

6. Experimental Protocol for Qualitative Controlled Extraction Studies on Material Test Articles Representative of Prefilled Syringe (PFS) and Small Volume Parenteral (SVP) Container Closure Systems. PQRI Parenteral and Ophthalmic Drug Products Leachables and Extractables Working Group, December 9, 2009. Available at http://www.pqri.org/commworking/minutes/pdfs/dptc/podpwg/Addl/PODP_Protocol_PhI.pdf.

7. Grob, K.; Grob, G.; Grob, K. Testing capillary gas chromatographic columns. *J. Chromatogr.* **1981,** *219* (1), 13–20.

8. Jenke D. 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. PQRI Workshop on Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products (PODP), February 22–23, 2011; available at http://www.pqri.org/workshops/PODP11/pdfs/posters/Experimental_Protocol_1.pdf.

9. Chapter 730 Plasma Spectrochemistry. In *The United States Pharmacopeia, USP 34;* The United States Pharmacopeial Convention, Inc.: Rockville, MD, 2010; pp 299–304.

10. Jenke, D. R. Extractable/Leachable substances from plastic materials used as pharmaceutical product containers/devices. *PDA Journal of Pharm. Sci. and Technol.* **2002**, 56(6), 332–371. See also Jenke, D.R. Extractable substances from plastic materials used in solution contact applications, An updated review. *PDA J. Pharm. Sci. Technol.* **2006**, 60(3), 191–207.

11. Ulsaker, G. A.; Korsnes, R. M. Determination of cyclohexanone in intravenous solutions stored in PVC bags by gas chromatography. *Analyst* **1977**, *102* (1220), 882–883.

12. Ulsaker, G. A.; Hoem, R. M. Determination by gas chromatography-single-ion monitoring mass spectrometry of phthalate contaminants in intravenous solutions stored in PVC bags. *Analyst* **1978**, *103*(1231), 1080–1083.

13. Arbin, A.; Ostelius, J. Determination by electron-capture gas chromatography of mono- and di-(2-ethylhexyl) phthalate in intravenous solutions stored in poly (vinyl chloride) bags. *J. Chromatogr., A* **1980**, *193* (3), 405–412.

14. Ching, N. P. H.; Jham, G. N.; Subbarayan, C.; Grossi, G.; Hicks, R.; Nealson, T. F. Gas chromatographic quantitation of two plasticizers contaminating intravenous fluids stored in plastic containers. *J. Chromatogr.* **1981**, *225* (1), 196–210.

15. Arbin, A.; Ostelius, J.; Callmer, K.; Sroka, J.; Hanninen, K.; Axelsson, A. Migration of chemicals from soft PVC bags into intravenous solutions. *Acta Pharm. Seuc*. **1983**, *3,* 20–33.

16. Ulsaker, G.; Teien, G. Determination of 9,10-epoxystearate ester in intravenous solutions stored in poly (vinyl chloride) bags, using gas chromatography-single ion monitoring mass spectrometry. *Analyst* **1984**, *109* (7), 967–968.

17. Srivastava, S. P.; Saxena, A. K.; Seth, P. K. Migration of di-(2-ethylhexyl) phthalate (DEHP) from plastic containers used for packaging of infusion solutions. *Indian J. Pharm Sci*. **1985**, *July/August,* 156–158.

18. Arbin, A.; Jacobsson, S.; Hanninen, K.; Hagman, A.; Ostelius, J. Studies on the contamination of intravenous solutions from PVC-bags with dynamic headspace GC-MS and LC diode array techniques. *Int. J. Pharm*. **1986**, *28* (2), 211–218.

19. Snell, R. P. Capillary GC analysis of compounds leached into parenteral solutions packaged in plastic bags. *J. Chromatogr. Sci.* **1989**, *27* (9), 524–528.

20. Chawla, A. S.; Hinberg, I. Leaching of plasticizers from and surface characterization of PVC blood platelet bags. *Biomater. Artif. Cells Immobilization Biotechnol.* **1991**, *19* (4), 761–783.

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21. Wright, D. W.; Mahler, K. O.; Davis, J. The application of multidimensional GC techniques to the analysis of sub-ppb levels of vinyl chloride monomer in polyvinylchloride. *J. Chromatogr. Sci.* **1992**, *30* (8), 291–295.

22. Ulsaker, G. A.; Teien, G. Identification of caprolactam as a potential contaminant in parenteral solutions stored in overwrapped PVC bags. *J. Pharm. Biomed. Anal.* **1992**, *10* (1), 77–80.

23. Khaliq, M. A.; Alam, M. S.; Srivastava, S. P. Implications of physico-chemical factors on the migration of phthalate esters from tubing commonly used for oral/nasal feeding. *Bull. Environ. Contam. Toxicol*. **1992**, *48* (4), 572–578.

24. Snell, R. P. Solid-phase extraction and liquid chromatographic determination of monophthalates and phthalide extracted from solution administration sets. *J. AOAC Int*. **1993**, *76* (3), 531–534.

25. Snell, R. P. Gas chromatographic determination of cyclohexanone leached from hemodialysis tubing. *J. AOAC Int.* **1993**, *76* (5), 1127–1132.

26. Pearson, S. D.; Trissel, L. A. Leaching of diethylhexyl phthalate from polyvinyl chloride containers by selected drugs and formulation components. *Am. J. Health-Syst. Pharm.* **1993**, *50* (5), 1405–1409.

27. Mass, B.; Huber, C.; Kramer, I. Plasticizer extraction of Taxol®-infusion solution from various infusion devices. *Pharm. World Sci.* **1996**, *18* (2), 78–82.

28. Hanawa, T. E.; Muramatsu, E.; Asakawa, K.; Suzuki, M.; Tanaka, M.; Kawano, K.; Seki, T.; Juni, K.; Kakajima, S. Investigation of the release behavior of diethylhexyl phthalate from polyvinylchloride tubing for intravenous administration. *Int. J. Pharm*. **2000**, *210* (1), 109–115.

29. Loff, S.; Subotic, U.; Reinicke, F.; Wischmann, H.; Brade, J. Extraction of di-ethylhexyl-phthalate from perfusion lines of various material, length and brand by lipid emulsion. *J. Pediatr. Gastroenterol. Nutr.* **2004,** *39* (4)*,* 341–345.

30. Hill, S. S.; Shaw, B. R.; Wu, A. H. B. Plasticizers, antioxidants, and other contaminants found in air delivered by PVC tubing used in respiratory therapy. *Biomed. Chromatogr.* **2003,** *17* (4), 250–262.

31. Loff, S.; Kabs, F.; Subotic, U.; Schaible, T.; Reinecke, F.; Langbein, M. Kinetics of diethylhexylphthalate extraction from polyvinylchloride-infusion lines. *J. Paren. Enteren. Nutr.* **2002,** *65* (5), 305–309.

32. Nakamura, Y.; Nakazawa, K.; Ohmori, S.; Kawano, K.; Shin'ichirou, N.; Kitada, M. Investigation of the involvement of a surfactant in the leaching of diethylhexyl phthalate from administration sets. *Iryo Yakugaku* **2004,** *30,* 180–184.

33. Schoff, H. W.; Rahman, M.; Brazel, C. S. Leaching and migration resistance of phosphonium-based ionic liquids as PVC plasticizers: comparative study of traditional phthalate and citrate plasticizers with ionic liquids. *Polymer Preprints* **2004,** *45,* 295–296.

34. Wang, Q.; Storm, B. K. Migration of additives from poly(vinyl chloride) (PVC) tubes into aqueous media. *Macromol. Symp.* **2005,** *225,* 191–203.

35. Masucci P.; Moffat, M. I. The diffusion of phenol and tricresol through rubber. *J. Pharm. Sci.* **1923**, *12,* 117–120.

36. McGuire, G.; Falk, K. G. The disappearance of phenols and cresols added to "biological products" on standing. *J. Lab. Clin. Med.* **1937**, *22,* 641–645.

37. Wiener, S. The interference of rubber with the bacteriostatic action of thiomersalate. *J. Pharm. and Pharmacol.* **1955**, *7* (2), 118–125.

38. Berry, H. Pharmaceutical aspects of glass and rubber. *J. Pharm. Pharmacol.* **1953**, *5* (12), 1008–1017.

39. Wing, W. T. An examination of rubber used as a closure for containers of injectable solutions. III. The effect of chemical composition of the rubber mix on phenol and chlorocresol absorption. *J. Pharm. Pharmacol.* **1956**, *8* (10), 738–744.

40. Lachman, L.; Weinstein, S.; Hopkins, G.; Slack, S.; Eisman P.; Copper, J. Stability of antibac-

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terial preservatives in parenteral solutions. I. Factors influencing the loss of antimicrobial agents from solutions in rubber-stoppered containers. *J. Pharm. Sci.* **1962**, *51* (3), 224–232.

41. Reznek, S. Rubber closures for containers of parenteral solutions. I. The effect of temperature and pH on the rate of leaching of zinc salts from rubber closures in contact with (acid) solutions. *J. Am. Pharm. Assoc.* **1953**, *42* (5), 288–291.

42. Milosovich, G; Mattocks, A. M. Haze formation of rubber closures for injections. *J. Am. Pharm. Assoc.* **1957**, *46* (6), 377–381.

43. Inchiosa, Jr., M. A. Water-soluble extractives of disposable syringes; nature and significance. *J. Pharm. Sci.* **1965**, *54* (9), 1379–1381.

44. Capper, K. R. Interaction of rubber with medicaments. *J. Mondial de Pharmacie* **1966**, *9* (4), 305–315.

45. Lachman, L.; Pauli, W. A.; Sheth, P. B.; Pagliery, M. Lined and unlined rubber stoppers for multiple-dose vial solutions. II. Effect of Teflon lining on preservative sorption and leaching of extractives. *J. Pharm. Sci.* **1966**, *55* (9), 962–966.

46. Petersen, M. C.; Vine, J.; Ashley, J. J.; Nation, R. L. Leaching of 2-(2-hydroethylmercapto)benzothiazole into contents of disposable syringes. *J. Pharm. Sci.* **1981,** *70* (10), 1139–1143.

47. Danielson, J. W.; Oxborrow, J. S.; Placencia, A. M. Quantitative determination of chemicals leached from rubber stoppers into parenteral solutions. *J. Paren. Sci. Technol.* **1984**, *38* (3), 90–93.

48. Reepmeyer, J. C.; Juhl, Y. H. Contamination of injectable solutions with 2-mercaptobenzothiazole leached from rubber closures. *J. Pharm. Sci.* **1983**, *72* (11), 1302–1305.

49. Salmona, G.; Assaf, A.; Gayte-Sorbier, A.; Airaudo, C. B. Mass spectral identification of benzothiazole derivatives leached into injections by disposable syringes. *Biomed. Mass Spectrometry* **1984**, *11* (9), 450–454.

50. Jaehnke, R. W. O.; Joerg, R. G. Interaction of rubber closures with powders for parenteral administration. *J. Paren. Sci. Technol*. **1990**, *44* (5), 282–288.

51. Jaehnke, R.W.O.; Linde, H.; Mosandl, A.; Kreuter, J. Contaimination of injectable powders by volatile hydrocarbons from rubber stoppers. The C-13-oligomer and determination of its structure. *Acta Pharm. Technol.* **1990**, *36* (3), 139–148.

52. Danielson, J. W. Toxicity potential of compounds found in parenteral solutions with rubber stoppers. *J. Paren. Sci. Technol.* **1992**, *46* (2), 43–47.

53. Norwood, D. L.; Prime, D.; Downey, D. P; Creasey, J.; Sethi, S. K.; Haywood, P. Analysis of polycyclic aromatic hydrocarbons in metered dose inhaler drug formulations by isotope dilution gas chromatography/mass spectrometry. *J. Pharm. Biomed. Anal.* **1995**, *13* (3), 293–304.

54. Paskiet, D. M. Strategy for determining extractables from rubber packaging materials in drug products. *PDA J. Pharm. Sci. Technol.* **1997**, *51* (6), 248–251.

55. Zhang, F.; Chang, A.; Karaisz, K.; Feng, R.; Cai, J. Structural identification of extractables from rubber closures used for pre-filled semisolid drug applicator by chromatography, mass spectrometry and organic synthesis. *J. Pharm. Biomed. Anal.* **2004**, *34* (5), 841–849.

57. Xiao, B.; Gozo, S. K.; Herz, L. Development and validation of LC methods for the determination of potential extractables from elastomeric stoppers in the presence of a complex surfactant vehicle used in the preparation of parenteral drug products *J. Pharm. Biomed. Anal.* **2007**, *43* (2), 558–565.

58. Bergendorff, O.; Persson, C.; Luedtke, A.; Hansson, C. Chemical changes in rubber allergens during vulcanization. *Contact Dermatitis.* **2007,** *57* (3), 152–157.

59. Norwood, D.; Ruberto, M.; DeGrazio, F.L.; Castner, J.; Wong, W.K.; Jenke, D. Extractables and leachables from rubber materials used in pharmaceutical systems. *Rubber & Polymer News* **2009**, *June 29,* 15–19.

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60. Sharma, B.; Bader, F.; Templeman, T.; Lisi, P.; Ryan, M.; Heavner, G. A. Technical investigations into the cause of the increased incidence of antibody-mediated pure red cell aplasia associated with EPREX®. *Eur. J. Hosp. Pharm.* **2004**, *5,* 86–91.

61. Boven, K.; Knight, J.; Bader, F.; Rossert, J.; Eckardt, K.; Casadevail, N. Epoetin-associated pure red cell aplasia in patients with chronic kidney disease: solving the mystery. *Nephr. Dialy. Trans.* **2005**, *20* (Suppl. 3), ii33–ii40.

62. Pang, J.; Blanc, T.; Brown, J.; Labrenz, S.; Villalobos, A.; Depaolis, A.; Gunturi, S.; Grossman, S.; Lisi P.; Heavner, G. A. Recognition and identification of UV-absorbing leachables in EPREX pre-filled syringes: an unexpected occurrence at a formulation–component interface. *PDA J. Pharm. Sci. Technol.* **2007**, *61* (6), 423–432.

63. Jenke, D. R. *Compatability of Pharmaceutical Products and Contact Materials—Safety Considerations Associated with Extractables and Leachables;* Wiley: New York, 2009.

64. Wong, W. K. Impact of elastomer extractables in pharmaceutical stoppers and seals, material supplier perspective. *Rubber World* **2009**, *240* (3), 20 – 29.

65. 3.1.5. Polyethylene with Additives for Containers for Parenteral Preparations and for Ophthalmic Preparations. In the *European Pharmacopoeia,* 7th ed.; Council of Europe: Strasburg, France, **2010**; pp 338–341.

66. Jagnandan, I.; Dunn, H.; Ambrosio, J.; Gilbert, S.G. Isolation and identification of 3,3',5,5'-tetra-bis (tertbutyl) stilbenequinone from polyethylene closures containing titanium dioxide and butylated hydroxytoluene. *J. Pharm. Sci*. **1979**, *68* (7), 916–917.

67. Goydan, R.; Schwope, A. D.; Reid, R. C.; Cramer, G. High-temperature migration of antioxidants from polyolefins. *Food Additives and Contaiminants* **1990**, *7* (3), 323–337.

68. Vom Bruck, C.; Rudolph, F. B.; Figge, K.; Eckert, W. R. Application of diffusion theory to migration of plastics components into packaged goods: Survey of recent migration studies. *Food Cosmet. Toxicol*. **1979**, *17,* 153–157.

69. Azuma, K.; Tanaka, Y.; Tsundo, H.; Hirata, T.; Ishitani, T. Effects of film variety on the amounts of carboxylic acids from electron beam irradiated polyethylene film. *Agric. Biol. Chem*. **1984**, *48,* 2003–2008.

70. Azuma, K.; Tanaka, Y.; Tsunoda, H.; Ishitani, T. Tanaka, Y. Identification of volatiles from low density polyethylene film irradiated with an electron beam. *Agric. Biol. Chem*. **1983**, *47* (4), 855–860.

71. Demertzis, P.G.; Franz, R.; Welle, F. The effects of gamma irradiation on compositional changes in plastic packaging films. *Packaging Technol. Sci*. **1999**, *12* (3), 119–130.

72. Schwope, A. D.; Till, D. E.; Ehntholt, D. J.; Sidman, K. R.; Whelan, R. H.; Schwartz, P. S.; Reid, R. C. Migration of BHT and Irganox 1010 from low-density polyethylene (LDPE) to foods and food-simulating liquids. *Food Chem. Toxicol.* **1987**, *25* (4), 317–326.

73. Helmroth, I. E.; Bekhuis, H. A. M.; Linssen, J. P. H.; Dekker, M. Direct measurement of additive migration from low-density polyethylene as a function of space and time. *J. Appl. Poly. Sci.* **2002,** *86* (12), 3185–3190.

74. Welle, F. Migration of radiolysis products from radiation-sterilized plastics. *Pharmazeutische Industrie* **2005,** *67*, 970–972.

75. Arias, M.; Penichet, I.; Ysambertt, F.; Bauza, R.; Zougagh, M.; Rios, A. Fast supercritical fluid extraction of low- and high-density polyethylene additives: comparison with conventional reflux and soxhlet extraction. *J. Supercritical Fluids* **2009**, *50* (1), 22–28.

76. Akapo, S. O.; McCrea, C. M. SPME-GC determination of potential volatile organic leachables in aqueous-based pharmaceutical formulations packaged in overwrapped LDPE vials. *J. Pharm. Biomed. Anal.* **2008**, *47* (3), 526–534.

77. Haishima, Y.; Hayashi, Y.; Yagami, T.; Nakamura, A. Elution of bisphenol-A from hemodia-

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lyzers of polycarbonate and polysulfone resins. *J. Biomed. Res.* **2001**, *58* (2), 209–215.

78. Sajiki, J.; Yonekubo, J. Degradation of bisphenol-A (BPA) in the presence of reactive oxygen species and its acccleration by lipids and sodium chloride. *Chemosphere* **2002**, *46* (2), 345–354.

79. Sajiki, J.; Yonekubo, J. Leaching of bisphenol-A from polycarbonate plastic to water containing amino acids and its degradation by radical oxygen species. *Chemosphere* **2004**, *55* (6), 861–867.

80. Sajili, J.; Yonekubo, J. Leaching of bisphenol A (BPA) to seawater from polycarbonate plastic and its degradation by reactive oxygen species. *Chemosphere* **2003**, *51* (1), 55–62.

81. Chang, C. M.; Chou, C. C; Lee, M. R. Determining leaching of Bisphenol A from plastic containers by solid-phase microextraction and gas chromatography-mass spectrometry. *Anal. Chim. Acta*, **2005**, *539* (1), 41–47.

82. Cao, X.; Corriveau, J. Migration of Bisphenol A from polycarbonate baby and water bottles into water under severe conditions. *J. Agric. Food Chem.* **2008**, *56* (15), 6378–6381.

83. Jakobs, A. Topas Cyclic-Olefin Copolymer—Advances in Pharma Packaging and Pre-Fillable Drug Delivery Systems. In *Medical Polymers 2000;* 14th International Conference, Vienna, Austria, September, 2000.

84. Grimm, M. Cyclic Olefin Copolymer (COC): An Innovative Transparent Plastic Material for Applications in Medical and Diagnostic. In *Medical Polymers 2006;* 5th International Conference Focusing on Polymers used in the Medical Industry, Cologne, Germany, June, 2006.

85. Shah, D.; Cronin, J.; Chacko, M. Gillum, A. Impact of formulation and processing parameters on silicone extraction from cyclic olefin copolymer (COC) syringes. *PDA J. Pharm. Sci. Technol*, **2011**, *65* (2), 109–115.

86. Jenke, D.; Odufu, A.; Couch, T.; Chacko, M.; Strathmann, S.; Edgcomb, E. Evaluation of the general solution compatibility of polymer materials used in medical devices such as syringes. *PDA J. Pharm. Sci. Technol*. **2012**, *66* (3), 286–306.

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