PDA Journal
of Pharmaceutical Science and Technology

The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP)

Diane Paskiet, Dennis Jenke, Douglas Ball, et al.

PDA J Pharm Sci and Tech **2013**, *67* 430-447
Access the most recent version at doi:10.5731/pdajpst.2013.00936

PQRI SPECIAL SECTION: The following article is an invited contribution submitted by the Product Quality Research Institute (PQRI) Leachables and Extractable Working Group. The article was internally reviewed by PQRI and FDA members and their affiliated companies and not peer-reviewed by the PDA Journal.

REVIEW

The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP)

DIANE PASKIET[1,*], DENNIS JENKE[2], DOUGLAS BALL[3], CHRISTOPHER HOUSTON[4], DANIEL L. NORWOOD[5], and INGRID MARKOVIC[6]

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

[1]West Pharmaceutical Services, Exton PA, USA; [2]Baxter Healthcare Corporation, Round Lake, IL, USA; [3]Pfizer, Inc., Groton, CT, USA; [4]Bausch & Lomb, Rochester, NY, USA; [5]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; and [6]United States Food and Drug Administration, Washington, DC, USA

ABSTRACT: The Product Quality Research Institute (PQRI) is a non-profit consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality and development. The collaborative activities of PQRI participants have, in the case of orally inhaled and nasal drug products (OINDPs), resulted in comprehensive and widely-accepted recommendations for leachables assessments to help ensure patient safety with respect to this class of packaged drug products. These recommendations, which include scientifically justified safety thresholds for leachables, represent a significant milestone towards establishing standardized approaches for safety qualification of leachables in OINDP. To build on the success of the OINDP effort, PQRI's Parenteral and Ophthalmic Drug Products (PODP) Leachables and Extractables Working Group was formed to extrapolate the OINDP threshold concepts and best practice recommendations to other dosage forms with high concern for interaction with packaging/delivery systems. This article considers the general aspects of leachables and their safety assessment, introduces the PODP Work Plan and initial study Protocol, discusses the laboratory studies being conducted by the PODP Chemistry Team, outlines the strategy being developed by the PODP Toxicology Team for the safety qualification of PODP leachables, and considers the issues associated with application of the safety thresholds, particularly with respect to large-volume parenterals. Lastly, the unique leachables issues associated with biologics are described.

KEYWORDS: Extractables, Leachables, Safety assessment, Safety qualification thresholds, Parenteral and ophthalmic drug products, Best practice recommendations, Biologic concerns, PQRI, Parenteral packaging, Ophthalmic containers.

LAY ABSTRACT: The Product Quality Research Institute (PQRI) is a non-profit consortium involving industry organizations, academia, and regulatory agencies that together provide recommendations in support of regulatory guidance to advance drug product quality. The collaborative activities of the PQRI Orally Inhaled and Nasal Drug Products Leachables and Extractables Working Group resulted in a systematic and science-based approach to identify and qualify leachables, including the concept of safety thresholds. Concepts from this widely accepted approach, formally publicized in 2006, are being extrapolated to parenteral and ophthalmic drug products. This article provides an overview of extractables and leachables in drug products and biologics and discusses the PQRI Work Plan and Protocols developed by the PQRI Parenteral and Ophthalmic Drug Products Leachables and Extractables Working Group.

*Corresponding Author: Diane Paskiet, West Pharmaceutical Services, 530 Herman O. West Drive, Exton PA 19341-1147. diane.paskiet@westpharma.com

doi: 10.5731/pdajpst.2013.00936

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.

Introduction

Pharmaceutical products are manufactured, stored, distributed, and/or administered in packaging systems, including bottles, bags, vials, ampules, prefilled syringes, inhalers, and others. Packaging systems are made up of components that are fabricated from materials, such as rubber, plastic, glass and metal, which contain both organic and inorganic chemical substances that are either added purposefully for functional reasons, or which are present as surface residues due to the packaging components' manufacturing. Packaging components can be in direct contact or indirect contact with the drug product formulation. During the time that the drug product and its packaging system are in contact, the two may interact. One such interaction is the migration, or leaching, of chemical substances out of the packaging system and into the drug product formulation. These chemical substances have the ability, under certain circumstances, to migrate out of the packaging system (extractables) and/or potentially affect the quality of the drug product and have an adverse effect on the patient.

Regulatory guidance documents on packaging systems, while missing sufficient guidance, have provided pharmaceutical manufacturers with a high level strategic process to assess and qualify the safety of extractables and leachables in various dosage forms using a risk-based approach and sound science. This strategic process includes identifying extractables, performing migration studies, and evaluating toxicity of extractables/leachables (1–4). While the guidance documents establish high-level strategies and processes, the practical implementation of this process is problematic because it suggests that all extractables and/or leachables, regardless of their accumulation levels, must be reported and undergo full toxicological safety assessments. Such an assessment would be necessary even when the concentration of the leachables in the drug product is so low that it is highly unlikely that it will adversely affect patient safety. However, some extractables may not be detected in the final drug product (i.e., they are not leachables), and some leachables may be present in the final drug product at levels so low as to be of negligible risk to human safety (5). Such a situation may be counterproductive, as regulatory and industry resources are most effectively used and ensure the greatest level of product safety when they are focused on those substances to which patients are actually exposed (i.e., leachables) and which are at levels that potentially affect patient safety. With the aim of balancing the absolute safety risk with the level of effort required to establish that risk, it is reasonable to propose that there is a dose threshold for leachables (or extractables as probable leachables) below which the vast majority of leachables (or extractables as probable leachables) will have an acceptably negligible potential safety impact.

This challenge of establishing such a threshold for the identification and qualification of leachables was addressed for orally inhaled and nasal drug products (OINDPs) by the Product Quality Research Institute (PQRI) Leachables and Extractable Working Group. PQRI is a non-profit consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality and development (see pqri.org). By virtue of its diverse membership, PQRI provides a unique forum to focus critical thinking, conduct research, exchange information, and propose methodology or guidance to pharmaceutical companies, regulators, and standard-setting organizations. The PQRI OINDP Working Group considered a risk-based approach to leachables safety assessment and developed and published recommendations related to both safety thresholds for leachables and best demonstrated practices for the chemical assessment of extractables and leachables (5). The PQRI OINDP process and these recommendations are considered in greater detail in the *Commentary* publication preceding this article.

Although the PQRI leachables qualification concepts were developed specifically for OINDP, it is reasonable to suggest that the general outline and concepts proposed for OINDP are also applicable to other relatively high-risk drug products, such as parenteral and ophthalmic drug products (PODP), considering that OINDP and PODP products are jointly classified by the Food and Drug Administration (FDA) in the quadrant of highest/high concern with respect to the risk associated with undesirable packaging system–drug product interactions (see Table I. Packaging Concerns for Common Classes of Drug Products; *1*). Nevertheless, specific differences between the OINDP and PODP dosage forms and their associated packaging systems (e.g., type of packaging material, drug formulation, drug volume administered, etc.) must be addressed if the OINDP principles are to be modified for application to PODP dosage forms. Thus, a PQRI Working Group comprised of toxicologists and chemists was tasked to extrapolate the OINDP threshold

Table I
Examples of Packaging Concerns for Common Classes of Drug Products[b]

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

[a]For the purpose of this table, the term suspension is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.
[b]From Guidance for Industry. Container Closure Systems for Packaging Human Drugs and Biologics (1).

concepts and best practices recommendations to PODP based on a three-point hypothesis (6):

1. Threshold concepts that have been developed for safety qualification of leachables in OINDP and the existing FDA/European Medicines Agency (EMEA) guidance documents can be extrapolated to the evaluation and safety qualification of packaging systems (such as container closure systems) for PODP.

2. The good science practices that were developed for the OINDP pharmaceutical development process can be extrapolated to packaging systems for PODP.

3. Threshold and best practices concepts can be integrated into a comprehensive process for characterizing packaging systems with respect to leachable substances and their associated impact on PODP safety.

Considering the specific characteristics of PODP, the PQRI Leachables and Extractables Work Group developed a Work Plan (7) and Testing Protocols (8), taking into account

- Materials components and/or packaging systems applicable to PODP,
- Expansion of OINDP extraction solvents to include aqueous systems, and
- Extraction and/or analysis methods which have unique applicability to PODP.

The PODP Working Plan was driven by the predicate knowledge gained by the OINDP Working Group, emphasizing concepts consistent with quality by design (9), including the expectations that

- Requirements and acceptance criteria are defined early in the development process so that material use decisions can be based on an understanding of the chemistry of the material,
- Container closure materials and components are evaluated to establish control points,
- Multi-disciplinary team members communicate and collaborate early in the product development stages to establish sound methods for reducing risk,
- Good science is used to develop and define effective processes and products, and
- Proper strategies are employed to ensure that quality products are generated based on systems to identify and control critical parameters.

The PODP Work Group divided the tasks established in the Work Plan into two work streams. A Chemistry Team was charged with developing Best Practice Recommendations for conducting PODP extractables and leachables studies and producing the data necessary to support and justify such recommendations. An important aspect of this team's task was extrapolating the OINDP analytical threshold concept to PODP dosage forms. Additionally, a Toxicology Team was formed to translate the OINDP safety qualification threshold concepts to PODP dosage forms. Both teams were tasked with using a risk management scheme consistent with the appropriate references found in the FDA Container Closure Guidance (1), the PQRI OINDP Threshold and Best Practices Recommendations (5), and the FDA Guidance on Quality Systems Approach to Pharmaceutical GMPs (9).

Chemical Aspects of Safety Assessment—The Chemistry Team

Background

The level of concern for potential patient safety issues associated with packaging component–dosage form interactions is ranked highest for injections and injectable suspensions and high for ophthalmic solutions and suspensions (1). Dosage forms delivered by these routes of administration have a history of reported leachables originating from various packaging system components and materials of construction. As (i) there is an abundance of polymer types and grades that are used to manufacture components for the manufacture, packaging, storage, and delivery of pharmaceutical products, and (ii) the chemistry of a given material, its polymerization process, formulation ingredients, physical properties, and manufacturing processes are wide-ranging, a wide spectrum of chemical entities can migrate or leach into drug products. Additionally, the diversity of leachables is exacerbated by the fact that a material's extractable (i.e., potential leachables) profile can also vary between material lots and be modified by exposure to various high-stress environments in material processing, drug product manufacturing, in storage, and in distribution. Reviews of typical extractables, spanning a broad range of materials used in pharmaceutical packaging, have been published by Jenke (10–12).

During the translation of OINDP principles to PODP dosage forms, it was recognized that PODP dosage forms are sufficiently different that certain allowances would have to be made. For example, translating the thresholds to large-volume parenterals (LVPs) is challenging because thresholds for products with large daily dose volumes could be so low that they are beyond the capabilities of modern analytical science (also see the *Commentary*). The fundamental concept of thresholds, introduced by the OINDP Leachables and Extractables Working Group, considered a *safety concern threshold* (SCT), that is, a value below which leachables are not considered for identification and toxicological qualification. The SCT would be used to derive an initial *analytical evaluation threshold* (AET) for extractables, which would lead to AETs for leachables. The AET is defined as the level at or above which a leachable and/or extractable should be reported and considered for potential toxicological assessment. The AET will vary depending on (i) the particular drug product configuration and (ii) the method(s) used to detect and quantify a leachable or extractable (5). For instance, Figure 1 contrasts the AETs between LVPs and dosage forms with small daily dose volumes based on the OINDP SCT of 0.15 μg/day. As daily dose volume increases, the value of the AET decreases. The effect of the decreasing AET is illustrated in Figure 2, which shows an extractables (or leachables) profile revealed in a chromatogram. The peaks in the chromatogram represent individual extractables and the size of the peak reflects the extractables' concentrations. The AET, shown as a line in this figure, divides the chromatographic peaks into two groups, those above the AET, which must be safety assessed, and those below the AET, which are deemed to be safe by virtue of their low concentrations and thus do not have to be assessed further. It is clear that as the AET decreases, the number of peaks that must be safety assessed increases. Not only does this circumstance increase the number of peaks that must be assessed, but it increases the level of effort required to perform the assessment as it is typically the case that the smaller the peak, the more difficult it is to do a proper chemical assessment.

To investigate and deal with the extenuating aspects of PODP dosage forms, the PODP Chemistry Team conceived a three-phase laboratory program consisting of three specific experiments:

1) A *controlled extraction study* is the initial step, designed to characterize the extractables profile of each material and, thus, inferring potential leachables. In addition to facilitating raw material and packaging component selection and providing an

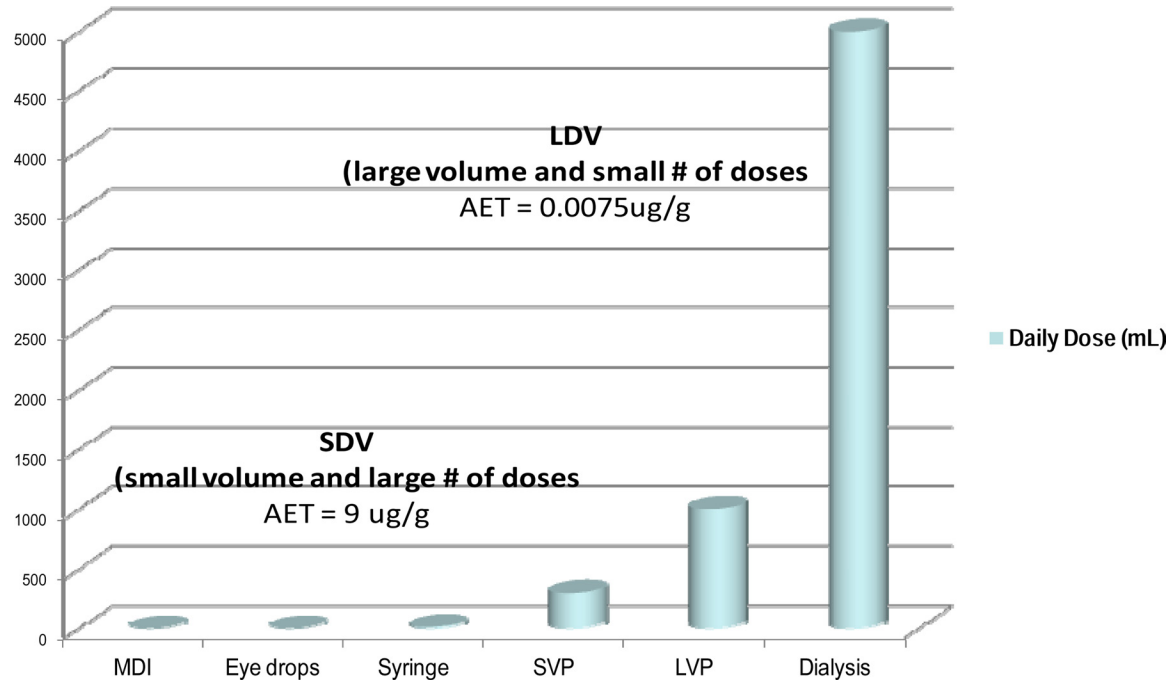

Figure 1

The effect of daily dose volume on the analytical evaluation threshold (AET). The daily dose volume varies greatly among various pharmaceutical dosage forms. Because the AET is related to the safety concern threshold (SCT), which is a fixed quantity (taken as the 0.15 μg/day OINDP SCT for this example), the value of the AET is inversely proportional to the daily dose volume. Thus an AET which is analytically achievable in a small daily dose volume (SDV) dosage form (e.g., metered dose inhaler, MDI) may not be achievable in a large daily dose volume (LDV) dosage form (e.g., large volume parenteral, LVP).

initial assessment of potential safety issues, such a study facilitates the development of analytical methodologies for leachables.

2) A *simulation study* is an intermediate step to more effectively delineate extractables as probable leachables. In this study, a mock, laboratory-prepared PODP packaging system was assembled, filled with extraction media relevant for PODP, and stored under accelerated use conditions. The resulting fill solutions will be characterized for extractables. The outcome of this study should provide the rationale for leachables assessment (as further discussed by Jenke, *13*) and would allow the application of thresholds in cases such as LVPs.

3) A *leachables study* is the final phase employing targeted validated methods to confirm the actual accumulation of target leachables in the drug product during shelf life.

According to this scheme, extraction studies are suggested as an excellent means to characterize packaging materials to develop a list of probable extractables and potential leachables. Leachable studies seek targeted leachables in actual drug product, but these studies may be challenging for LVPs owing to extremely low AETs in potentially complex media. The concept of a simulation study is to match the leaching propensity of the drug product vehicle as closely as possible with a simple solvent system. A simulation study might use accelerated (not exaggerated) conditions to mimic worst-case conditions. The output of such a study would be "extractables" with a high probably of becoming leachables.

Simulation studies ameliorate the challenge posed by LVPs in several ways. First, unlike the metered dose inhalers considered by the PQRI OINDP team (where "all extractables are leachables"), an aqueous, LVP is expected to present a subset of possible extractables as potential leachables. By using a more relevant solvent system for the simulation study, extractables with low propensity to extract into product would be eliminated

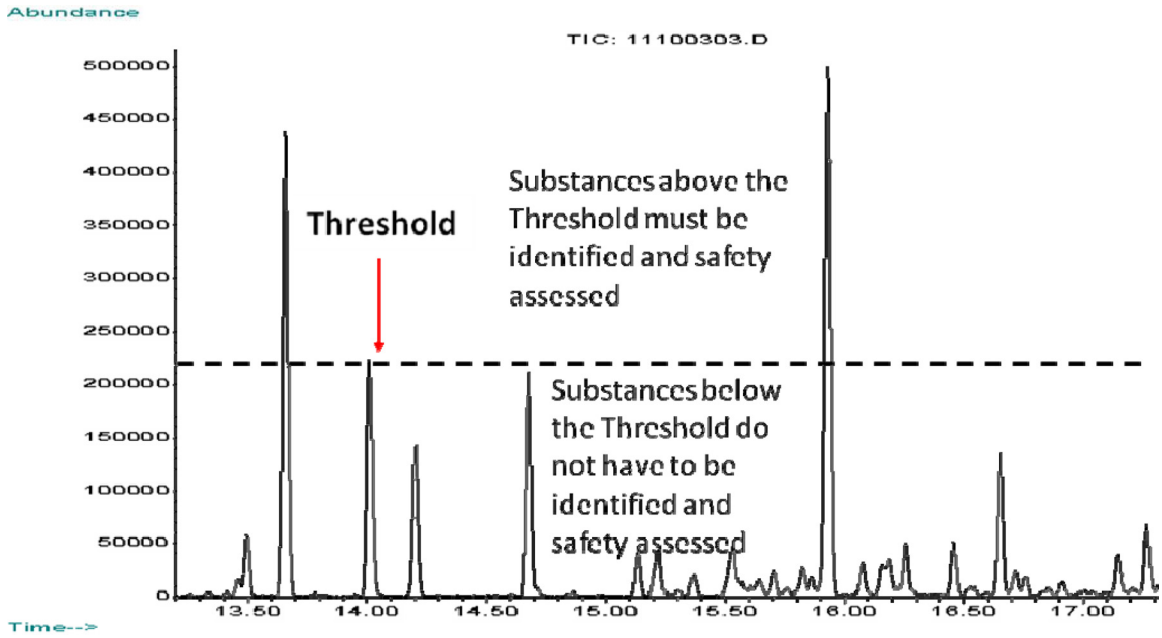

Figure 2

The concept of a reporting threshold for extractables and leachables. Pictorially, the concept of the threshold can be envisioned through the use of a chromatogram, which is the means by which information about organic leachables or extractables is obtained. In the chromatogram, each peak corresponds to a substance that was present in the test sample, and the size of the peak (either its height or its area) is proportional to the amount of that substance that is present in the test sample. A threshold, representing that amount of any individual substance that will not produce an undesirable safety outcome, can be superimposed on the chromatogram as a straight line at its corresponding response level. Those substances whose responses are below the threshold do not have to be considered further (e.g., identified), as their dose will be too low to produce an unacceptable safety outcome. Those substances whose responses are above the threshold have the potential to produce an unacceptable safety outcome. In order to more precisely specify the actual safety risk for such substances, they must be identified so that their actual safety risk can be individually established. As the threshold decreases, the number of substances (peaks) that have to be identified increases. Furthermore, the complexity of establishing the identity increases as the peaks get smaller.

from consideration, thus reducing the number of compounds under scrutiny to those most pertinent to the drug product. Second, the observed extractables will be present at more realistic concentrations, thus aiding safety assessment. Finally, use of a simulating medium less complex than the drug product formulation facilities the analytical testing and identification of those compounds above the AET.

Phase I: The Controlled Extraction Study

The objective of the Chemistry Team was to establish best demonstrated practices for the identification and safety qualification of leachables in PODP, recognizing the means by which extractables information can support and facilitate such qualifications. Relevant dosage forms within scope of the work plan included prefilled syringe (PFS), small- and large-volume parenteral (SVP and LVP), and topical ophthalmic routes of administration. These practices could also apply to materials if used for short-term or intermediate storage such as disposable systems. To accomplish their objective as it relates to extractables, the Chemistry Team acquired five materials typical of those used in packaging systems for PODP with the purpose of producing extractables data to evaluate their hypothesis. These materials, along with their typical uses, are described in Table II. An understanding of the types of materials used in packaging components and their potential leachables dictated the choice of the materials for the PODP evaluations. These five materials are among the most common and diverse classes of materials used in components of PODP packaging systems, and all five materials are known to have extract-

Table II
Description of the Test Materials Used in the Chemistry Team Controlled Extraction Study

Test Materials	Article	Composition	Application	Category
Bromobutyl Rubber (BIIR)	Compression Molded Sheet	• Brominated Isobutylene Isoprene Copolymer (57.3%)	Closures Plungers Gaskets	SVP or LVP for Multiple Doses per Day
		• Calcined Aluminum Silicate (38.2%)		
		• Titanium Dioxide (1.2%)		
		• Zinc Oxide, (0.6%)		
		• Polyethylene (0.6%)		
		• Carbon Black (0.4%)		
		• Calcined Magnesium Oxide (0.3%)		
		• Morpholine/polyisobutylene (0.3%)		
Polyvinyl Chloride (PVC)	Pellets	• PVC Resin	Bags Tubing	LVP
		• DEHP (30%)		
		• Epoxidized Soybean Oil (7%)		
		• Zn Stearate (0.5%)		
		• Ca Stearate (0.5%)		
		• Stearamide (1%)		
Low-Density Polyethylene (LDPE)	Blown Film	• Irganox B215 (Irgaphos 168 and Irganox 1010 Blend	Over-pouch BFS Containers	BFS, SVP, LVP
		•(1000 ppm)		
		• BHT (200 ppm)		
		• Calcium Stearate (500 ppm)		
		• Erucamide (500 ppm)		
		• Chimassorb 944 (2000 ppm)		
Cyclic Olefin Copolymer (COC)	Plaques	Irganox 1010 **Ultramarine Blue**	Syringes Vials	PVS, SVP or LVP for Multiple Doses per Day
Polycarbonate (PC)	Injection Molded Plaques	Irganox 1076 (0.05 PHR)	Ports Tubes	LVP
		Irgaphos 168 (0.1 PHR)		

ables that could become leachables in contained drug products. Considering the rubber material, for example, butyl and halobutyl rubbers (isobutylene/isoprene copolymer base) are commonly used with sterile parenteral products and migration of chemical substances can occur, including the rubber's formulation ingredients and substances or degradation products formed during molding and sterilization processes (14–15). Furthermore, the conditions of contact between the elastomeric components of packaging systems and a therapeutic product can include elevated temperatures and long contact times. Lastly, pharmaceutical products may contain solubilizing agents in their formulation that may increase the potential for leaching.

Given the nature of the rubber (e.g., complex chemistry and transport properties) and the conditions of contact, consequential interactions between elastomeric parts and parenteral solutions and pharmaceutical products have been reported (16–23).

Considering the other test articles, thermoplastics are another broad class of polymers commonly used in the pharmaceutical industry. Unlike conventional rubbers, they can be melted and then reformed. Polymerization mechanisms for thermoplastics typically involve an addition or condensation reaction. For example, polyvinyl chloride (PVC) is manufactured by the addition reaction of substituted ethylene compounds (24). PVC was included in the PODP protocol because it is one of the most common materials used in components (e.g., tubing) and packaging (e.g., blood bags and IV bags). The leaching of chemicals from PVC and into parenteral products is well-documented (25–33). The potential for plasticized, PVC-related substances to leach into drug product formulations and produce adverse events in patients has been considered in studies evaluating risk for various patient populations (34).

Polyolefin is the generic term for a family of plastics derived by addition of ethylene and/or propylene and it is used for various types of drug product contact surfaces (35). Given their wide use in the food and pharmaceutical industries, a plethora of information is available on polyolefins. Polyethylene components have been extensively characterized for extractables and leachables in numerous applications (36–39). The PODP Chemistry Team evaluated two types of materials from the olefins family, a low-density polyethylene (LDPE) formulation and a cyclic polyolefin copolymer (COC). Cyclic olefin polymers and copolymers have been gaining interest in the pharmaceutical industry as they are recognized as having very low levels of potential leachables (40, 41).

Polycarbonate (PC) is another material that was considered as it is frequently used in connectors and ports for large volume parenteral systems. The polymerization mechanism for PC involves condensation in which two reactive molecules join to form a new compound; common PC materials are formed from bisphenol A (BPA) and phosgene (24). PC has been extensively researched in terms of its leaching potential because concerns have been raised about the safety of BPA. In 2008, a subcommittee of the FDA's science board raised questions about whether FDA's review had adequately considered the most recent scientific information available. As recently as March 30, 2012, the FDA issued an interim update finding that BPA remains safe in food contact materials with the exception of those applications intended for pediatric use (42). The migration of BPA from food and pharmaceutical packaging has been studied (43).

Secondary components such as labels with varnishes used on packages have also been reported as sources of leachables in ophthalmic products during stability (44). In light of concerns for migration of extractables through semipermeable containers, the PODP project also considered controlled extraction studies related to secondary packaging labels (45).

Formulation information for the five PODP test articles was provided by their various suppliers. However, in addition to these anticipated extractables, unexpected extractables could be revealed by the testing performed in this study due to the materials' multifaceted supply chains. While the test articles were representative of materials used in pharmaceutical applications, the specific test articles themselves are not used in commercial packaging systems.

A semi-quantitative extractables protocol was developed by the Chemistry Team with the objective of acquiring "first pass" data to characterize representative materials used in components for packaging parenteral and ophthalmic drug products for extractables. This protocol, consistent with the predicate OINDP study, incorporated multiple solvents, extraction techniques, and analytical methods (5, 8). The extractions utilized organic and additional aqueous-based solvent systems associated with PODP formulations and involved extraction techniques relevant to the PODP dosage forms. The resultant extracts were characterized for extractables by multiple orthogonal analytical techniques, including gas chromatography/mass spectrometry (GC/MS), gas chromatography flame ionization detection/ (GC/FID), liquid chromatography/mass spectrometry (LC/MS), inductively doupled plasma/ mass spectrometry (ICP /MS), and headspace GC/MS. Specific details associated with the extraction and analysis processes are contained in a companion manuscript appearing in this issue of the *PDA Journal.* The analytical testing was performed so that extractables with estimated concentrations of 10 μg/g or greater were targeted for identification.

The "first pass" PODP data were acquired by industry volunteer laboratories and were presented, in a pre-

liminary manner, at the 2011 PODP Workshop on Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products (46). A more extensive presentation of these study results and their implications to best demonstrated practice recommendations is contained in the companion manuscript in this current issue of the *PDA Journal.*

Phase 2: The Simulation Study

Adopting the three-step approach described above led to the generation and implementation of a Phase II Protocol which involves a migration, or simulation, study. This study is being conducted on a laboratory-produced "packaging system" modeled after the flexible bottle typically employed with ophthalmic products, including secondary labels. This study, whose design is indicated in the relevant PQRI Work Plan (45), is currently ongoing; results from this study and their implications with respect to best demonstrated practices and thresholds will be the subject of future communications.

Toxicological Aspects of Safety Assessment—The Toxicology Team

The PQRI OINDP Leachables and Extractables Working Group developed the concept of the *analytical evaluation threshold* (AET), which is to be applied to data from controlled extraction or leachable studies; this threshold is a benchmark to allow for a preliminary determination of which extractables should be identified and quantified (5). This benchmark is derived from the SCT relative to doses per day and doses per container where the SCT is defined as the threshold in which a leachable would have a dose so low as to present negligible safety concern from carcinogenic and noncarcinogenic effects. This SCT differs from the threshold of toxicological concern (TTC) (47, 48), as it is used as a benchmark for identification purposes, not as a safety control limit. A similar concept is reflected in the qualification threshold (QT), where the QT is a threshold below which a given noncarcinogenic leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents a structural–activity relationship.

Building on the threshold concepts developed for OINDP, specifically the SCT and QT, the Toxicology Team considered the unique circumstances of PODP dosage forms and packaging systems to establish comparable thresholds for PODP products. Specifically, proposed toxicological thresholds were developed for PODP, based on a classification strategy and an additional uncertainty factor to account for dose administration differences. The developed qualification classification included a risk assessment model and decision trees, as appropriate, to account for the PODP routes of administration, dose, duration, local vs systemic exposure, and patient population. The Toxicology Team evaluated the use of existing standards and best practices—environmental pollutants, indirect food additive regulations, International Conference on Harmonisation (ICH), USP monographs, ISO standards, EMEA guidance on genotoxic impurities—for application to PODP.

This classification process proceeded as follows. The Toxicology Team, together with the Chemistry Team, compiled a list of ~600 potential chemicals associated with leachables and/or extractables to explore a classification scheme for leachables in PODP. The list of leachable and extractable chemicals was initially sorted via ToxTree (49) into Cramer classes as follows (50):

- Class 1: substances of simple chemical structure with known metabolic pathways and innocuous end products which suggest a low order of oral toxicity.
- Class 2: substances that are intermediate; possess structures that are less innocuous than those in Class 1 but they do not contain structural features that are suggestive of toxicity like those in Class 3.
- Class 3: substances with chemical structures that permit no initial presumption of safety and may even suggest significant toxicity.

In addition to the traditional three Cramer classes that sort chemicals into categories from least toxic to most toxic (1800 to 90 μg/day), a fourth class was added to capture chemicals of known or suspect genotoxic potential using Deductive Estimation of Risk using Existing Knowledge (DEREK) software (51). Additional safety factors to account for body weight (BW) and route of administration differences (oral vs parenteral) were considered to add orders of magnitude to the already conservative estimates established by Cramer and refined by Munro (51). The sorting produced a recognizable and actionable distribution of compounds among the four classes. As was anticipated, the sorting indicated that approximately 10% of the Class 3 chemicals sorted by ToxTree are known hu-

Table III
Proposed Safety Classification of Extractables/ Leachables

Class	Threshold	
	μg/day	μg/kg/day, Adult
Initial PQRI Classification for PODP		
1 (low toxicity)	150	3
2 (moderate toxicity)	50	1
3 (marked toxicity)	5	0.1
4 (genotoxicant)	0.15	0.003
Current PQRI Classification of PODP		
1 (general toxicity, QT)	150	3
2 (sensitizers)	5	0.1
3 (genotoxicant, SCT)	1.5	0.003

man carcinogens and/or known mutagens (e.g., polynuclear aromatic hydrocarbons (PNAs), nitrosamines).

With the four categories fully populated, the Toxicology Team considered appropriate thresholds for each class. Consistent with the sorted data and with current thinking on genotoxic impurities with regard to compounds of concern, the daily limit for exposure to a Class 4 chemical was initially set at 0.15 μg/day as the starting point for PODP safety assessment. This train of thought led to an initial classification proposal, as indicated in Table III. In considering thresholds for the other classes, the Toxicology Team recognized that the degree of risk associated with a Class 3 chemical may not significantly differ from that for a Class 1 chemical, suggesting that only three classes instead of five classes were relevant. The Team validated the need for three distinct classes by evaluating twenty-five Class 3 chemicals for acute and repeat dose toxicology, developmental and reproductive toxicology, genetic toxicology, carcinogenicity, and any other pertinent information related to risk. With three exceptions, the evaluation demonstrated that, where data were available, there was at least a 100 fold margin from the No Observed Adverse Effect Level in an animal study when compared to the dose of the chemical in a 50 kg human. None of the 25 chemicals had published study results suggesting genotoxicity or carcinogenicity. Based on the risk assessments of the 25 Class 3 chemicals and discussions with regulators around the acceptable level for genotoxicants (1.5 μg/day) in PODP, the classification was modified to produce 3 classes with the proposed thresholds as noted in Table III. When compared to Cramer, the PQRI Class 1 level of 150 μg/day is similar to a Cramer class 3 (90 μg/day) chemical (52). In other words, the overall approach in sorting known chemicals that have extracted or leached from packaging components puts them into a single class that establishes a conservative estimate of risk. Note that the lowest threshold of concern for genotoxicants was raised to 1.5 μg/day versus the OINDP SCT of 0.15 μg/day. The OINDP SCT was derived assuming a 10^{-6} lifetime risk of carcinogenicity. This conservative value was chosen because of the chemical nature of likely extractables and leachables from metered dose inhaler (MDI) packaging systems, the strong solvents present in MDI formulations that significantly enhance the likelihood of leaching, and the fact that the dose is delivered directly to the diseased organs of a sensitive patient population. The higher working value for PODP (1.5 μg/day) is less conservative than the OINDP SCT and is strongly influenced by the nature of PODP vehicles (primarily aqueous) and packaging systems such that the team determined that a less conservative threshold was logical for PODP.

An additional safety endpoint that the Toxicology Team considered was irritation and sensitization. The PQRI OINDP best practices recommendation provided a rationale that the qualification threshold for chemicals with known or suspect sensitization or irritation potential is 5 μg/day (46). No additional data were found to suggest that the qualification threshold should be any different for PODP and thus this value was preserved for PODP. Ultimately, this thought process led to the current proposed PQRI classification shown in Table III.

A challenge recognized by the Toxicology Team is whether or not all PODP dosage forms have the same safety concerns. For example, parenteral dosage forms can reasonably be assessed for their systemic safety impact. As with OINDP, cancer risk serves as a conservative endpoint in those cases. On the other hand, ophthalmic solutions and suspensions are applied locally as topicals and ocular irritation is commonly regarded as a key endpoint. These differences between parenteral and ophthalmic dosage forms may drive separate strategies. By way of example, the FDA assesses drug product leachables against a set of concentration-based thresholds: Reported at above 1 ppm; Identified at 10 ppm, and Qualified at 20 ppm (53). This is a different paradigm than the exposure-based thresholds typically applied in the evaluation of sys-

temic toxicology. As a result, ophthalmics may be best served by the development of a threshold for ocular irritation. Moreover, on-eye concentration may be more relevant for ocular irritation than daily exposure (the FDA approach serves as a precedent for this idea). The strategy for ophthalmic solutions and suspensions is still evolving.

Lastly, the PQRI Toxicology Team recognizes that the subject of thresholds for potentially genotoxic substances in marketed drug products continues to be a matter for international discussion (ICH M7, Step 2, 2012) (54) and the acceptable limit for a genotoxic impurity may be higher based on multiple factors. As noted in the original PODP hypothesis, although the individual threshold values may differ from OINDP, the threshold concepts remain the same. Thus, the PODP thresholds serve as reporting or identification thresholds and not as TTC-like control thresholds or limits.

Safety and Compatability Considerations for Leachables and Extractables in Biologics

The PODP Working Group recognizes that, in addition to primary safety issues (i.e., safety issues due to the intrinsic toxicity of the leachable), leachables can also exert an undesired effect to product quality thereby altering physico-chemical, biological (i.e., potency), and/or stability properties of the active pharmaceutical ingredient. Some of the plausible mechanisms by which leachables interact with therapeutic proteins include a direct effect on the recombinant therapeutic protein catalyzing oxidation, aggregation, truncation, formation of protein adducts; or indirect effects, via interaction with formulation excipients inducing formation of particulates; or by affecting the upstream steps of production causing altered protein translation or post-translational events during fermentation (55–57). Potential leachables (e.g., silicon oil, monoethylhexylphthalate, (di-2-ethylhexyl phthalate polycyclic aromatic hydrocarbons, alkyl phenols, metals, etc.) from various sources have similarly been implicated to act as adjuvants (e.g., inducing antibody response) and/or as general immune-modulators (e.g., causing up- or down-regulation of specific cytokines) in animal studies thus providing further support for immunogenicity as a plausible mechanism of leachable action (58–68).

The nature of biologic therapeutics may render them especially susceptible to the impact of leachables due to their

- Large size (e.g., recombinant human erythropoietin is ~30 kD and an average antibody molecule is ~150 kD);
- Complex structure (e.g., secondary, tertiary, and quaternary) whereby changes in protein configurations via random unfolding or other possible conformational changes may lead to a loss of protein structure and/or function, which may lead to adverse safety outcomes due to exposure of immunogenic epitopes that were originally buried in the protein interior;
- Extensive surface area providing numerous reactive sites, which may serve as nucleation zones for structural and chemical modifications including those that have been previously discussed in this paper (e.g., aggregation, degradation, oxidation, etc); and
- Amphiphilic nature whereby proteins possess both hydrophilic and hydrophobic sites possibly making them more effective solubilizers of leachables compared to small-molecule compounds.

Additional risks for leachables may not be limited to biologics, but contribute to the overall risk assessment including

- Systemic administration allowing 100% bioavailability and access to critical tissues;
- Administration at relatively high volumes,
- Administration with high frequency (in many cases).

For these and other possible reasons, special consideration may need to be given to therapeutic biologic molecules when designing production, quality, and packaging components in order to minimize undesirable product quality and safety outcomes. For the purpose of the PODP Work Plan, thresholds are being considered for identification of chemical constituents based on the safety aspect with the understanding that other thresholds may be applicable to address quality and efficacy concerns.

Conclusions

The PQRI PODP Leachables and Extractables Working Group started with the hypothesis that safety thresholds for leachables and best demonstrated prac-

tices for performing controlled extraction studies, developed for OINDP dosage forms, could be extrapolated to the PODP dosages forms; taking into account the clear differences between OINDP and PODP drug products and their associated packaging systems. To facilitate the extrapolation, the PODP Chemistry Team devised a three-phase laboratory investigation, designed to address SVP, LVP, PFS, and ophthalmic solution and suspension dosage forms. Phase 1 of the investigation involved characterizing five materials typically used in PODP packaging systems for extractables; the design of this study and the results obtained are considered in greater detail in a companion manuscript in this issue of the *PDA Journal*. Phase 2 of the investigation, the migration or simulation study, involves the accelerated aging of a mock packaging system filled with simulating solvents, and is currently ongoing. Data obtained from this second-phase study will guide the design of the third phase of the investigation, which will involve leachables testing of one or more laboratory-generated drug products (or simulants) stored in the mock packaging system. Ultimately such experimental data will be instrumental in establishing and justifying best demonstrated practice recommendations for performing extractables and leachables studies for PODP.

Additionally, the PODP Toxicology Team has proposed a three-tier classification scheme for leachables, proposing safety thresholds for the three categories of leachables. The classification scheme, based on structure activity relationships analysis of a database of approximately 600 known extractables/leachables and rigorous safety assessment of a smaller subset of these chemicals and designed to be consistent with relevant related regulatory guidance, assigns a SCT of 1.5 μg/day for genotoxicants, a threshold of 5 μg/day for sensitizers/irritants, and a QT of 150 μg/day for compounds that exhibit general toxicity. It is important to note that these thresholds apply to parenteral products with systemic dosing; a strategy for topical ophthalmics is still developing.

Lastly, the Chemistry and Toxicology Teams continue to collaborate to establish means by which the best demonstrated practices and safety thresholds can be applied to dosage forms with large daily dose volumes so as to provide for effective and efficient safety assessments for such dosage forms.

Invaluable contributions from industry subject matter experts, national and international regulators, and volunteer laboratories and suppliers led to a well-defined process for understanding the science of packaging component materials of construction in relation to extractables, and correlation to leachables in support of drug product quality. Sound science is demonstrated based on the PQRI PODP Work Plan and Protocols that will lead to recommendations to augment guidance to pharmaceutical manufacturers and enable appropriate selection and qualification of packaging systems early in the drug development process.

The ongoing efforts to develop best practices for secondary components, specifically the ongoing simulation studies, will be completed in 2013, at which time the teams will finalize their recommendations and build consensus with input from U.S. FDA and Health Canada regulators. In addition, reviews from Medicines and Healthcare products Regulatory Agency (MHRA) and other industry organization will be conducted prior to submitting the PODP recommendations to the PQRI steering committee and subsequent submission to the FDA. All research work is supported under the direction of the PQRI organization; the leachable and extractable activities, work plan and protocols are publically available for both OINDP and PODP on the PQRI website (www.PQRI.org). The PQRI Working Group gratefully acknowledges participation by the following industry experts, regulators, laboratories, and suppliers.

PQRI PODP Leachables and Extractables Working Group

Diane Paskiet, Director of Scientific Affairs, West Pharmaceutical Services, Chair

Douglas J. Ball, Research Fellow, Pfizer, Inc., Toxicology Team Chair

Dennis Jenke, Ph.D. Baxter Distinguished Scientist, Baxter Healthcare, Chemistry Team Chair

Frank Holcombe, Jr., Ph.D. U.S. FDA, PQRI Development Technical Committee Liaison

Chemistry Team Members:

- Jim Castner, Ph.D., Pharma Interface Analysis, LLC.
- Thomas Egert, Boehringer Ingelheim Pharma GmbH & Co. KG

- Thomas Feinberg, Ph.D., Director, Structural Chemistry, Catalent Pharma Solutions
- Alan Hendricker, Ph.D., Principal Scientist, Catalent Pharma Solutions
- Christopher Houston, Ph.D., Senior Principal Scientist, Bausch & Lomb
- Desmond G. Hunt, Ph.D., Scientist, Dept. of Standards Development, USP
- Michael Lynch, Ph.D., Associate Research Fellow, Reg CMC, Pfizer
- Ingrid Markovic, Ph.D., Special Advisor to the Associate Director for Review Management, Office of the Center Director, CBER, FDA
- Kumudini Nicholas, Team Leader, Pharmaceutical Quality Review, Bureau of Pharmaceutical Sciences, Health Canada
- Daniel L. Norwood, M.S.P.H., Ph.D., Distinguished Research Fellow, Boehringer Ingelheim Pharmaceuticals, Inc.
- Michael Ruberto, Ph.D., Material Needs Consulting, LLC
- Art Shaw, Ph.D., Associate Research Fellow, Pfizer
- Edward J. Smith, Ph.D., Packaging Science Resources, LLC

Toxicology Team Members:

- Stephen A. Barat, Ph.D., Senior Director, Toxicology and Operations, Forest Laboratories
- Steve Beck, CEMDD Liaison, GlaxoSmithKline
- William P. Beierschmitt, Ph.D., Associate Research Fellow, Pfizer, Inc.
- Abigail Jacobs, Ph.D., Associate Director for Pharmacology/Toxicology, CDER, FDA
- Jacqueline A. Kunzler, Ph.D., Director of Life Sciences Technology Resource Division, Baxter Healthcare
- Mary Richardson, Ph.D., Executive Director, Preclinical Development, Bausch & Lomb
- Timothy Robison, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
- Alisa Vespa, Ph.D., Assessment Officer, Metabolism and Musculoskeletal Drugs Division, Bureau of Metabolism, Oncology and Reproductive Sciences, Therapeutic Products Directorate, Health Canada

Volunteer Laboratories

Baxter

- Roopang Shaw, Research Associate II
- Marek Ciosla, Research Associate II
- Frank (Yousheng) Hua, Research Scientist

Bausch & Lomb

- Christopher Houston, Senior Principal Scientist
- John Rider, Research Scientist

Boehringer Ingelheim Pharmaceuticals, Inc.

- Daniel L. Norwood
- Scott Pennino
- Jamie O. Mullis

Boehringer Ingelheim Pharma GmbH & Co. KG

- Thomas Egert
- Jürgen Mattes
- David Strassburger

Catalent Pharma Solutions

- Paul Cvetich
- Kimberly Davis

- Michelle Cree
- Tom Feinberg
- Alan Heindricker

Pfizer Inc.

- Cindy Magee
- Miguol Sandoval
- Arthur Shaw

Toxicology Support

- Breda Seidman, PhD, TOX-RSA, LLC
- Angela Howard, PhD Cosmetic Ingredient Review
- Russel Naven QSAR, DEREK, ToxTree, Pfizer, Inc.
- Patricia Ellis, QSAR, DEREK, ToxTree, Pfizer, Inc.
- David Jones, Principal Scientific Officer, New Chemical Entities Unit, MHRA

Supplier Support

- Stephanie Hubers, Cameo Craft
- Micheal Ruberto, Ciba Specialty Chemicals
- Horst Koller, Schott
- Peter Galland, Teknor Apex
- Jeff Smythe, West Pharmaceticals Services Inc.

References

1. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). *Guidance for Industry—Container Closure Systems for Packaging Human Drugs and Biologics*, 1999.

2. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Draft Guidance for Industry—Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug* Products, 1998.

3. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Guidance for Industry—Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation*, 2002.

4. European Medicines Agency, Committee for Medicinal Products for Human and Use (CHMP) and Committee for Medicinal Products for Veterinary Use (CVMP). *Guideline on Plastic Immediate Packaging Materials,* 2005.

5. Product Quality Research Institute (PQRI), Leachables and Extractables Working Group. *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products*; Product Quality Research Institute: Arlington, VA, 2006.

6. Ball, D.; Paskiet, D.; Norwood, D. L.; Jenke, D. *PQRI Research Project Proposal: Reporting and Qualification Thresholds in Parenteral and Ophthalmic Drug Products;* Product Quality Research Institute: Arlington, VA March 2007; available at http://www.pqri.org/commworking/minutes/pdfs/dptc/podpwg/Addl/PQRI_PODP_proposal_04072.pdf.

7. PQRI. Parenteral and Ophthalmic Drug Products (PODP) Work Plan; Product Quality Research Institute: Arlington, VA, 2008; available at http://www.pqri.org/commworking/minutes/pdfs/dptc/podpwg/Addl/podp_work_plan_schedule.pdf.

8. Study Protocol—Stage 1 Experimental Protocol for Qualitative Controlled Extraction Studies for Material Test Articles Representative of Prefilled Syringe (PFS) and Small Volume Parenteral (SVP) Container Closure Systems, Amendment #1; Product Quality Research Institute: Arlington, VA, September 2011; available at http://www.pqri.org/commworking/minutes/pdfs/dptc/podpwg/Addl/StudyProtocolStage1amend1.pdf.

9. U.S. Department of Health and Human Services, Food and Drug Administration, *Pharmaceutical Quality for the 21st Century A Risk-based Ap-*

proach. 2009; available at http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/questionsandanswersoncurrentgoodmanufacturingpracticescgmpfordrugs/ucm071836.

10. Jenke, D. Extractable/leachable substances from plastic materials used as pharmaceutical product containers/devices. *PDA J. Pharm. Sci. Technol.* **2002**, *56* (6), 332–371.

11. Jenke, D. Extractable substances from plastic materials used in solution contact applications: an updated review. *PDA J. Pharm. Sci. Technol.* **2006**, *60* (3), 191–207.

12. Jenke, D. *Compatibility of Pharmaceutical Products and Contact Materials*; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2009.

13. Jenke, D. A general strategy for the chemical aspects of the safety assessment of extractables and leachables in pharmaceutical drug products: the chemical assessment triad. *PDA J. Pharm. Sci. Technol.* **2012**, *66* (2), 168–183.

14. International Atomic Energy Agency. Controlling Degradation Effects in Radiation of Processing Polymers, IAEA-TECDOC 1611, Vienna, Austria, 2009, ISSN 1011–4289.

15. Curry W., Conway, S.; Goodfield, C.; Miller, K.; Mueller, R. L.; Polini, E. Reducing the risk of contamination of sterile parenteral products using ready-to-use components. *AAPS PharmSciTech* **2010**, *11* (4) 1572–1579.

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

17. 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.

18. 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.

19. Jaehnke, R. W. O.; Linde, H.; Mosandl, A.; Kreuter, J. Contamination 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.

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

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

22. 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.

23. 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.

24. Driver, W. E. *Plastics Chemistry and Technology;* Van Nostrand Reinhold Co.: New York, 1979.

25. 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.

26. 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.

27. 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.

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

29. 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.

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

31. 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* (7), 1405–1409

32. 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.

33. 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. *Jpn. J. Pharm. Health Care Sci.* **2004,** *30* (3), 180–184.

34. The National Toxicology Annual Report, 2011, The Phthalate Initiative, NIH 12-5971, http://ntp.niehs.nih.gov/ntp/Pubs/NTP2011_AnnualReport_508.pdf#search=dehp.

35. Seymour, R. B.; Cheng, T. *Advances in Polyolefins: The World's Most Widely Used Polymers;* University of California; Plenum Press, 1987.

36. Nollet, L. M. L. *Handbook of Food Analysis*, 2nd ed.; Marcel Dekker: New York, 2004.

37. Jenke, D. R.; Zietlow, D.; Garber, M. J.; Sadain, S.; Reiber, D.; Terbush, W. Accumulation of extractables in buffer solutions from a polyolefin plastic container. *PDA J. Pharm. Sci. Technol.* **2007**, *61* (4), 286–302.

38. Chang, J. Y.; Xiao, N. J.; Zhu, M.; Zhang, J.; Hoff, E.; Russell, S. J.; Katta, V, Shire, S. J. Leachables from saline-containing IV bags can alter therapeutic protein properties. *Pharm. Res.* **2010,** *27* (11), 2402–2413.

39. Klapperich, C.; Pruitt, L.; Komvopoulos, K. Chemical and biological characteristics of low-temperature plasma treated ultra-high molecular weight polyethylene for biomedical applications. *J. Mater. Sci. Mater. Med.* **2001,** *12* (6), 549–556.

40. 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.

41. 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.

42. U.S. Food and Drug Administration. Response to Petition on Bisphenol A (BPA). Available at http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm166145.htm

43. Haishima, Y.; Hayashi, Y.; Yagami, T.; Nakamura, A. Elution of bisphenol-A from hemodialyzers of polycarbonate and polysulfone resins. *J. Biomed. Res.* **2001**, *58* (2), 209–215.

44. Pan, F.; Harmon, K.; Toscano, F.; Liu, R.; Vivilecchia, A. Strategy for identification of leachables in packaged pharmaceutical liquid formulations *J. Pharm. Biomed. Anal.* **2008**, *46* (3), 520–527.

45. Study Phase 2 Experimental Protocol for Simulation Study of Blow-Fill-Seal (PFS), PODP Container Closure Systems, September 2011, http://www.pqri.org/commworking/minutes/pdfs/dptc/podpwg/Addl/StudyProtocolStage2.pdf.

46. Product Quality Research Institute (PQRI) PODP Working Group. PQRI Workshop on Safety Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products; and Poster Exhibit, Bethesda, MD, February 22–23, 2011; http://www.pqri.org/workshops/PODP11/pdfs/Agenda_final_program.pdf.

47. Munro, I. C.; Ford, R. A.; Kennepohl, E.;

Sprenger, J. G.; Maier, A.; Dourson, M. Correlation of structural class with no-observed effect levels: A proposal for establishing a threshold of concern. *Food Chem. Toxicol.* **1996,** *34* (9), 829–867.

48. Kroes, R.; Renwick, A.; Cheeseman, M.; Kleiner, J.; Mangelsdorf, I.; Piersma, A.; Schilter, B.; Schlatter, J.; van Schothorst, F.; Vos, J.; Würtzen, G. Structure-based threshold of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food. Chem. Toxicol.* **2004**, *42* (1), 65–83.

49. ToxTree. Toxic Hazard Estimation by Decision Tree Approach; http://ihcp.jrc.ec.europa.eu/our_labs/predictive_toxicology/qsar_tools/toxtre.

50. Cramer, G. M.; Ford, R. A.; Hall, R. L. Estimation of toxic hazard—a decision tree approach. *Food Cosmet. Toxicol.* **1978,** *16* 3, 255–276.

51. Deductive Estimation of Risk from Existing Knowledge (DEREK); https://www.lhasalimited.org/derek_nexus

52. Ball, D. J. Establishing Threshold Levels of Extractables & Leachables in Pre-Filled Syringes. Second World Pre-Filled Syringe Summit, September 19–20, 2012, Washington, DC.

53. Ng, L.; FDA Office of New Drug Quality Assessment. Current Regulatory Recommendations for Leachables in Ophthalmic Products. Presented at PQRI Workshop on Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products, Bethesda, MD, February 22–23, 2011.

54. International Conference on Harmonization (ICH) M7; Assessment and Control of DNA (Mutagenic) Reactive Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, February 2013; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_2.pdf.

55. Markovic, I. Challenges associated with extractables and/or leachable substances in therapeutic biological protein products. *Am. Pharm. Rev.* **2006**, *9* (6), 20.

56. Markovic, I. Evaluation of safety and quality impact of extractable and leachable substances in therapeutic biologic protein products; a risk-based perspective. *Am. Pharm. Rev.* **2007**, *6* (5), 487–491.

57. Markovic, I. Risk management strategies for safety qualification of extractables and leachable substances in therapeutic biological protein products. *Am. Pharm. Rev.* **2009**, *12* (4), 96.

58. Marth, E.; Jelovcan, S.; Kleinhappl, B.; Guschi, A.; Barth, S. The effect of heavy metals on the immune system at low concentrations, *International Journal of Occupational Medicine and Environmental Health.* **2001**, *14*, 375–386.

59. Yano, K.; Ohno, S.; Nakajima, Y.; Toyoshima, S.; Nakajin, S. Effects of Various Chemicals Including Endocrine Disruptors and Analogs on the Secretion of Th1 and Th2 Cytokines from Anti CD3-Stimulated Mouse Spleen Cells, *Journal of Health Science.* **2003,** *49*, 195–204.

60. Beck-Speier, I.; Kreyling, W. G.; Maier, K. L.; Dayal, N.; Schladweiler, M. C.; Mayer, P.; Semmler-Behnke, M.; Kodavanti, U. P. Soluble iron modulates iron oxide particle-induced inflammatory responses via prostaglandin E_2 synthesis: *In vitro* and *in vivo* studies, *Particle and Fibre Toxicology*. **2009**, *6*, 34–46.

61. Lovik, M.; Hogseth, A. K.; Gaarder, P. I. Hagemann R, Eide I. Diesel exhaust particles and carbon black have adjuvant activity on the local lymph node response and systemic IgE production to ovalbumin. *Toxicology*. **1997;** *121*:165–178.

62. Nilsen, A.; Hagemann, R.; Eide, I. The adjuvant activity of diesel exhaust particles and carbon black on systemic IgE production to ovalbumin in mice after intranasal instillation. *Toxicology* **1997;** *124*:225–232.72.

63. Larsen, S. T.; Lund, R. M.; Nielsen, G. D.; Thygesen, P.; Poulsen, O. M. Di-(2-ethylhexyl) phthalate possesses an adjuvant effect in a subcutaneous injection model with BALB/c mice. *Toxicol Lett.* **2001;** *125*(1–3):11–18.

64. Larsen, S. T.; Hansen, J. S.; Thygesen, P; Begtrup, M., Poulsen, O. M.; et al. Adjuvant and immuno-suppressive effect of six monophthalates in a subcutaneous injection model with BALB/c mice. *Toxicology*. **2001;** *169*:37–351.

65. Larsen, S. T.; Nielsen, G. D. The adjuvant effect of di-(2-ethylhexyl) phthalate is mediated through a PPARalpha-independent mechanism. *Toxicol Lett*. **2007;** *170*:223–228.

66. Locatelli, F.; Aljama, P.; Barany, P.; et al. Erythropoiesis-stimulating agents and antibody-mediated pure red-cell aplasia: where are we now and where do we go from here? *Nephrol Dial Transplant.* **2004;** *19*:288–293.

67. Naim, J. O.; Ippolito, K. M.; Lanzafame, R. J.; van Oss, C. J. The effect of molecular weight and gel preparation on humoral adjuvancy of silicone oils and silicone gels. *Immunol Investig*. **1995;** *24*:537–547.

68. Naim, J. O.; Satoh, M.; Buehner, N. A.; Ippolito, K. M.; Yoshida, H.; Nusz, D.; Kurtelawicz, L.; Cramer, S. F.; Reeves, W. H. Induction of hypergammaglobulinemia and macrophage activation by silicone gels and oils in female A.SW mice. *Clin Diagn Lab Immunol*. **2000;** *7*:366–370.

PDA Journal
of Pharmaceutical Science and Technology