PQRI

Product Quality Research Institute

Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular)

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Submitted to the PQRI Development Technical Committee, PQRI Steering Committee and US Food and Drug Administration by the PQRI PODP Leachables and Extractables Working Group

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PQRI PODP Leachables and Extractables Working Group

Forward

Leachables in drug products that originate from the components used in packaging, delivery and manufacturing systems can compromise the quality of drug products and impact patient safety. The materials of construction associated with these components should be assessed for suitability in early drug development phases based on extractable profiles and correlated to potential and confirmed leachables. In 1999 the PQRI Leachables and Extractables (L&E) Working Group was established with the goal of reducing leachable uncertainty in Orally Inhaled and Nasal Drug Products (OINDP), using a science and risked based approach. The Working Group was made up of highly experienced scientists including toxicologists, analytical chemists, and others, from industry, government, and academia. The culmination of these efforts resulted in E&L recommendations to the USFDA. "Safety Thresholds and Best Practices for Extractable and Leachables in OINDP" was published in 2006 and since has been recognized by FDA and global regulatory authorities.

In 2008 the Parenteral and Ophthalmic Drug Product (PODP) L&E Working Group was formed to extrapolate the OINDP risked–based approach for evaluation and safety qualification of extractables and leachables in PODP. Specific factors associated with parenteral and ophthalmic drug products were considered that included patient population, dose, duration, and additional product-dependent characteristics. The PODP L&E Working Group conducted and evaluated the results of extraction studies on polymeric materials and evaluated a database of over 600 potential leachables using existing toxicological qualification approaches to justify thresholds for PODP. The proposed PODP identification and qualification thresholds were published in a 2013 manuscript followed by workshops. Subsequently, recommendations for "Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (PDP)," was thoroughly examined and consideration was given to factors related to new modalities. After rigorous review from industry and regulators a consensus was reached.

This document describes recommendations for E&L assessments of small volume, large volume parenterals and prefilled syringes with additional considerations for biological products. The field of biological products is rapidly advancing and with unique risks to product quality and patient safety. Study designs for E&L will consider intended use and regulatory jurisdiction and should be discussed early with the Regulatory Agency to understand proper application of the analytical evaluation threshold (AET), extraction concentrations, solvents, exposure conditions and analysis. There are unique considerations for ophthalmic drug products (ODP), and safety thresholds do not apply. Because of the unique considerations for ophthalmic drug products, extractables and leachables assessments are described in a separate manuscript entitled, "Principles for Management of Extractables and Leachables in Ophthalmic Drug Products." PDA Journal of Pharmaceutical Science and Technology February 2022, pdajpst.2022.012744. DOI: https://doi.org/10.5731/pdajpst.2022.012744. Parenteral products administered by the intrathecal, intra-cerebroventricular, intra-articular, epidural, and perineural routes are out of scope. The PDP recommendations were the result of understanding a broad range of E&L applications over several years of building consensus with leaders in scientific and regulatory community. The views expressed in these documents are not necessarily those of individual companies or US Food and Drug Administration.

Contributions of individuals from the core team, extended teams, reviewers and advisors are sincerely appreciated. The members of the PODP L&E Working Group acknowledges the Product Quality Research Institute and its member organizations for providing this forum to make this collaboration possible. We also would like to recognize the dedicated scientists in volunteer laboratories that provided the essential data to make the reccomendations possible.

The Working Group hopes that the recommendations contained in this document will serve to guide the pharmaceutical development process for PDP and facilitate the approval and manufacture of safe, effective, and quality medicines.

On behalf of the PQRI PODP L&E WG

Diane Paskiet, MS
Chair of PODP L&E Working Group
Chair of PQRI Steering Committee
Representing the Parenteral Drug Association

Douglas Kiehl, MS
Chair of Development Technical Committee
Representing the United States Pharmacopeia

Authors

Diane Paskiet, West Pharmaceutical Services Inc. Exton PA, USA
Douglas J. Ball, D&B ChemTox, LLC, Southbury, CT, USA
Dennis Jenke, Triad Scientific Solutions, LLC, Hawthorn Woods, IL, USA
Stephen A. Barat, HTG Molecular, Tucson, AZ, USA
Steve Beck, Xellia Ltd, Zagreb, Croatia
William P. Beierschmitt, D&B ChemTox, LLC, Southbury, CT, USA
James Castner, Pharma Interface Analysis, MA, USA
Thomas Egert, Boehringer Ingelheim Pharmaceuticals, Inc., Ingelheim/Rhein, Germany
Thomas Feinberg, FNA Pharma Consulting, LLC, Chapel Hill, NC, USA
Alan Hendricker, Becton Dickenson, Raleigh, NC, USA
Frank Holcombe, Jr., US Food and Drug Administration (USFDA), Silver Spring, MD, USA
Christopher Houston, Bausch & Lomb, Rochester, NY, USA
Desmond G. Hunt, United States Pharmacopeia, Rockville, MD, USA
Abigail Jacobs, US Food and Drug Administration (USFDA), Silver Spring, MD, USA
David Jones, Medicines and Healthcare products Regulatory Agency (MHRA), London, UK
Douglas Kiehl, Eli Lilly and Company, Indianapolis, IN, USA
Jacqueline A. Kunzler, Baxter Healthcare Corporation, Round Lake, IL, USA
Michael Lynch, Pfizer Groton, CT, USA
Ingrid Markovic, US Food and Drug Administration (USFDA), Silver Spring, MD, USA
Kumudini Nicholas, Health Canada, Ottawa, ON, Canada
Daniel Norwood, FNA Pharma Consulting, LLC, Chapel Hill, NC, USA
Mary Richardson, Iuvo BioScience, Rush, NY, USA
Timothy W. Robison, US Food and Drug Administration (USFDA), Silver Spring, MD, USA
Mike Ruberto, Materials Needs Consulting LLC, Montvale, NJ, USA
Edward Smith, Packaging Science Resources, Audubon, PA, USA
Cheryl LM Stults, C & M Technical Consulting, LLC, San Mateo, CA, USA
Alisa Vespa, Health Canada, Ottawa, ON, Canada

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

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Laboratory Services

Baxter Healthcare Corporation, Round Lake, IL, USA
Roopang Shah
Marek Ciesla
Frank (Yousheng) Hua

Pfizer, Groton, CT, USA
Cindy Magee
Miguel Sandoval
Art Shaw

Becton Dickenson, Raleigh, NC, USA
Alan Hendricker
John Lennon

Bausch & Lomb, Rochester, NY, USA
Christopher Houston
John Rider

Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA & Ingelheim/Rhein, Germany
Daniel L. Norwood
Scott Pennino
James O. Mullis
Thomas Egert
Jurgen Mattes
David Strassburger

Catalent Pharma Solutions, Morrisville, NC, USA
Paul Cvetich
Kimberly Davis
Michelle Cree
Tom Feinberg

Toxicology Services and Analysis

Pfizer Groton, CT, USA DEREK/Toxtree
Russell Naven
Patricia Ellis

TOX-RSA, LLC
Angela Howard
Brenda Seidman

ELSIE Consortium Washington, D.C., USA

Intertox, Seattle, WA, USA
Rick Pleus
Gretchen Bruce

Nelson (Toxikon) Leuven, Belgium
Piet Christiaens
Christopher Brynczka

Biologics Subteam

Amgen, Thousand Oaks, CA, USA
Kim Li

Johnson& Johnson (Momenta Pharmaceuticals) Cambridge, MA, USA
Jamie Tsung

Ophthalmics Subteam

IUVO BioScience, Rush, NY, USA
Mary Richardson

Bausch & Lomb, Rochester, NY, USA
Christopher Houston

AbbVie (Allergan), Irvine, CA, USA
Tao Wang
Brenda Birkestrand Smith
Andrea Desantis Rodrigues

Suppliers

Cameo Crafts Ltee-Ltd Saint-Laurent, Quebec, Canada
***BASF Schweiz AG, Basle Swtizerland* (CIBA):** Michael Ruberto
***Schott Mainz, Germany*:** Horst Koller
***Teknor Apex, RI, USA*:** Peter Gallard Pawtucket
***West Pharmaceutical Services Inc. Exton PA, USA*:** Jeff Smythe

US Food and Drug Administration: Advisors/Reviewers

Xiaochun Chen, Division of Pharmacology-Toxicology for Immunology & Inflammation (DPT-II), CDER
Eleni Salicru, DPT-II, CDER
Luqi Pei, DPT-OII, CDER
Jackye Peretz, DPT-II, CDER
David Joseph, DPT-II, CDER

Taro Akiyama, DPT-CHEN, CDER
Rama Dwivedi, DPT-CHEN, CDER
Huiqing Hao, Division of Metabolic and Endocrine Drug Products (DMEP), DPT-CHEN,
Sree Rayavarapu, Division of Pharmacology & Toxicology for Cardiology, Hematology, Endocrinology and Nephrology (DPT-CHEN), CDER
Marlene Kim, Office of the Commissioner
Naomi Kruhlak, Division of Applied Regulatory Science (DARS), CDER
Curran Landry, DARS, CDER
Lidiya Stavitskaya, DARS, CDER

Dan Mellon, Division of Pharmacology-Toxicology for Neurology (DPT-N), CDER

Carlic Huynh, DPT-N, CDER
Misol Ahn, DPT-N, CDER
Newton Woo, DPT-N, CDER
Irene Surh, DPT-N, CDER
Katie Sokolowski, DPT-N, CDER
Jaime D'Agostino, DPT-N, CDER
Jay Chang, DPT-N, CDER
Timothy McGovern, Office of New Drugs Immediate Office (OND IO), CDER

Jane Sohn Office of Nonprescription Drug Products (ONDP), CDER
Julia Pinto Office of Product Quality (OPQ), CDER

Valerie Amspacher, OPQ, CDER
Melanie Mueller, Office of Generic Drugs (OGD), CDER
Narendranath Reddy Chintagari, OGD, CDER

PQRI Secretariat: Faegre Drinker Biddle & Reath LLP, Washington, D.C., USA

Lee Nagao
Jillian Brady
Mary Devlin Capizzi
Dede Godstrey

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Part 1. Introduction and Summary of Recommendations

I. Introduction

In 2008, the Product Quality Research Institute (PQRI) established the Parenteral and Ophthalmic Drug Products (PODP) Working Group to develop safety thresholds and analytical best practice recommendations for leachables and extractables in Parenteral Drug Products (PDP), building off of the well-received 2006 PQRI recommendations for safety thresholds and best practices for Orally Inhaled and Nasal Drug Products (OINDP) [1]. This document contains the PODP Working Group's Final Recommendations for parenteral drug products as well as rationales and illustrative data supporting these Recommendations.

- Part 1 of this document includes a brief background on the overall PODP Working Group effort and summary of the overall Recommendations.
- Part 2 proposes, describes and justifies a framework for toxicological evaluation of leachables for parenteral drug products.
- Part 3 provides explanations and illustrative data for best practice recommendations for analytical evaluation of extractables and leachables with respect to parenteral drug products, including a detailed perspective on the unique pharmaceutical development issues regarding biological drug products.
- Part 4 describes extractables and leachables chemistry and toxicological considerations for biologic products.

Note that the toxicological evaluation and threshold recommendations in Part 2 and the analytical recommendations in Part 3 pertain to PDP.

II. Background and Scope

Leachables in PDP are those substances (both organic and inorganic) that are present in the final packaged drug product due to the transport of substances from packaging systems (also known as container closure systems, or CCS [2]) to the drug product formulation, with subsequent delivery to patients. Such leachables are associated with the components and/or materials of construction (raw materials) of CCS that are in direct or indirect contact with the PDP. Leachables from indirect contact CCS components (e.g., labels, inks, and adhesives affixed to plastic bottles) that cross a barrier into the drug product formulation are sometimes referred to in this document as "migrants." Leachables generally correlate with extractables, which are those substances that can be extracted from the packaging system and/or its associated components and materials of construction under experimental laboratory conditions using appropriate solvents, extraction techniques and extraction conditions. It is important to note that drug product leachables can have other sources than the CCS. For example, "process-derived leachables" are associated with various aspects of the drug product manufacturing system (e.g., manufacturing process components, plastic tubes, single-use containers, etc.) and can be particularly significant in the manufacture of biological drug products. "Environmental leachables" are derived from the

general environment in which the packaged drug product is shipped and stored (e.g., a volatile organic compound in the air surrounding a drug product, which can infiltrate the drug product's CCS). Although both process and environmental leachables can be significant in certain circumstances, and all pharmaceutical development scientists should be aware of this potential, the PDP effort and therefore this Recommendation Document is focused on packaging system–derived leachables.

Because some leachables have the potential to adversely affect the safety, stability, efficacy and/or overall quality of packaged drug products, regulatory guidance and guideline documents applicable to packaging systems provide some recommendations regarding the product impact assessment of such substances. For example, the U.S. Food and Drug Administration (FDA) issued *Container Closure Systems for Packaging Human Drugs and Biologics – Chemistry, Manufacturing and Controls (CMC) documentation Guidance for Industry* in May 1999, (referred to hereafter as the "FDA 1999 Packaging Guidance").[2] In addition, the European Medicines Agency (EMA) issued its *Guideline on Plastic Immediate Packaging Materials* in May 2005. [3] Specific Guidance with respect to extractables and leachables for OINDP is contained in: (i) the Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products--Quality Considerations, Draft Guidance April 2018, (referred to here as the "MDI/DPI Draft Guidance,") [4]; (ii) the *Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation* (July, 2002) [5]; and (iii) the Health Canada and EMA guidelines on *Pharmaceutical Quality of Inhalation and Nasal Products* [6].

These guidance documents provide drug product sponsors with a high-level strategic process to assess and qualify extractables and leachables associated with various dosage forms. Such a high-level process involves four primary steps:

1. Demonstrating that the materials of construction meet the relevant Compendial Monographs and chapters, and/or standards from the International Organization for Standardization (ISO);

2. Performing an extraction study to identify and, as appropriate, quantify all relevant extractables;

3. Performing a leachables study to measure the levels of leachables in a drug product under conditions of intended use, and;

4. Performing a toxicological assessment of the extractables and/or leachables information to specifically address the safety impact of individual leachables at their specific accumulation levels under the specific conditions and dosing associated with drug product use.

A fifth step that may be included in this process is a reconciliation or correlation of the extractables and leachables information for the purpose of establishing worst-case scenarios and packaging component control.

The practical implementation of this overall process is problematic because it suggests that all extractables and/or leachables, regardless of their accumulation levels, must be reported and must undergo full toxicological safety assessments. However, some extractables may not be

present 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. For example, the FDA OINDP-focused guidance documents appear to require full toxicological assessment on compounds to which the patient will either never be exposed, or that might exist at levels that present negligible safety risk.

In September 2006, PQRI issued a Recommendation entitled "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products." This Recommendation provided a scientific rationale and process to identify, quantify and establish the health risk (i.e., qualify) of leachables and/or extractables where appropriate, in OINDP. The fundamental concept proposed by PQRI was a Safety Concern Threshold (SCT) that would establish a threshold below which a leachable would present minimal safety concerns to the patient with regard to carcinogenic and noncarcinogenic toxic effects unless the leachable is identified as a "special case compound." A Qualification Threshold (QT) would establish a threshold below which the leachable is not considered for safety qualification unless the leachable presents structure-activity relationship (SAR) or other safety concerns. Both thresholds assume that toxicological qualification should be performed on leachables and on a case-by-case basis for extractables. The SCT is used to develop an Analytical Evaluation Threshold (AET) that permits application of the SCT to leachables profiles of particular drug products with consideration of drug product dependent parameters such as dosing schedule and the analytical technique or method used to produce a particular leachables (or extractables) profile. The general application of these concepts is described in the OINDP Recommendations.

The threshold concept utilizes a risk management approach that is consistent with the recommendations of PQRI and FDA guidance documents for container closure systems as well as with the ICH Q9 Quality Risk Management guideline [7], the ICH Q3A-D guidelines [8,9,10,11], and the 2006 FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulation [12]. In addition, the rationale for threshold concepts can be applied to support comprehensive studies for certain drug products as outlined in the EMA Guideline on Plastic Immediate Packaging.

As noted in the FDA 1999 Packaging Guidance the universe of drug products includes other high-risk dosage forms in addition to OINDP, such as injections and ophthalmic solutions. Given their similar level of risk, it was reasonable to hypothesize that best practices suitable for OINDP could be applicable to PODP; that is, many of the concepts developed in the OINDP recommendations could be adapted to and customized for PODP. The PQRI PODP Working Group developed the following working hypotheses:

- Threshold concepts that have been developed for safety qualification of leachables in OINDP can be extrapolated to the evaluation and safety qualification of leachables in PODP, with consideration of factors and parameters such as dose, duration, patient population and additional product-dependent characteristics unique to various PODP types.

- The "good science" best demonstrated practices that were established for the OINDP pharmaceutical development process can be extrapolated to container closure systems for PODP.

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

It became apparent to the Working Group that parenteral drug products (PDP) and ophthalmic drug products (ODP) are sufficiently different that they cannot be readily treated in the same manner. For parenteral drug products, an SCT could be generated based on principles consistent with those established by the OINDP Working Group. Typical ODP, on the other hand, are dosed topically in small aliquots directly to the eye. Currently there is not a sufficient database developed on all the relevant toxicity endpoints to allow the Working Group to recommend specific safety thresholds (i.e., sensitization, ocular irritation) for ODP at this time. Thus, the hypothesis that threshold principles could be extrapolated from OINDP to ophthalmic solutions and suspensions lacked sufficient scientific support to develop a recommendation. From this point forward, the current document focuses on recommendations for extractables and leachables studies with PDP. The reader is referred to the document entitled "Principles for Management of Extractables and Leachables in Ophthalmic Drug Products" for information on ophthalmic drug products.

The scope of the PDP recommendations includes prefilled syringes (PFS) and small and large volume parenterals (SVP and LVP) contained in vials or flexible bags. Recommendations on extractables/leachables studies considered three critical dimensions that define the drug product/packaging system, i.e., the nature of the dosage form, compatibility between a formulation and a packaging system, and the context of the formulation/packaging system contact. Parenteral drug products that are in scope are limited to intravenous, subcutaneous, and intramuscular routes of administration. Examples of parenteral drug products that are considered out of scope include: intraocular intrathecal, intra-cerebroventricular, intra-articular, epidural, and perineural routes of administration.

The threshold definitions originally proposed by PQRI have been retained and are as follows:

- The SCT is defined as the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects.

- The QT is defined as the threshold below which a given leachable is not considered for safety qualification (toxicological assessment) unless the leachable presents structure activity relationship (SAR) concerns.

- The AET is defined as the threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment.

The PQRI PODP Working Group conducted and evaluated the results of extraction studies on a variety of polymeric materials, conducted and evaluated the results from a "simulation study" on a model PDP system, and evaluated a database of over 600 potential leachables using current toxicological qualification approaches in order to generate data and

information supporting the above hypotheses. From these study results and assessments, the Working Group proposes the recommendations provided below. The recommendations highlight those unique to the parenteral drug products study and evaluations completed by the Working Group and are not duplicative of the recommendations for OINDP. General considerations such as the use of multiple, and complementary analytical techniques, careful sample preparation, calculation and application of an AET, and developing an extractables and leachables correlation are discussed as best practices in Part 3 of this document.

III. Recommendations

1. An SCT approach can be applied to leachables and extractables qualification in parenteral drug products.

    a. Based on most Parenteral Drug Product (PDP) formulations, an SCT of 1.5 µg/day for an individual organic leachable can be used to calculate an AET. An SCT that is lower than 1.5 µg per day may be warranted for certain classes of compounds such as those within the cohort of concern (e.g., aflatoxin-like, N-nitroso- and alkyl-azoxy compounds).

2. The QT developed for OINDP was evaluated and it was determined that when no concern for genotoxic or carcinogenic potential is identified, a QT of 5 µg/day is appropriate in the absence of supporting general toxicology data and an identified potential for irritation or sensitization in PDP. Above the QT additional toxicology evaluation is necessary to qualify individual organic leachable.

3. Extractables assessments and extraction studies for PDP may be considered as appropriate for specific application to materials of construction, finished components, or complete packaging systems (i.e., container closure systems).

4. Extractables assessments and extraction studies for PDP packaging systems should include aqueous-based extraction solvents with appropriate consideration of extraction pH, organic solvent content, and other appropriate extraction conditions (e.g., extraction time, extraction temperature, extraction technique, and sample-to-solvent ratio).

    a. Extractable studies for CCS used with complex drug products should consider appropriate solvent propensity to establish the extractable profile to guide optimization of nontargeted screening methods for placebo or leachables.
    Note: Examples of complex products include complex API (e.g., polymeric compounds, peptides), complex formulations (e.g., liposomes, emulsions, suspensions), complex routes of delivery (e.g., topical), complex dosage forms (e.g., long-acting injectables), and complex drug-device combinations (e.g., prefilled syringes, autoinjectors)

5. Where appropriate; extractables assessments, extraction studies, and leachables assessments for parenteral drug products and their packaging systems should consider the possibility of migration across packaging barriers (i.e., drug product labels, adhesives, inks, etc.).

6. In situations of analytically challenging AETs for certain PDP (e.g., large volume parenterals), a simulation study, may supplement and guide subsequent drug product

leachables studies. These studies can establish an extractables profile to inform a probable leachables profile of the packaged drug product that the study simulates. Use of a simulation study would need to be appropriately justified.

7. Biological products have unique considerations compared to chemically synthesized drug products. Comprehensive risk assessments should consider biological activity, efficacy and safety and may include the following:
    a. Leachable interactions affecting product quality attributes, i.e., degradation, oxidation, chemical modification, aggregation, immune adjuvant activity
    b. Material compatibility, surface characteristics, organic/inorganic alert compounds
    c. Individual components and system interfaces, performance and functionality
    d. Leachables assessment performed on the product under accelerated storage/stress conditions, and during stability storage.

Note: Due to the increasing complexity of pharmaceutical products and container closure systems, justifications and documentation for the AET, extraction conditions, extraction solvents and analysis should be discussed early with the Regulatory Agency/Division.

In "Part 2: Justification of Thresholds for Leachables in PDP," the process of development of safety-based thresholds for leachables and extractables in PDP will be discussed. (recommendations 1 and 2).

In "Part 3: Best Practices for Extractables and Leachables in PDP," the recommendations related to pharmaceutical and analytical development for leachables and extractables in PDP will be discussed and compared to similar recommendations put forward for OINDP (recommendations 3 through 6).

In Part 4, addressing special topics, additional comprehensive discussions are presented regarding the special considerations required for parenteral drug products for which active ingredient(s) are biological molecules (recommendation 7).

IV. References

1. L/E Recommendations to the FDA, PQRI, Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, September 2006 Publications – Product Quality Research Institute (pqri.org)

2. Guidance for Industry, Container closure systems for packaging human drugs and biologics. Chemistry, manufacturing, and controls documentation. US Department of Health and Human Services. Food and Drug Administration. May **1999**. https://www.fda.gov/downloads/drugs/guidances/ucm070551.pdf

3. Guideline on plastic immediate packaging materials. Committee for Medicinal Products for Human Use and Committee for Medicinal Products for Veterinary Use. European Medicines Agency. December **2005**.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003448.pdf

4. Draft Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products--Quality Considerations, Pharmaceutical Quality/CMC, April 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/metered-dose-inhaler-mdi-and-dry-powder-inhaler-dpi-drug-products-quality-considerations

5. Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, CDER, July 2002. https://www.fda.gov/media/70857/download

6. Guidance for Industry-Pharmaceutical Quality of Inhalation and Nasal Products, Health Canada, Ministry of Health. October 2006. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-industry-pharmaceutical-quality-inhalation-nasal-products.html

7. ICH Quality Guideline Q9 Quality Risk Management, November 2005, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH; International Council for Harmonization). https://www.ich.org/page/quality-guidelines

8. ICH Quality Guideline Q3A(R2), Impurities in New Drug Substances, October 2006, International Council for Harmonisation. https://www.ich.org/page/quality-guidelines

9. ICH Quality Guideline Q3B(R2), Impurities in New Drug Products, June2006, International Council for Harmonisation. https://www.ich.org/page/quality-guidelines ICH Quality Guideline (Q9) Quality Risk Management, November 2005, International Council for Harmonisation. https://www.ich.org/page/quality-guidelines

10. ICH Quality Guideline Q3C(R8) Residual Solvents, April 2021 International Council for Harmonisation. https://www.ich.org/page/quality-guidelines

11. ICH Quality Guideline Q3D(R1) Elemental Impurities, March 2019, International Council for Harmonisation. https://www.ich.org/page/quality-guidelines

12. Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations, CDER, CBER, CVM, ORA (September 2006). https://www.fda.gov/media/71023/download

Part 2. Justification of Thresholds for Leachables in PDP

I. Introduction

The safety assessment of identified extractables and leachables from a container closure system is a complex process. The number of identified extractables or leachables can be large (e.g., beyond 50). There is minimal information for many of these chemicals in the published scientific literature and various other sources (e.g., National Toxicology Program [NTP], Environmental Protection Agency [EPA] Integrated Risk Information System database [IRIS], National Institutes of Health ToxNet, American Conference of Governmental Industrial Hygienists, National Institute for Occupational Safety and Health, etc.) particularly with regard to chronic exposure. The PQRI Leachables and Extractables Working Group, a collaboration of chemists and toxicologists from the FDA, industry, and academia developed safety thresholds for leachables and extractables in orally inhaled and nasal drug products (OINDP) [1, 2]. A second PQRI Working Group was formed to evaluate whether concepts from the OINDP best practices could be applied to qualification of leachables and extractables in parenteral and ophthalmic drug products.

The PQRI PODP Toxicology Subteam, composed of experts from FDA, Health Canada, and industry, evaluated the OINDP best practices and concluded that:

- An SCT approach developed for OINDP can be applied to leachables and extractables qualification for PDP.
- Based on most aqueous-based PDP formulations, a SCT of 1.5 µg/day can be used to calculate an AET.
- The QT developed for OINDP was evaluated and it was determined that when no concern for genotoxic or carcinogenic potential is identified, a QT of 5 µg/day is appropriate in the absence of supporting general toxicology data and an identified potential for irritation or sensitization in PDP.
- A third threshold based on a modified Cramer Classification method [3, 4] that would be appropriate when no concern for genotoxic, carcinogenic, irritation or sensitization potential is present to be used in the absence of supporting general toxicology data and identified potential for systemic toxicity was evaluated and could not be recommended at this time

An integral part of extractable and leachable qualification is the safety assessment of chemicals that leach from the container closure system (CCS) into the final drug product. An inadequate assessment of extractables and leachables during product development can potentially result in drug approval delays. In some instances, additional nonclinical toxicology studies may be conducted for the qualification of leachables for which information in the public domain is inadequate to assess safety and/or have not yet been characterized during drug development. For OINDP, the approach described by PQRI and Ball [1, 2] has generally streamlined the process for safety qualification of extractables and leachables, minimizing potential delays while seeking

to ensure high quality and safe products. The intent of this best practice is to extend this safety qualification process to qualify leachables in parenteral drug products.

Leachables are impurities in the drug product that are unrelated to drug substance manufacture and/or the active pharmaceutical ingredient. Therefore, the approaches described in the ICH Q3A and Q3B guidelines for qualification of impurities in the drug substance or degradation products in the drug product, respectively, are not applicable. However, regulatory guidance clearly indicates that chemicals that leach from the CCS should not alter the efficacy or stability of the active pharmaceutical ingredient or present a toxicological risk [5, 6]. Packaging components should be constructed of materials that will not leach substances that present a significant toxicological risk to a patient when being treated with the drug product. This consideration is especially important for those packaging components that may be in direct contact with the formulation, but it is also applicable to any component from which substances may migrate into the formulation (e.g., secondary packaging materials). Current good manufacturing practice (cGMP) requirements for finished pharmaceuticals include control of drug product containers and closures in 21 CFR Parts 211Subpart E (211.80-211.94) and 210.1(a) identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration. For example, the kind of information that should be provided about a packaging system for an injectable dosage form or a drug product for inhalation is often more detailed than that which should be provided for a solid oral dosage form. As noted in the FDA 1999 Packaging Guidance, for a high-risk drug product, e.g., injection, inhalation, comprehensive studies of packaging components are generally required. This involves:

- Extraction studies on the packaging components to determine which chemicals may potentially leach into the drug product.
- Leachable studies to detect, identify and quantify leachables and correlate with extractables. It is important to note however that while most leachables may have previously been identified as extractables, not all leachables may represent previously identified extractables (e.g., unanticipated leachables from manufacturing systems and interaction products)
- A toxicological evaluation of leachables to assess the health risks presented by the leachables under the intended use conditions of the drug product.

Available guidelines are limited in scope regarding the process of how to conduct a toxicological qualification of leachables and, more importantly, do not establish any safety qualification thresholds for leachables [5, 6]. The key concept developed for OINDP, via the PQRI OINDP L&E Working Group, was the SCT concept of 0.15 µg/day, a dose below which concern for carcinogenicity and noncarcinogenic toxicity is negligible, and identification of leachables below this threshold is generally not necessary [2].

For PDP, the PQRI PODP Toxicology Subteam thus investigated the following:

- Confirmation that the SCT approach developed for OINDP is applicable to PDP

- Determine appropriate level of risk for PDP: 1:1,000,000 (0.15 µg/day) or 1:100,000 (1.5 µg/day)
- Verify that the QT concept (developed for OINDP) is applicable to PDP
- Evaluate whether a third threshold based on systemic toxicity could be proposed

II. Parenteral Drug Products (PDP) Leachables Thresholds

For any chemical, an increase in dose is associated with an increase in effect. Where human and/or animal data are available, and for a chemical that exhibits undesirable toxicity, a dose level below which an adverse effect is not expected can be determined, and a safe level of exposure can be derived. If human exposure to the chemical is below the calculated safe level of exposure (e.g., acceptable daily intake (ADI) derived for food intake [6,7], permitted daily exposure (PDE) values as defined in ICH Q3C [8]), there is no cause for a health concern within a population and over a lifetime of exposure.

Alternatively, comparing expected exposure to derived acceptable dose levels, no-effect levels in acceptably conducted animal studies, or for example, EPA reference doses (RfD) established for human safety are also acceptable methods to evaluate safety. Importantly, qualified leachable concentrations should take into consideration both safety and quality attributes in final drug product.

For unstudied chemicals, (where little to no human or animal data are available) the Threshold of Toxicological Concern (TTC) concept has widespread application within the pharmaceutical industry as it defines an acceptable intake level that poses a negligible risk of carcinogenicity or other toxic effects [9]. The TTC is derived by linear extrapolation from the dose giving a 50% tumor incidence from the most sensitive species and at the most sensitive site in carcinogenicity studies down to a theoretical 1 in 10^6 cancer incidence (0.15 µg/day). For pharmaceuticals, a theoretical 1 in 10^5 cancer incidence is considered justified and a daily intake value of 1.5 µg per day for an unstudied impurity is calculated [9]. Thus, there is no appreciable increase in cancer incidence over a lifetime of human exposure if exposure to the impurity is at or below the TTC of 1.5 µg per day. Most parenteral drug products consist of aqueous formulations. Due to the chemical nature of leachables formed under aqueous conditions, the Working Group considered the TTC of 1.5 µg per day to also be appropriate for leachables in parenteral drug products. In the context of leachables, the TTC of 1.5 µg per day is used as the basis to derive the AET and is equivalent to the SCT. That is, below the SCT of 1.5 µg per day, the dose of a leachable would be so low that the chemical would pose a negligible safety concern from mutagenic/carcinogenic and other toxic effects. Of note, a threshold dose that is lower than 1.5 µg per day may be warranted for certain classes of compounds such as those within the cohort of concern (e.g., aflatoxin-like, N-nitroso- and alkyl-azoxy compounds).

If the total daily dose of a leachable exceeds the threshold dose of 1.5 µg per day, the chemical is evaluated for potential mutagenicity. If sufficient data are available on the chemical of interest, this assessment can be completed by searching the literature and/or databases for relevant data on mutagenicity. If insufficient mutagenicity data are available, an in-silico

assessment can be performed per the ICH M7 (R1) Guidance [9]. If the chemical is not a potential mutagen because it does not contain a structurally alerting functional group for mutagenicity, the leachable is qualified with respect to mutagenicity. If the chemical is identified as a potential mutagen by containing a structurally alerting functional group for mutagenicity, it should be controlled based on the principles and limits noted in ICH M7 [9].

For compounds that are not mutagenic or potentially mutagenic, a Qualification Threshold of 5 µg/day based on the endpoint of sensitization/irritation can be applied. If the total daily dose of a leachable exceeds the threshold dose of 5.0 µg per day, the chemical is evaluated for mutagenic potential as well as irritation and/or sensitization potential. If sufficient data are available on the chemical of interest, this assessment can be completed by searching the literature and/or databases for relevant data on mutagenicity and sensitization/irritation. Historically, in silico tools have not been shown to perform well for the prediction of sensitization/irritation. However, model improvements for skin sensitization have been observed within the last few years. If the output of this analysis suggests that the chemical is neither a mutagen nor a sensitizer/irritant the leachable is qualified and a more elaborate safety assessment is not warranted. If the chemical is not identified as a potential mutagen and is identified as a potential sensitizer/irritant or has other general toxicology findings, it should be qualified at the level found or reduced to not more than the practical limit of 5.0 µg per day. If the chemical is identified as a potential mutagen, it should be reduced to the appropriate exposure according to ICH M7 [9].

For leachables (or extractables as probable leachables), the PODP Working Group sought to extend the concept and application of exposure-based threshold doses for unstudied chemicals to include additional safety endpoints. Specifically, the Working Group confirmed a threshold dose (based on TDI) for sensitizers/irritants and sought to develop a threshold dose for chemicals that are neither mutagenic nor sensitizers or irritants but have general toxicity endpoints for parenteral drug products. The Chemistry subteam provided a list of over 600 chemicals (see Appendix 1) that have been known to extract or leach from manufacturing equipment and/or container closure components for PDP and were representative of the various classes (e.g., fillers, mold agents, slip agents, antioxidants, UV stabilizers) routinely observed in L&E qualification assessments. The list of compounds was sorted according to mutagenic potential, sensitization potential and systemic toxicity utilizing in silico tools, available data in the public domain, and modified Cramer classifications [3, 4]. The list contained over 60 compounds that were predicted sensitizers and over 100 compounds that were predicted mutagens. The remaining compounds were classified according to a modified Cramer classification as low, intermediate, high toxicity. A subset of primarily intermediate and high toxicity compounds (N=60) with experimental data was further evaluated to determine acceptable daily intakes. After extensive efforts to develop and validate a third threshold based on systemic toxicity, it was determined that a definitive recommendation could not be made at this time. Two exposure-based thresholds are recommended based on the endpoints of mutagenicity and sensitization/irritation.

It is important to note that organic leachables found at levels higher than the respective thresholds can be allowed in a particular drug product with a suitable safety qualification based on a combination of in silico (i.e., mutagenicity only), publicly available information, and/or proprietary data.

A review of the safety information in the public domain may be utilized to qualify a leachable for which the dose level exceeds the threshold dose for mutagenicity and sensitization. For example, consider a drug product in which a 0.5 mL PFS is administered subcutaneously (once every 2 weeks) for management of a chronic disease and contains diphenylamine (CAS[i] number 122-39-4) as a leachable at 50 ppm. The total daily dose of diphenylamine is 25 µg/day (50 µg/mL * 0.5 mL = 25 µg/day). This dose level exceeds the TTC for mutagenicity and QT for sensitization/irritation. A review of the available toxicity data indicates that diphenylamine is negative in the *in vitro* bacterial reverse mutation assay (i.e., Ames test) and the *in vivo* mouse micronucleus assay. Diphenylamine is not a skin sensitizer. Although diphenylamine can cause severe irritation to the eyes if applied without rinsing, the results are not considered relevant to the parenteral route of administration. There are no data to suggest that diphenylamine exhibits carcinogenic potential in humans or experimental animals.

Although diphenylamine is negative for mutagenicity and sensitization/irritation, the leachable dose level exceeds the threshold doses for mutagenicity and sensitization/irritation. However, it may be qualified using the PDE approach summarized below, because there is sufficient toxicological information available to derive a PDE.

Further evaluation of the literature suggests that an ADI has been established for diphenylamine. Specifically, in 1969, the Joint FAO/WHO meeting on Pesticide Residues [100] evaluated the data available for diphenylamine and derived an ADI of 0.025 mg/kg on the basis of a no observed adverse effect level (NOAEL) of 2.5 mg/kg in a two-year dog study [10].The ADI for diphenylamine was re-assessed in 1976, 1979, 1984 and finally 1998, during which an ADI of 0–0.08 mg/kg of body weight was established on the basis of the NOAEL of 150 ppm, equal to 7.5 mg/kg/day, from the two-year rat toxicity and carcinogenicity study and applying a 100-fold uncertainty factor. The same study was used to establish an ADI of 0.075 mg/kg of body weight by the European Food Safety Authority [11]. In this study, male and female rats received diets containing technical grade diphenylamine at concentrations of 0, 200, 750, 3750 or 7500 ppm in males and 0, 150, 500, 2500 or 5000 in females for up to 102 weeks. The NOAEL was considered to be 150–200 ppm, equal to 7.5 mg/kg/day, due to changes in hematological parameters including erythrocyte counts, hemoglobin and hematocrit. Histological alterations in the spleen, kidney and bone marrow were also observed and were considered related to the noted hematological effects [12]*in* [10].

To calculate a permissible daily exposure (PDE) for a leachable in a parenteral drug product using Equation 2.1, (see Appendix 2) the Working Group recommends using a 50 kg mass adjustment and applying the uncertainty factors outlined in ICH Q3C (F1 through to F5 [8]). An additional uncertainty factor, per the ICH Q3D Guidance [13], may be considered to adjust for oral to parenteral administration (F6).

Equation 2.1. PDE = NO(A)EL x Mass Adjustment/(F1 x F2 x F3 x F4 x F5 x F6).

Where,

F1 = A variable factor to account for extrapolation between species

[i] Chemical Abstracts Service, a division of the American Chemical Society.

F2 = A factor to account for variability between individuals

F3 = A variable factor to account for toxicity studies of short-term duration

F4 = A variable factor that may be applied in cases of severe toxicity

F5 = A variable factor that may be applied if the no (adverse) effect level was not established.

F6 = A factor to adjust for oral to parenteral administration (e.g.,1 to 100)

In the case of diphenylamine, the 2-year rat toxicity and carcinogenicity study was considered the most relevant for calculating the PDE [12] *in* [10]. Therefore:

PDE = 7.5 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 1) = 7.5 mg/day x 1000 (µg/mg) = 7500 µg per day

In this example,
F1 = 5 to account for the extrapolation from rats to humans
F2 = 10 to account for variability between individuals
F3 = 1 as the study was 102 weeks in duration
F4 = 1 as severe toxicity was not observed
F5 = 1 as a NOAEL was established
F6 = 1 to adjust for oral to parenteral administration (~100% bioavailability [12])

Since sufficient data are available on diphenylamine to derive an PDE of 7500 µg per day and this level is much greater than the leachable dose level (total daily dose = 25 µg per day) the leachable is considered qualified for safety. However, this level of diphenylamine will also need to be assessed for potential impacts to the quality of the final drug product.

A. QT Verification

One subset of leachables and extractables are the known sensitizers and/or irritants. The PQRI Qualification Threshold for OINDP was established at 5 µg/day. This threshold was based on inhalation toxicity data (150 inhaled compounds) from which Reference Doses (RfD) were calculated [1]. In addition, the PQRI OINDP Working Group considered acute respiratory irritation, since airway irritation and paradoxical bronchospasms are possible adverse effects based on OINDP-related leachables. Using a calculated µg dose, the Working Group determined there was an additional 30-fold margin for respiratory irritation that was considered sufficient for sensitive populations such as asthmatics [2].

There is no single, consistent scientific approach to determine the dose response relationship and/or thresholds for sensitizers. The proposed threshold dose of 5 µg/day is considered a practical limit based on the fact that the PQRI PODP Toxicology Team has found no data to suggest that the qualification threshold should be any different for PDP. Case examples of practical limits for sensitizers are presented below. The routes of administration for these examples do not match the parenteral routes, covered by the current document, and the type of hypersensitivity for each example is different (i.e., Type IV and Type I); however, the

examples are still considered valuable for demonstrating practical limits. A review of the literature as well as regulatory trends suggest potential development of practical limits for sensitizers as an effective method of assessing these chemicals, which would be protective for the general population.

Example #1: The existence of known sensitizers and allergens in marketed cosmetic products is recognized. To address that, the Scientific Committee on Consumer Safety (SCCS) developed a pragmatic administrative decision based on available animal and/or human data. The SCCS examined available elicitation dose-response data to decide whether safe thresholds can be established for the fragrance allergens of concern, i.e., those found to pose a high risk of sensitization to consumers. The SCCS considered that thresholds based on elicitation levels in sensitized individuals will be sufficiently low to protect both the majority of sensitized individuals as well as most of the nonsensitized consumers from developing contact allergy. As data from human dose elicitation experiments are very limited, no levels that could be considered safe for the majority of contact allergic consumers (Type IV hypersensitivity; T-cell mediated) were established for individual substances. However, the available data indicate that a general level of exposure of up to 0.8 µg/cm² (0.01% in cosmetic products) may be tolerated by most consumers, including those with contact allergy to fragrance allergens. [14]

The response (adverse effect) for contact allergens from fragrance allergens and sensitization from a leachable in a parenteral drug product differ. However, for comparative purposes, the 5 µg/day dose was converted to a surface area dose to determine the margin difference between PQRI and the SCCS surface area dose of 0.8 µg/cm².

The PQRI proposed limit of 5 µg/day corresponds to a sensitization/irritation value of 0.1 µg/kg assuming a 50 kg human. Using the FDA conversion factor of 37 kg/m^2 [15], the surface area dose would be 3.7 µg/m^2. To convert this dose to µg/cm^2 for purposes of comparison:

10000cm^2 = 1 m^2 yields

3.7 µg/10000cm^2 = 0.00037 µg/cm^2

Margin = 0.8 µg/cm^2/0.00037 µg/cm^2 = 2162

That is ~2200-fold multiple for the 5 µg/day dose when converted to a surface area dose and compared to the SCCS tolerable dose for contact allergens of 0.8 µg/cm^2

Based on evaluations made for both OINDP and fragrance allergens in cosmetics, a dose of 5 µg/day is expected to provide an adequate level of protection to sensitizers and irritants identified as leachables in PDP. We recognize there are differences between topical (skin) administration versus systemic exposure, however the proposed 5µg/day is significantly less than the SCCS value for a skin sensitizer.

Example #2: The FDA Center for Food Safety and Applied Nutrition has a Threshold Working Group that is considering biological concepts and data needed to evaluate various approaches to establish thresholds for food allergens that would be scientifically sound and efficacious in relation to protection of public health. This effort is part of the Food Allergen

Labeling and Consumer Protection Act of 2004 (FALCPA), which amends the Federal Food, Drug, and Cosmetic Act and requires that the label of a food product that is or contains an ingredient that bears or contains a "major food allergen (Type I hypersensitivity; IgE-mediated)" declare the presence of the allergen as specified by FALCPA. Four approaches that could be used to establish thresholds include:

1. Analytical methods–based thresholds are determined by the sensitivity of the analytical method(s) used to verify compliance;

2. Safety assessment–based: a "safe" level is calculated using the lowest observed adverse effect level (LOAEL) or NOAEL from human challenge studies and an appropriate uncertainty factor applied to account for knowledge gaps;
3. Risk assessment–based: examines known or potential adverse health effects resulting from human exposure to a hazard and quantifies the levels of risk associated with specific exposures and the degree of uncertainty inherent in the risk estimate; and
4. Statutorily derived: uses an exemption articulated in an applicable law and extrapolates from that to other potentially similar situations. These approaches are very similar to those described in the current document.

Penicillin can be considered as a practical example for Ige an orally administered systemically available allergen. A potential for harm cannot be completely eliminated for sensitive individuals, although a large majority of the population would be protected. With known thresholds, sensitive individuals can make informed choices about what foods can be consumed.

According to the FDA, residual penicillin G levels of 5 ppb (5 ng/mL) are acceptable in milk (*M-I-18-9): Tolerance and/or Safe Levels of Animal Drug Residues in Milk*. February 2018 [16]. In the publication *Dietary Guidelines for Americans 2010*, the U.S. Departments of Agriculture and Health and Human Services recommend milk consumption of 3 cups (710 mL) milk per day for adults [17]. Based on this information, a safe daily exposure level to penicillin of 3.55 µg is calculated using Equation 2.2.

Equation 2.2 Daily Exposure Level

$$5\ ppb = 0.005\,\frac{\mu g}{mL}$$

$$\text{Daily Exposure} = \frac{0.005 \mu g}{mL} \times \frac{710 mL}{day} = 3.55\,\frac{\mu g}{day}$$

Thresholds cannot be derived for sensitizers. However, practical limits on sensitizers have been proposed for the oral, topical and inhaled routes of administration. In each of these cases, a practical limit appears to be protective of the general population. Based on the limits proposed for oral, topical and inhaled routes, the toxicology work team proposes a practical limit of 5 µg/day for PDP, which is judged to be sufficiently conservative.

B. SCT Verification

PQRI OINDP best practices established the SCT concept, which the PQRI PODP group proposes to apply for parenteral drug product leachables. The SCT is a dose below which there is negligible toxicological and carcinogenic risk associated with CCS leachables. For OINDP, the SCT was set at 0.15 µg/day. The rationale for this conservative approach was the likelihood that chemicals of concern could be found as leachables in a metered dose inhaler, in particular [1], and that leachables of concern could be delivered directly to a diseased organ by any inhalation product, in general. ***Unlike the Threshold for Toxicological Concern (TTC), there is no intent that all leachables have to be below the SCT; rather the SCT is used to derive an Analytical Evaluation Threshold, which is then applied to identify leachables in OINDP.***

Separately, the TTC concept had been developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects. The methods upon which the TTC is based are generally considered to be very conservative since they involve a simple linear extrapolation from the dose giving a 50% tumor incidence (median toxic dose, or TD_{50}) to a 1 in 10^6 incidence, using TD_{50} data for the most sensitive species and most sensitive site of tumor induction. For application of a TTC in the assessment of acceptable limits of mutagenic impurities in drug substances and drug products, a value of 1.5 µg/day corresponding to a theoretical 10^{-5} excess lifetime risk of cancer, can be justified (ICH M7 (R1) Guidance). These risk levels represent a minimal theoretical increase in risk when compared to human overall lifetime incidence of developing any type of cancer, which is greater than 1 in 3 [18].

Some structural groups were identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group of high potency mutagenic carcinogens referred to as the "cohort of concern," comprises aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds [9]. A compound specific safety limit should be determined on a case-by-case basis for these classes of compounds. Based upon knowledge of CCS material composition, processing conditions and results from extraction studies the likelihood for the presence of the cohort of concern chemicals as leachables should be evaluated.

Based on the *aqueous content* of a majority of PDP formulations, there is generally a low likelihood of observing cohort of concern chemicals as leachables. Therefore, an SCT of 1.5 µg/day is considered an acceptable dose to derive the Analytical Evaluation Threshold to identify leachables in PDP.

III. Conclusion

The CCS is an integral component of a drug product. In part, the CCS serves to ensure that the critical quality attributes of the drug product are maintained throughout the labelled shelf-life. Over the drug product shelf-life, chemicals can leach from the CCS. Many of these chemicals have toxicological properties distinctly different from impurities in final drug products related to API manufacture (drug substance) and final drug product. Therefore, leachables are out of scope in ICH Q3A and Q3B. Safety qualification of leachables is discussed in other guidelines and standards (FDA, EMA, ISO, USP, etc.), but these sources generally do not

provide a rationale for setting or utilizing safety thresholds to qualify leachables in drug products.

PQRI developed best practice recommendations for PDP has adapted three threshold concepts; two are safety related (SCT and QT) and the other related to compound identification (AET). The SCT concept provides a safety rationale based on lifetime carcinogenic risk. From an extensive evaluation of the available data, a SCT of 1.5 µg/day was recommended. The SCT represents the level of leachables below which there would not be a significant carcinogenic or noncarcinogenic risk to the patient.

The SCT is utilized by analytical chemists to calculate the AET. The AET is the level above which all leachable compounds should be identified in PDP and reported for toxicological assessment. The AET is not a safety or control threshold, rather it is an identification threshold.

In addition to the SCT, a QT of 5 µg/day is recommended as a threshold for toxicological assessment of identified compounds based on primary endpoints of irritation and sensitization. Identified leachables below the QT are considered to present minimal risk to the patient for noncarcinogenic toxicity. The QT is not intended to be a control threshold.

In many cases, leachables in drug products are at levels that exceed the QT for PDP. These leachables require thorough assessment to ensure patient safety based on the level present in a drug product. In most cases, qualification of these leachables is performed using results from in silico assessments and evaluation of data from published studies and regulatory reports. In cases where there is insufficient data, in vitro and in vivo hazard assessment studies may be conducted to qualify individual leachables.

The qualification of leachables and extractables in PDP follows a similar approach proposed in the PQRI OINDP best practices that is applicable to decision making based on toxicology considerations. The approach is summarized in Figure 2-1 Qualification of Leachables in PDP. The key points to consider in qualification are:

- Identification of the leachable (structure and CAS #)
- In silico assessment
  - Utilize expert rule-based and statistical-based (Q)SAR methodologies to assess mutagenic potential [9]
  - In silico tools should not be considered as conclusive for the prediction of sensitization/irritation.
- Review of published data to determine:
  - PDE based on NOAEL, NOEL, LOEL from available animal data
  - ADI based on human data (RfD, IARC, ACGIH, NIOSH, OSHA. etc.)
  - if there is mutagenic, sensitization, or irritation potential
- Utilize PQRI thresholds

  If in silico assessment/published literature determines mutagenic risk for compound > TTC

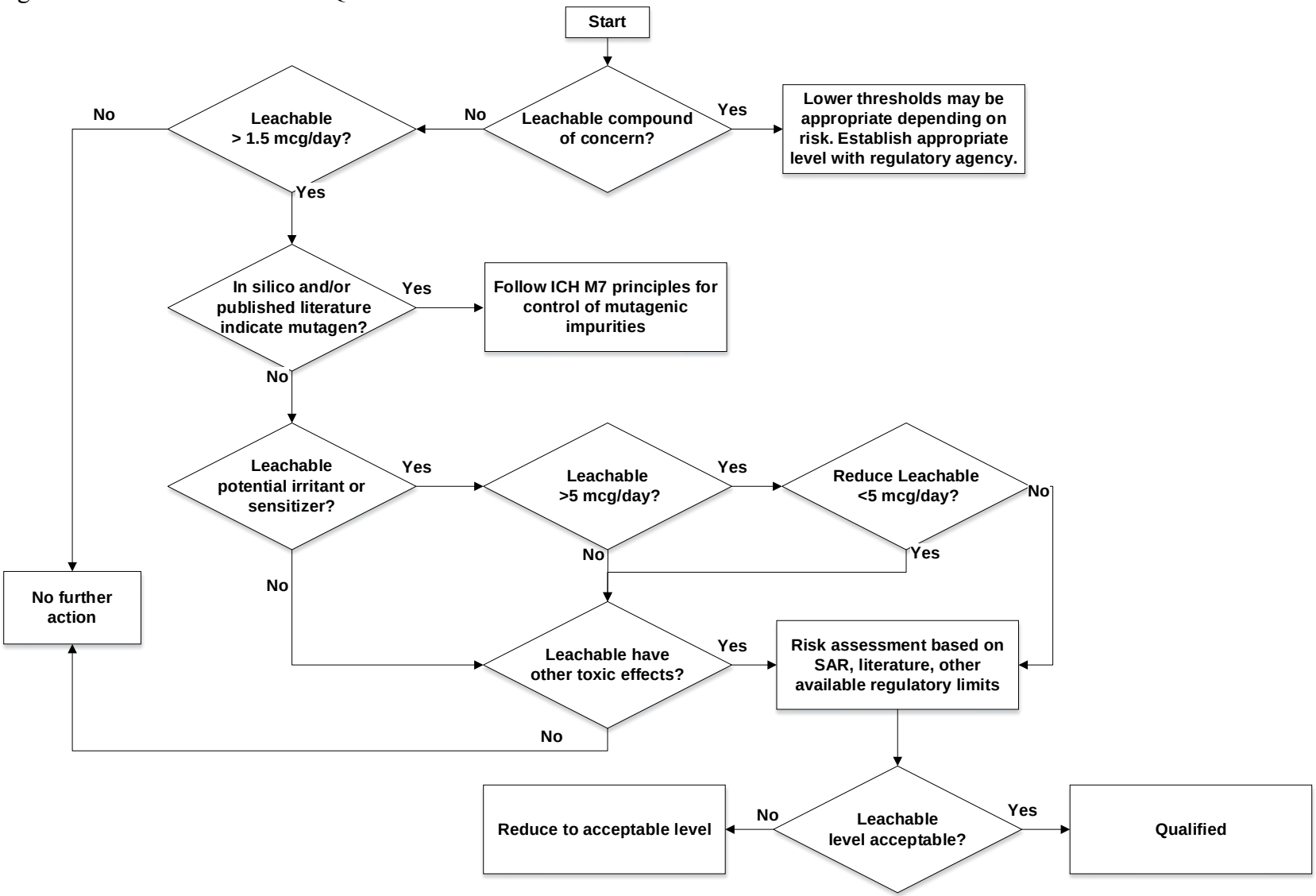
  - apply ICH M7 principles to qualify the level of the leachable in the drug product

If in silico assessment/published literature determines a sensitization and/or irritation risk for compound > QT

- Provide assessment to support a higher dose
- Or, Lower dose to ≤5 µg/day

- In the event that in silico assessment and/or published literature are insufficient to qualify, conduct in vitro and or in vivo assessment to assess:
  - mutagenic risk
  - local and systemic toxicity risk (e.g., repeat dose toxicity study one species, 14–90 day duration)
  - potential for sensitization (e.g., local lymph node assay) or irritation (e.g., acute dermal irritation study)
  - specific risk using other toxicity studies as appropriate

Figure 2-1 Process Flow for Qualification of Leachables in PDP



IV. References

1. Norwood D, Ball D, Blanchard, J, et al. Safety thresholds and best practices for extractables and leachables in orally inhaled and nasal drug products. Product Quality Research Institute. September 8, **2006**. http://pqri.org/wp-content/uploads/2015/08/pdf/LE_Recommendations_to_FDA_09-29-06.pdf

2. Ball D, Blanchard J, Jacobson-Kram D, et al. Development of safety qualification thresholds and their use in orally inhaled and nasal drug product evaluation. *Toxicol Sci* **2007**. 97(2):226–36.

3. Cramer GM, Ford RA, and Hall RL. Estimation of toxic hazard – a decision tree approach. *Food and Cosmetic Toxicology*. **1978**. 16:255–76

4. Munro IC, Fors Ra, Kennepohl, et al. Correlation of a structural class with no observed-effect-levels: a proposal for establishing a threshold of concern. *Food Chem Toxicol*. **1996**. 34:829–67.

5. Guidance for Industry. Container closure systems for packaging human drugs and biologics. Chemistry, manufacturing, and controls documentation. US Department of Health and Human Services. Food and Drug Administration. May **1999**. https://www.fda.gov/downloads/drugs/guidances/ucm070551.pdf

6. Guideline on plastic immediate packaging materials. Committee for Medicinal Products for Human Use and Committee for Medicinal Products for Veterinary Use. European Medicines Agency. December **2005**. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003448.pdf

7. Priority-based assessment of food additives (PAFA). US Code of Federal Regulations (21 CFR) Parts 175–178.

8. ICH guideline Q3C (R6) on impurities for residual solvents. International Council for Harmonisation. October **2016**. https://database.ich.org/sites/default/files/Q3C-R6_Guideline_ErrorCorrection_2019_0410_0.pdf

9. ICH Harmonized Guideline M7(R1), Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. March **2017**. https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf

10. Report of the 1969 Joint meeting of the FAO working party of experts on pesticide residues and the WHO expert group on pesticide residues. World Health Organization. December **1969**. http://apps.who.int/iris/bitstream/10665/40800/1/WHO_TRS_458.pdf

11. Conclusion on the peer review of the pesticide risk assessment of the active substance diphenylamine. European Food Safety Authority Journal. 2012. http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2486/epdf

12. Protzel A. Diphenylamine (addendum) JMPR. Environmental Protection Agency. 1998. http://www.inchem.org/documents/jmpr/jmpmono/v098pr07.htm

13. ICH Harmonized Guideline, Q3D(R1) Guideline for elemental impurities. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use . March **2019**. https://database.ich.org/sites/default/files/Q3D-R1EWG_Document_Step4_Guideline_2019_0322.pdf

14. Opinion of fragrance allergens in cosmetic products. Scientific Committee on Consumer Safety. June **2012**. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf

15. Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. CDER. July **2005** https://www.fda.gov/media/72309/download

16. *FDA, Tolerance and/or Safe Levels of Animal Drug Residues in Milk*. February 2018 http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Milk/ucm077350.htm

17. *Dietary Guidelines for Americans 2010*, the U.S. Departments of Agriculture and Health and Human Services,https://health.gov/sites/default/files/2020-01/DietaryGuidelines2010.pdf

18. : Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, SteliarovaFoucher E, Swaminathan R, Ferlay J, editors (2014). Cancer Incidence in Five Continents, Vol. X. IARC Scientific Publication No. 164. Lyon: International Agency for Research on Cancer.

Part 3. Best Practices for Extractables and Leachables Assessment in PDP

I. The Link between OINDP and PDP Best Practice Recommendations

The essential hypothesis upon which the PDP effort was based is that the "good science" best demonstrated practices that were established for the OINDP pharmaceutical development process can be extrapolated to container closure systems for PDP. In 2013, seven years after the initial release of the OINDP recommendations, a commentary on these recommendations was published by Norwood, et al. [1]. The authors were closely involved in the development and subsequent implementation of the OINDP recommendations. While noting that "although the PQRI (*re OINDP*) recommendations, including the safety-based thresholds and best practices, have been generally accepted by both industry and regulators for inhalation drug products" the authors also observed that "certain questions and concerns have been raised since their initial release." Two of these concerns involved:

- Best practices for controlled extraction studies
- Extension to other drug product types – "The AET Challenge"

Regarding controlled extraction studies, it was observed that the laboratory extraction studies accomplished by the PQRI OINDP Working Group to assist in the development and illustration of their recommendations, were designed with metered dose inhaler (MDI) rubber and plastic componentry in mind [2]. The MDI model was chosen "because the MDI is the only drug product type in which there is an almost certain 1:1 correlation … between critical component extractables (i.e., potential leachables) and actual identified leachables." Although there was no intention on the part of the OINDP group to exclude extraction techniques and extraction solvents more applicable to componentry related to other dosage forms, a gap clearly existed in the OINDP extraction study work, in relating these studies directly to other dosage forms. The PODP Working Group recognized these gaps and undertook extraction studies using extraction techniques and solvent systems more appropriate for these dosage forms and their largely aqueous formulations. The test articles in the extraction studies were plastic and elastomeric materials of construction chosen to represent PDP packaging components and systems. The results of these extraction studies have been reported [3], and were used to assist the PDP group in developing their recommendations, extrapolating the OINDP recommendations to PDP dosage forms, and generalizing the OINDP recommendations for other dosage forms beyond PDP. Therefore, PDP general recommendations 3 and 4 are:

3. ***Extractables assessments and extraction studies for PDP may be considered as appropriate for specific application to materials of construction, finished components, and complete packaging systems (i.e., container closure systems).***

4. ***Extractables assessments and extraction studies for PDP packaging systems should include aqueous-based extraction solvents with appropriate consideration of extraction pH, organic solvent content, and other appropriate extraction conditions (e.g., extraction time, extraction temperature, extraction technique, and sample-to-solvent ratio).***

It is also recommended that extractable studies for CCS used with complex drug products should consider appropriate solvent propensity to establish the extractable profile to guide optimization of nontargeted screening methods for placebo or leachables.

Note: Examples of complex drug products include complex API (e.g., polymeric compounds, peptides), complex formulations (e.g., liposomes, emulsions, suspensions), complex routes of delivery (e.g., topical), complex dosage forms (e.g., long-acting injectables), and complex drug-device combinations (e.g., prefilled syringes, autoinjectors).

Concurrent with development of the PQRI PDP Recommendations, the USP developed three informational general chapters related to extractables and leachables (4–6). These include the following:

USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems. 2015 [4].

USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems. 2015 [5].

USP <1664.1> Orally Inhaled and Nasal Drug Products. 2015 [6].

The USP is a PQRI member, and several members of the Expert Committee that created these general chapters were also members of the PQRI OINDP and PODP Working Groups, therefore it is reasonable that these general chapters reflect the consensus science-based thinking of PQRI. The PQRI OINDP recommendations are generally reflected in these chapters. For example, as stated in USP <1663>:

"In order to assess…risks and manage the potential issues posed by leachables, it is necessary to know the identities and the levels to which leachables will accumulate in the finished drug product over its shelf-life. These two pieces of information can be used to establish the magnitude of patient exposure (dose) and therefore the safety risk posed by an individual leachable, as well as the likelihood of any compatibility issues involving the drug product.

Since the pharmaceutical packaging/delivery system is the primary source of potential leachables, it is generally appropriate that any leachables assessment be preceded by an extractables assessment performed on the packaging/delivery system, its primary and certain critical secondary packaging components that are noncontacting but potentially interacting, and/or packaging and delivery system materials of construction; consistent with regulatory guidelines and best-practice recommendations." [4]

The term "Extractables Assessment" refers to the process by which chemical entities are extracted from a test article (e.g., material of construction, component, finished packaging system), detected through chemical analysis of extracts, identified through structural analysis, and quantitated. Extractables assessments necessarily involve an "Extraction Study" (Controlled Extraction Study) and result in the creation of "Extractables Profiles" (e.g., the list of identified and unknown organic and inorganic extractable chemical entities, amount present, and level of confidence in the identity). These concepts and principles have been investigated and included in

development of the PQRI PDP Recommendations. There are various reasons for accomplishing extractables assessments (e.g., materials characterization and selection, identification of potential leachables, etc.) and these are listed in detail in USP <1663>. Comprehensive datasets typically include the identity and estimated amount of detectable organic and inorganic extractable chemical entities, indication of criteria for confidence level in identification of chemical entities, and supporting analytical data such as chromatograms, mass spectra, NMR spectra, etc. These principles remain unchanged from the original PQRI OINDP Recommendations.

II. Material/Component Characterization and Selection

PDP general recommendation #3 emphasizes materials of construction, finished components and complete packaging systems. The pharmaceutical product manufacturer typically has responsibility for establishing a comprehensive understanding of the requirements for manufacturing, packaging, storage and delivery of a unique pharmaceutical product safely and effectively to an intended patient population. The pharmaceutical product manufacturer may work collaboratively with specific suppliers to enable selection of an appropriate materials or components that will ultimately satisfy the pharmaceutical product manufacturer's unique manufacturing, packaging storage and delivery requirements.

The type of information that is required for material/component selection varies depending on the route of administration and dosage form. The level of concern associated with a particular material/component is directly related to the type of interaction with the dosage form [7]. Therefore, critical components are those that have high concern because of potential interaction with the dosage form (e.g., liquids) and those that have negligible interaction with the dosage form (e.g., powders) have low concern. Critical components require comprehensive information that may include extractables and other charterization information. The OINDP recommendations recognized high concern components as critical. In a follow-on effort by IPAC-RS, "Baseline Requirements for OINDP" was published in 2011 and updated in 2017 (https://www.ipacrs.org/publications), and took into consideration the level of concern not only for components but also for materials of construction, and finished packaging/delivery systems. Likewise, PDP has taken a risk-based approach to characterization and selection of materials of construction, components and finished systems.

The OINDP recommendations regarding material/component selection can thus be broadened as follows:

- The pharmaceutical product development and manufacturing team should obtain any/all available information on the composition and manufacturing/fabrication processes for each material of construction and finished component utilized in a complete packaging system (i.e., container closure/delivery system).

- The information thus obtained, augmented with appropriate testing of the materials of construction and finished components (see Table 3-1), should drive material/component selection.

- Material and component selection should be based on an assessment of potential risk of patient leachables exposure or formulation compatibility issues, which should consider the criticality with consideration of the material, finished component or complete system in which it is used.

The PDP recommendations for materials/component selection is based on the OINDP recommendations while widening them to include consideration of materials of construction, drug product dosage form and route of administration, with the recognition that selection may be facilitated by performing extractables assessments and other relevant testing.

Table 3-1 Types of Controlled Extraction Studies

Controlled Extraction Studies	Purpose	Output
Semiquantitative Broad Based/Screening		**Potential Leachables**
Expected/Unforeseen Extractables	Material Characterization	Understanding Materials Chemistry
Concentrated Extraction Solutions	Chemical Composition Information	Guide Simulation and Leachable Studies
Aggressive Conditions	Hazard Assessment	
Simulation Study		**Probable Leachables**
Target Extractable Screens	Chemical Migration Potential	Identify Leachable Targets
Justifed Similated conditions	Mimic Intended Use	Assessment of All Extractables > AET
	Potential Safety Risks	Guide Leachables studies
Leachables Study		**Confirmed Leachables**
Validated Quantitative Robust Methods	Detect Leachable Targets	Establish the actual accumulation of all leachables
Targeted and Unanticipated Leachables	Identify Unexpected Leachables > AET	Toxicological assessment of all leachables
	Monitor and Control as needed	

III. Characterization Studies

As with Material/Component Characterization and Selection, the OINDP group's detailed recommendations related to "Controlled Extraction Studies" have been extrapolated to PDP as follows:

- Controlled extraction studies of appropriate design should be performed for all PDP container-closure systems.

- The controlled extraction study should be designed for the study's specific purpose. Outputs from extractable studies are typically used to guide leachable method optimization and extractable monitoring as necessary. This information may include non-target chemical characterization of component(s) to establish a semi-quantitative extractable profile, compound specific quantitation to establish a component's maximum extractable levels to correlate to leachables, simulation with the final CCS to establish the collective probable leachable profile, and potential for chemical migration across semipermeable materials.

- Controlled extraction studies should use a combination of multiple relevant extraction solvents of varying chemical nature (e.g., pH, polarity) with suitable sample preparation, extraction temperatures, durations and extraction and analytical techniques as appropriate for, and consistent with, the intent and purpose of the controlled extraction study.

- A Controlled Extraction Study should utilize an analytical approach with thoughtfully chosen multiple complementary analytical techniques for the purpose of detecting, identifying and quantifying relevant and appropriate extractables.

- The analytical approach should include careful and thoughtful sample preparation based on thorough knowledge of the material or component being extracted, the qualitative and quantitative capabilities of the analytical techniques employed, the chemical nature of the extracting media and the probable chemical nature of the extracted chemical entities.

- A controlled extraction study should be guided by an AET that is typically based on an accepted and relevant threshold such as the Safety Concern Threshold (SCT), particularly if the objective of the controlled extraction study is to support the assessment of any extractables identified and reported in the study as probable leachables for a unique drug product.

- The controlled extraction study should include a defined and systematic approach for the identification and quantitation of individual extractable chemical entities and generation of a comprehensive extractables profile.

- A meaningful correlation should be established between an extractables profile and the available compositional and manufacturing/fabrication information for the relevant materials of construction, finished componentry, and the finished packaging system.

- The term "Controlled Extraction Study" is understood in the context of its definition as provided in the original OINDP Recommendations document:

  "A Controlled Extraction Study is a laboratory investigation into the qualitative and quantitative nature of extractables profiles of critical components of an OINDP container/closure system." [8]

However, when the concept of a controlled extraction study is expanded to include additional dosage forms, a somewhat different definition may be appropriate:

> *A Controlled Extraction Study is a laboratory investigation into the qualitative and quantitative nature of extractables profiles of a container/closure system, its critical components and/or assembled system with consideration of its materials of construction.*

It is important to observe that the terms "Extractables Assessment," "Extraction Study" and "Controlled Extraction Study" have some overlap and in many cases can be used interchangeably. In the context of this document and within the previously listed USP general chapters, the more general term "Extractables Assessment" necessarily includes an "Extraction Study" and/or a "Controlled Extraction Study." "Controlled Extraction Study" has historically referred to an extraction study designed specifically for the assessment of extractables as potential worst-case leachables, with the results of the study intended for regulatory submission as such [7].

Given the nature of the solvents used in OINDP, a controlled extraction study could be envisioned as a single study, utilizing multiple solvents, for each critical component. Such a study could serve numerous purposes, including estimation of a leachables profile and characterization of a critical component. As the concept of a controlled extraction study is expanded to dosage forms that vary greatly in terms of their chemical composition and characteristics, it becomes possible that extraction studies may be designed differently depending on their purpose. For example, consider an aqueous PDP. A controlled extraction study whose purpose is to produce an extractables profile to estimate the drug product's worst-case leachables profile may be quite different in its design from an extraction study whose purpose is to fully characterize a critical component for all extractables. Thus, the PDP recommendations build on the essential concept of the OINDP controlled extraction study by noting that although controlled extraction studies may differ depending on their purpose, all controlled extraction studies should be optimally and appropriately designed to fulfill that purpose, including a clear description of extraction, identification, quantitation and reporting criteria.

As was noted previously, the OINDP published extraction studies were based on the MDI model, and the MDI uses an organic solvent as its drug product vehicle. Thus, the OINDP recommendations regarding the chemical nature of extracting solvents is predicated on using solvents of varied polarity to obtain a comprehensive extractables profile and that at least one solvent should have similar extracting properties to the drug product vehicle

In many cases, the PDP vehicle is an aqueous solution whose composition is established to facilitate the stability and utilization of the drug product. While the polarity of these aqueous

vehicles remains an important consideration in choosing extraction solvents for PDP extraction studies, there are other solvent properties to consider. For example, it has been well-established that the pH of an aqueous extracting solvent can have a profound effect on a component or material extractables profile. Furthermore, it is also well-known that the presence of certain chemical entities in a drug product vehicle can increase the extraction of elemental entities (i.e., trace metals such as Zn). It is possible that one set of extraction solvents may be utilized to simulate the extracting properties of several drug product vehicles that are used with the same CCS. Thus, an extraction solvent recommendation that is applied to multiple, chemically varied dosage forms must consider and address all the compositional characteristics of drug product vehicles that might affect the drug product's "leaching power" and thus the selection and justification of extraction solvents.

Considering pH specifically, the following recommendations are made:

1. *The proper pH range for extracting solvents used in extraction studies designed to forecast aqueous drug product leachables spans the pH range of the relevant drug products.*

2. *Extraction solvents with a neutral pH between 6 and 8 should not be used to establish an organic worst-case extractables profile (i.e., greatest number of extractables at their highest levels).*

3. *Simulation studies requires the use of extraction solvents with pH values closely matching the extreme pH values of the drug products.*

4. *Expanding the pH range of the extracting solvents beyond the pH range of the drug products with increasing temperature produces an extractables profile that will exaggerate the drug products' leachables profile.*

Combining aqueous extracting solvents with different pH and organic solvent content is often appropriate for controlled extraction studies of PDP-related materials, components and finished packaging systems. Some example extractables profiles from the PDP group's extraction studies [3] are shown in **Error! Reference source not found.**.

Perhaps one of the more powerful of the original OINDP Recommendations involves the recognition that no single analytical technique is capable of elucidating a full extractables or leachables profile. The validity of this statement is borne out when one considers the wide diversity of materials used in packaging systems, in packaged drug products and in the conditions under which a packaged drug product and its packaging are in contact. Although under specific circumstances an extractables profile that is appropriate for a specific purpose (e.g., understanding of extractable elemental impurities, volatile organic chemical entities, etc.) can be generated with a single analytical method, it is nevertheless the case that no single analytical technique can be universally applied to produce a comprehensive extractables profile in all cases. Thus, a scientifically sound analytical approach that involves complementary techniques and associated methods is commonly and routinely applied to the profiling process. For clarity and purpose of this and subsequent discussion, an analytical method may be generally described as application of one or more analytical techniques in the identification and/or

quantitation of unique organic or inorganic chemical analytes, using well-defined detection, quantitation, and reporting criteria.

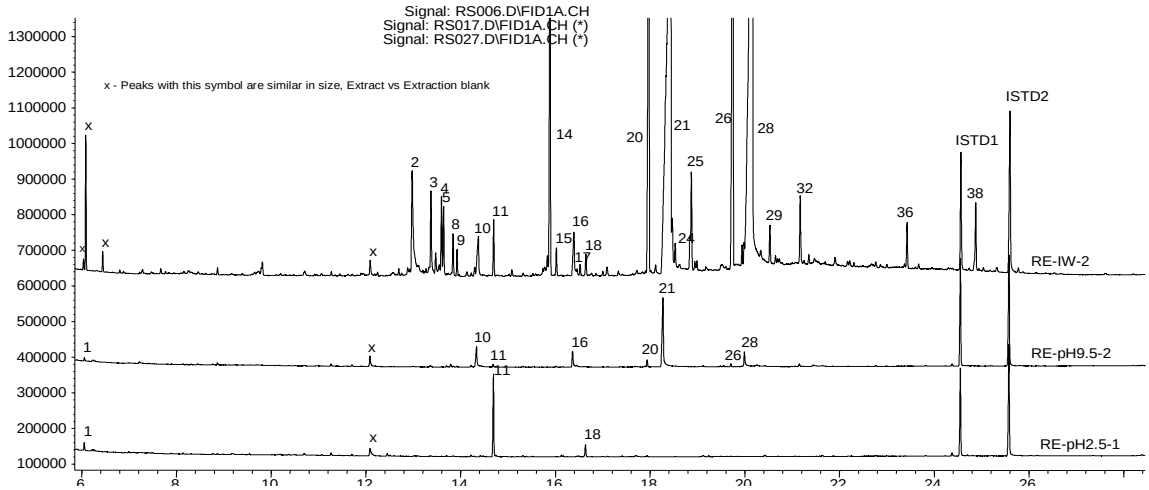


Figure 3-1 Example extractables profiles, in the form of Gas Chromatography/Mass Spectrometry Total Ion Chromatograms, from a typical PDP elastomer. [3] Top: 50:50 isopropanol:water; Middle: pH 9.5 aqueous; Bottom: pH 2.5 aqueous. Note that numbered extractables were identified, and ISTD refers to added internal standards. This type of extraction would represent that done for a multi-use component.

Best intentions notwithstanding, it is a practical reality that use of a truly comprehensive suite of complementary analytical methods represents a considerable commitment of resources. Furthermore, it is generally the case that the most commonly employed analytical methods are sufficiently broad in scope that the most frequently encountered extractables/leachables are captured by these methods. Thus, the risk associated with either (a) the analytical methods failing to detect a "significant" extractable or (b) the analytical method greatly underestimating the level of a "significant" extractable is generally perceived to be low.

However, "low risk" is not the same as "no risk" and the pursuit of scientific rigor demands that some means be employed to establish that the generated extractables (or leachables) profile is complete and accurate to a reasonable degree of scientific certainty and represents the application of due diligence. It is beyond the scope of this document to establish a single means of accomplishing the objective of establishing the completeness and accuracy of an extractables or leachables profile. Although the concept of reconciliation (e.g., applying Total Organic Carbon) *has* been proposed and utilized in certain cases with purely aqueous extracts, the concept is not universally applicable and is not without its own potentially considerable challenges. Therefore, this PDP focused document cannot recommend any universally valid scientific process for reconciliation, specifically as applied to determination of "mass balance" in individual extracts.

IV. Leachables Assessment for Parenteral Drug Products

This section addresses specific considerations for leachables in PDP as assessed against an SCT of 1.5 µg/day. Product types discussed include prefilled syringes (PFS), small volume parenterals (SVP), and large volume parenterals (LVP). Note that the following discussion is primarily devoted to organic leachables.

Parenteral drug products are generally recognized as high-risk dosage forms with respect to leachables, owing to a high likelihood of interaction with the packaging system and the highest degree of concern associated with the route of administration [7]. The packaging systems used in these drug products incorporate components of various types, including components composed of polymeric (plastic or elastomeric) raw materials with complex chemical compositions and therefore a variety of potential leachables. Chemical entities may leach into the formulation when there is direct contact with the primary packaging and delivery components for extended periods of time. In cases where the drug product primary container is semipermeable, compounds migrating from secondary or tertiary packaging components pose a significant concern, and such components (e.g., product labels, inks, adhesives, unit cartons, etc.) may be deemed critical with respect to potential leachables.

Parenteral drug products typically require:

- A leachables study for drug product registration that supports intended storage and use conditions throughout the proposed shelf-life, ideally performed on primary drug product stability batches manufactured with the same lots of packaging components used in extraction studies (in order to facilitate a leachables-extractables correlation);
- Sensitive, selective, and demonstrably fit-for-purpose analytical methods for leachables during pharmaceutical development and fully validated methods for ongoing testing of targeted leachables in marketed products.
- Non-targeted screening methods for detection of unanticipated leachables and interaction products (which do not supersede employment of a fully validated method to monitor a specific, targeted leachable of potential concern);
- Leachables assessments based on safety thresholds: 1.5 µg/day for unknown and genotoxic leachables as well as other thresholds for known, nongenotoxic compounds.
- Complete qualitative and quantitative leachables-extractables correlations (which require that extractables assessments be accomplished on all critical packaging components);
- Leachables specifications including acceptance criteria (assumes a complete extractables assessment for each critical packaging component).

  Note that the development and application of extractables/leachables specifications with appropriate acceptance criteria is a regulatory issue, and therefore must be accomplished on a case-by-case basis with input from the regulatory authority.

A. Parenteral Drug Product Dosage Forms

The key issue in leachable assessment for parenteral products is application of the SCT (1.5µg/day) to derive an appropriate AET. Some parenteral drug products may present a particular challenge in this regard. Given the inverse relationship between dose volume and AET, parenteral drug products with large daily dose volumes may require AETs so low as to hinder the detection of leachables in drug product. Managing AETs for PDP can be challenging and strategies for calculating AETs for parenteral products will be discussed.

The AET will depend on the type of system and dosing considerations (e.g., dose volume, frequency, duration of treatment). Calculation of the AET can be expressed in terms of µg per container, to represent the extractables based on the entire container closure system, µg per dose volume relative to patient dose, and µg/g of component material to indicate the concentration extractable in solutions. Application of the AET is demonstrated in the following systems to illustrate the range of AETs that can occur and influence the design of the study.

- PFS: 1mL luer lock cyclic olefin barrel, 6.4 mm diameter elastomer plunger stopper and tip cap
- Pen: 2 mL glass cartridge, 6.4 mm diameter elastomer plunger stopper and seal
- Mutli Dose Vial: 10mL glass vial and 20 mm diameter elastomer stopper
- Single Dose Vial/Multiple Doses: 2mL glass vial and 13mm diameter elastomer stopper
- Single Dose Vial/Single Dose/Day: 2mL glass vial and 13 mm diameter elastomer stopper
- Single Dose Bag: 120mL polymer bag and elastomer sleeve stopper
- IV Bag/Single Dose/Day: 1000mL polymer bag and elastomer sleeve stopper
- IV Bag/Multiple Bags/Day: 1000mL polymer bag and elastomer sleeve stopper

i. Prefilled Syringes (PFS)

PFS are unit dose delivery systems that are prefilled with drug product. Advantages of PFS include convenience in administration, the elimination of overfills (e.g., to ensure sufficient deliverable volume from a vial), and elimination of preservative (e.g., relative to a multidose vial). Whereas a syringe used to draw and administer drug product from another container will only contact drug product for a brief time, prefilled syringe systems are in continuous contact with the formulation until it is dispensed. Essentially, PFS systems function both as primary packaging as well as administration devices. As such a PFS is a combination product and can be used in autoinjectors or pen systems. Considering the PFS as a drug container, the orientation of

the test sample for worst case contact should be considered. Considering the PFS as a device, additional thresholds may be applicable (e.g., ISO 10993-18 and ISO TS 21726) [9,10]. The following example is based on a PFS acting as a container closure system. The basic components of a PFS include a barrel, plunger rod, plunger stopper and a needle shield for staked needles or tip cap for luer lock.

Leachables in PFS should be characterized at levels at or above a calculated AET. *It must be emphasized that the AET is not a control threshold like the TTC, but rather a concentration at or above which detected leachables need to be identified and toxicologically assessed.* An AET can be calculated for PFSs with consideration of the parenteral SCT (i.e., 1.5 µg/day for an individual organic leachable). An example AET calculation for a PFS follows:

Consider a PFS containing a 0.8 mL unit dose of drug product: one PFS is used per day and constructed from a cyclic olefin copolymer (COC) barrel (1.2 g) with a brominated isobutylene-isoprene elastomer plunger stopper (0.22 g), the following estimated AET can be calculated for an individual organic leachable:

Equation 3.1 Estimated Leachable AET per CCS

$$\textbf{AET µg/CCS} = \frac{\textbf{(SCT (µg/day))}}{\left(\#\frac{\boldsymbol{dose}}{\boldsymbol{day}}\right)} \times \left(\frac{\textbf{\# labeled Doses}}{\boldsymbol{CCS}}\right)$$

$$\text{AET} = \left(\frac{1.5\ \mu\text{g / day}}{1\ \text{dose / day}}\right) \times (1\ \text{labeled dose / PFS}) = 1.5\ \mu\text{g/PFS}$$

Alternatively, the AET for a PFS can be expressed on the basis of leachable concentration in drug product:

Equation 3.2 Estimated Leachable AET per Dose Volume (mL)

$$\textbf{AET (µg/mL)} = \frac{\textbf{(SCT (µg/day))}}{\left(\frac{\textbf{doses}}{\textbf{day}}\right)} \times \left(\frac{\textbf{dose}}{\textbf{volume (mL)}}\right)$$

$$\text{AET} = \left(\frac{1.5\ \mu\text{g / day}}{1\ \text{dose / day}}\right) \times \left(\frac{1\ \text{dose}}{0.8\ \text{mL}}\right) = 1.9\ \mu\text{g / mL}$$

An estimated extractable AET of a PFS barrel and plunger stopper is a useful guide for characterizing extractables representing potential leachables:

Equation 3.3 Estimated Extractable AET per component mass

$$\text{AET (µg/g)} = \frac{(\text{SCT (µg/day)})}{\left(\#\frac{\text{CCS}}{\text{day}}\right)} \times \left(\frac{\text{CCS / \#Component}}{\text{Mass(g) / Component}}\right)$$

$$\text{AET (barrel)} = \frac{(1.5\ \mu g/day)}{\left(\frac{1\text{PFS}}{\text{day}}\right)} \times \left(\frac{\text{PFS / 1 barrel}}{1.2\ \text{g / barrel}}\right) = 1.3\ \mu g/g$$

$$\text{AET (plunger stopper)} = \frac{(1.5\ \mu g/day)}{\left(\frac{1PFS}{day}\right)} \times \left(\frac{\text{PFS /1 plunger stopper}}{0.22\ \text{g /plunger stopper}}\right) = 6.8\ \mu g/g$$

A PFS is considered the device constituent of a drug-device combination product and can also be part of a multidose pen injector which would impact the AET due to multiple doses in a container. Examples of AET for small and large volume parenterals are illustrated in the following Tables: Table 3-2 AET as a Function of Container; Table 3-3 AET as a Function of Dose Volume; and Table 3-4 AET as a Function of Component Mass.

Table 3-2 Example of Estimated Leachable AET Values for SVPs and LVPs as a Function of Container

	Container Closure System	Doses/ Day	Labeled Doses/Container	AET µg/Container
	PFS	1	1	**1.5**
SVP	**Pen Injector**	1	10	**15**
	Multi-Dose Vial	1	5	**7.5**
	Single-Dose Vial: Multiple Doses/day	3	1	**0.5**
	Single Dose Vial: Single Dose/day	1	1	**1.5**
LVP	**Single Dose Bag**	1	1	**1.5**
	IV infusion	1	1	**1.5**
	IV Infusion	2	1	**0.75**

ii. Small Volume Parenterals (SVP)

SVP are defined as solutions or suspensions less than or equal to 100 mL per USP<659> [11]. They may be packaged in bags, vials (often, glass or plastic with an elastomeric septum closure and sleeve stopper), or a PFS. Some SVP are manufactured and packaged as ready to use solutions and others may be powdered or lyophilized, thus requiring reconstitution in an appropriate solvent before administration. SVP may be unit dose or intended for multidose use.

Leachables in SVP should be characterized at levels at or above a calculated AET. *As stated previously, it must be emphasized that the AET is not a control threshold like the TTC, but rather a concentration at or above which detected leachables need to be identified and toxicologically assessed.* An AET can be calculated for SVP with consideration of the parenteral SCT (i.e., 1.5 µg/day for an individual organic leachable).

Estimated AETs for SVP and LVP components can be calculated according to Eq 3.1 for an individual leachable in the products configured as shown in Table 3-2.

Alternatively, the AETs can be expressed on the basis of leachable concentration in drug product according to Eq. 3.2 and shown in Table 3-3.

Table 3-3 Example of Estimated Leachable AET Values for SVPs and LVPs as a Function of Dose Volume

	Container Closure System	Doses/ Day	Dose Volume (mL)	AET µg/mL
	PFS	1	0.8	**1.9**
SVP	**Pen Injector**	1	0.2	**7.5**
	Multi-Dose Vial	1	0.8	**1.9**
	Single-Dose Vial: Multiple Doses/day	3	1	**0.5**
	Single Dose Vial: Single Dose/day	1	1	**1.5**
LVP	**Single Dose Bag**	1	120	**0.013**
	IV infusion	1	1000	**0.0015**
	IV Infusion	2	1000	**0.00075**

Table 3-3 clearly demonstrates the inverse proportionality between dose volume and estimated AET, with values in product ranging from part-per-million to part-per-billion. Although AETs in the low part-per-billion range or lower are analytically feasible for targeted analysis, they may present a challenge for the detection and identification of unknown leachables in the drug product formulation. This challenge is a hallmark of large volume parenterals and the reader is referred to Section C, below, for strategies to manage very low AETs (e.g., Simulation Studies). In fact, a 50 mL dose administered five times each day clearly moves this scenario into the realm of large volume parenterals from the perspective of patient dose.

iii. Large Volume Parenterals (LVP)

LVP are defined as solution products containing more than 100 mL per USP <659>. Typical packaging systems for LVP are polymeric bags or bottles, but commonly include elastomeric closures for bottles and ports made of other plastic materials for bags.

Ideally, leachables in LVP should be characterized at levels at or above a calculated AET as described for other parenteral dosage forms. However, owing to the large dose volume, applied AETs in LVP may be so low as to significantly challenge the sensitivity and detection capabilities of advanced analytical instrumentation and techniques, and therefore may not

adequately enable detection and identification of unknown leachables in drug product. Nonetheless, an AET can be calculated for LVP with consideration of the parenteral SCT (i.e., 1.5 µg/day for an individual organic leachable). An example AET calculation for an LVP follows.

Given an LVP containing 1 L of drug product in a polyvinylchloride (PVC) bag (20 g), the following estimated AET can be calculated per Eq. 3.1 for an individual organic leachable:

$$\text{AET} = \left(\frac{1.5\ \mu\text{g / day}}{1\ \text{dose / day}}\right) \times (1\ \text{labeled dose / LVP}) = 1.5\ \mu\text{g / LVP}$$

Expressing this AET in terms of concentration in drug product according to Eq. 3.2,, presents a challenge:

$$\text{Leachables Estimated AET} = \left(\frac{1.5\ \mu\text{g / day}}{1\ \text{dose / day}}\right) \times \left(\frac{1\ \text{dose}}{1000\ \text{mL}}\right) = 0.0015\ \mu\text{g / mL}$$

To calculate an estimated extractable AET, per Eq 3.3 would be a useful guide for characterizing extractables representing potential leachables via extraction studies of the bag:

$$\text{ExtractablesEstimated AET} = \left(\frac{1.5\ \mu\text{g/day}}{1\ \text{LVP/day}}\right) \times \left(\frac{\text{LVP}\ /1\ \text{bag}}{20\ \text{g / bag}}\right) = 0.075\mu\text{g/g}$$

Extractables representing potential leachables can range from µg to ng levels depending on the volume of solvents and mass of component. The ranges of estimated AET levels for SVP and LVP based on intended use are illustrated in Table 3-4.

Although low AET values may be analytically feasible for some targeted analyses or analyses of extractables in clean solvents, they may present a significant challenge for the detection and identification of previously unknown leachables present in formulated drug product. In such cases, determining an appropriate approach to safety qualification of packaging components would benefit from consult with the regulatory authority. Although the following recommendations are generally applicable to any parenteral dosage form, they are particularly relevant to LVP.

(a) A Possible Approach to Manage Safety Qualification for LVP Packaging

Scenarios in which low AETs exist, such as those presented above for LVP serve to emphasize the value of extractable studies for the purpose of detecting, identifying, and quantifying extractables as potential leachables. Generally, extraction solvents present fewer analytical challenges than formulated drug products with respect to interferences, thus facilitating detection and identification of extractables at lower concentrations. Furthermore, simulation studies designed to mimic drug product that use solvents (as opposed to placebo formulations) may highlight those extractables most likely to leach into the LVP (i.e., probable

leachables) and simplify the scope of targeted analysis at low levels in drug product (see section C. Simulation Studies).

Table 3-4 Example Estimated Extractable AET Values for SVPs and LVPs as a Function of Component Mass

	Container Closure System	Doses/ day	Components (g)*	µg/g Component
SVP	PFS	1	Plunger Stopper (0.22)	**6.8**
			Tip Cap (0.61)	**2.5**
			COP Barrel (1.2)	**1.3**
	Pen Injector	1	Plunger Stopper (0.31)	**4.8**
			Seal (0.16)	**9.4**
			Glass Cartridge (2.2)	**0.68**
	Multi-Dose Vial	1	Stopper (1.8)	**0.83**
			Glass Vial (8.7)	**0.17**
	Single-Dose Vial: Multiple Doses/day	3	Stoppers x3 (1.7)	**0.88**
			Glass Vial x 3 (6.6)	**0.23**
	Single Dose Vial: Single Dose/day	1	Stopper (0.56)	**2.7**
			Glass Vial (2.2)	**0.68**
LVP	Single Dose Bag	1	Sleeve Stopper (0.66)	**2.3**
			120mL Bag (2.4)	**0.63**
	IV infusion	1	Sleeve Stopper (0.66)	**2.3**
			1000mL Bag (20)	**0.075**
	IV infusion	2	Sleeve Stopper x 2 (1.3)	**1.2**
			1000mL Bag (20) x2 (40)	**0.04**
*Approximate weights subject to actual system				

Extraction profile data may be applied in two ways. First, during component selection, extraction profiles may be used to make suitable design choices to reduce downstream drug product leachable risk. Second, these levels of identified potential leachables can be subject to toxicological assessment and may be useful for justification of reporting thresholds for identified leachable targets, particularly in cases of challenging AETs for LVP.

Note: J*ustifications for the AET or alternative reporting thresholds above AET, extraction conditions, extraction solvents and analysis should be discussed early with the Regulatory Agency and Division.*

(b) Extrapolation of Controlled Extraction Study Results to Estimate Leachables Levels for LVP Products

When analytical limitations preclude establishing an AET for a LVP and alternative approaches are considered necessary, data from a properly designed controlled extraction study may need to be leveraged to inform the overall assessment for these products. For a properly designed controlled extraction study, concentrations of extractables would be expected to exceed leachable concentrations from the formulated drug product. In this case, an extractable, once identified, could be shown to pose negligible risk to the patient population at the higher level, then it could reduce the need to look for that specific compound as a leachable at a lower level (AET) in the formulated drug product. Alternative reporting threshold approaches may be justified, depending on the total body of evidence for safety, intended product use and benefit-risk to patient. Because use of extraction data to justify setting a compound-specific AET for a leachable study that is higher than the recommended AET should be considered only when technical limitations exist, discussion with the review division is recommended should this approach be considered.

To facilitate toxicological assessment of extractables, the concentration of an observed extractable can be mathematically converted to an estimated dose. For example, consider a 20 g PVC bag intended to contain a single daily dose of 1 L. A 5 g portion of the bag was extracted in 200 mL of solvent and an extractable was observed at 0.1 µg/mL, which is above the AET of 0.0015 µg/mL. Per Equation 3.4, the estimated daily dose would be 80 µg/day.

Equation 3.4 Conversion of Found Extractable Concentration to Estimated dose

$$\text{Estimated Daily Dose} = 0.1\ \mu\text{g/mL} \times \left(\frac{200\ \text{mL solvent}}{5\ \text{g bag}}\right) \times \left(\frac{20\ \text{g}}{1\ \text{bag}}\right) \times \left(\frac{1\ \text{bag}}{1\ \text{day}}\right) = 80\mu\text{g/day}$$

iv. Considerations for Optimal Extract Concentrations:

The ratio of the packaging component mass to solvent volume is a key factor and the first step in an extractable study plan. The stoichiometric relationship between the AET expressed in µg/mL (Eq 3.2) and the sensitivity of the detection technology can guide the proper ratio of component mass or surface area to achieve optimal concentration for chemical characterization purposes. The concentration of an extracted compound when expressed in µg/g is a measure of the total capacity by weight that an individual component could contribute leachables. To calculate the critical mass required to achieve the AET in µg/mL calculated by Equation 3.2, the dose volume per component can be utilized as shown in Equation 3.5. For example, if the dose volume is 0.8 mL and the desired extraction volume is 100 mL, then a minimum of 125 plunger stoppers would be required.

Equation 3.5 Estimated number of components needed to achieve AET

$$\textbf{Number of Components Needed} = \left(\frac{\text{extract vol (mL)}}{\text{dose vol (mL)}}\right)$$

$$\text{Plungers} = \left(\frac{100\text{mL}}{0.8\ \text{mL/plunger}}\right) = 125\ \text{plungers}$$

This information will assist to set up the proper component to solvent ratio (or concentration of extract as needed) to achieve the estimated AET based on the intended analytical method.

B. Migrants and Migration

PDP general recommendation 5 reads as follows:

5. ***Where appropriate, extractables assessments, extraction studies, and leachables assessments for parenteral drug products and their packaging systems should consider the possibility of migration across packaging barriers (i.e., drug product labels, adhesives, inks, etc.).***

i. Migrants from Secondary Packaging

As an example, consider potential migrants that can appear in drug product from secondary packaging:

For those dosage forms packaged in semipermeable containers, chemical entities may migrate into drug products from nonproduct contact (secondary) packaging components. Pressure sensitive labels affixed directly to the exterior of the primary container are common sources for such migrants, though other source components such as product information inserts and unit cartons are known as potential migrant sources. A typical example of this migration is the appearance of a photoinitiator in the drug product that is a component of a UV-cured ink applied to a product label.

Evaluation of migrants in this category is no different from that of leachables arising from primary components. For example, consider a single label applied to a 120 mL, multiple doses, low density polyethylene bottle designed to hold 90 mL of a formulated parenteral drug product intended for 1.5 mL daily dosing (60 labeled doses per container).

Equation 3.6 Estimated Leachables AET per Container Label

$$\text{Leachables Est. AET} = \left(\frac{1.5\ \mu\text{g / day}}{1\ \text{dose/day}}\right) \times \left(\frac{60\ \ \text{doses}}{1\ \text{bottle}}\right) \times \left(\frac{1\ \text{bottle}}{1\ \text{label}}\right) = 90\mu\text{g/label}$$

Alternatively, expressed on the basis of leachable concentration in drug product:

Equation 3.7 Estimated AET Leachables per Dose Volume

$$\text{Leachables Estimated AET} = \left(\frac{1.5\ \mu\text{g / day}}{1\ \text{dose / day}}\right) \times \left(\frac{1\ \text{dose}}{1.5\ \text{mL}}\right) = 1.0\ \mu\text{g / mL}$$

The PODP Working Group has completed and published a detailed simulation study that included an investigation of migration behavior of chemical entities in a paper label. [12]

C. Simulation Studies

PDP general recommendation 6 reads as follows:

6. ***In situations of analytically challenging AETs for certain PDP (e.g., large volume parenterals), a simulation study, may supplement and guide subsequent drug product leachables studies. These studies can establish an extractables profile to inform on a probable leachables profile of the packaged drug product that the study simulates. Use of a simulation study would need to be appropriately justified***.

Establishment of a drug product leachable profile is the most definitive means of providing the information that is necessary to assess potential patient exposure and product impact. Generation of the leachables profile is a multifaceted undertaking, and often difficult to accomplish because this requires that all leachables present in a drug product at a level above a well-defined and justified threshold (e.g., AET) to be detected, identified and quantified.

It is not uncommon that PDP have daily doses of one or more liters (i.e., LVP) which leads to challenges in utilizing the AET. As shown in Figure 3-2, the daily dose volume can vary from less than 1 mL to greater than 2000 mL; as the daily dose volume increases, the AET decreases significantly. At some daily dose volume, the magnitude of which varies based on the therapeutic intent, the AET may become so low that it cannot analytically be achieved. In such a circumstance, potentially impactful leachables may go either undetected or uncharacterized and an impact assessment based on the analytically generated leachables profile will be incomplete.

An approach to the issue described above is to simplify the chemical nature of the sample that is being tested. This can be achieved using a solvent to simulate the product formulation. This approach has three primary benefits. First, analysis of the extract obtained with a simulation solvent will produce a background response that is lower or less variable than that background response generated by analysis of the more complicated drug product. Thus, responses produced by the compounds of interest (extractables as potential leachables) will be more prominent versus the lower and less variable background. Second, the simulation extract will be more amenable to sample preparation for analytical testing. Last, analytical interferences caused by drug product formulation will be reduced when the simulation solvent is used.

The use of the simulation extract in place of the more chemically complex and more analytically challenging drug product is to mimic the “leaching power” of the drug product. In this respect, a study in which the simulation solvent serves as a surrogate for the drug product is termed a “simulation study.” Since by classical definition a leachable profile is a profile obtained by testing the drug product, the profile generated in a simulation study cannot be a leachables profile and thus is a special type of extractables profile. Thus, the simulation study is one type of a controlled extraction study.

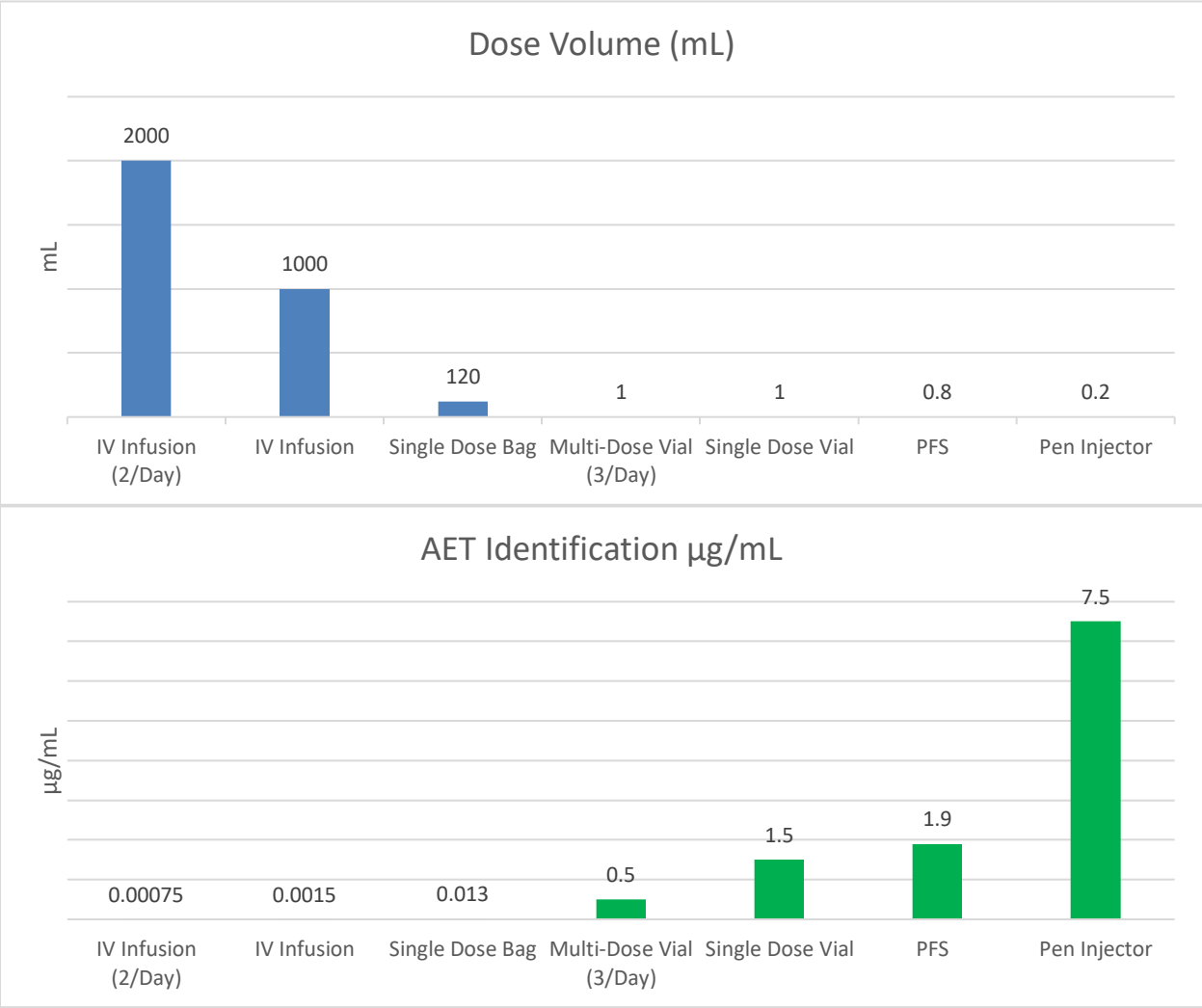


Figure 3-2 Consideration of the Analytical Challenge Associated with the Daily Dose Volume. The value of the AET is inversely proportional to the daily dose volume. Thus, drug products with a high daily dose volume will have low AETs.

By definition, a simulation study is a controlled extraction study; the purpose of which is to produce an extractables profile for a packaging system that represents the leachables profile that a drug product stored in the packaging system may have. The value in performing the simulation study is that the simulating solvents are more analytically expedient than the drug product. This facilitates the process of detecting, identifying and quantitating the packaging system extractables and informing potential drug product leachables.

The success of the simulation study depends on the degree to which the "extracting power" of the simulation solvent is consistent with the "leaching power" of the drug product.

Thus, this design parameter must be justified and is essential for establishing the validity and applicability of a simulation study.

The simulation study provides significant value by focusing the subsequent leachables study. For example, the simulation study's extractables profile would reveal probable leachables. Such a strategy facilitates the leachables study as generally more feasible to measure targeted analytes in drug products at their expected accumulation levels.

Note: J*ustifications for the AET or alternative reporting thresholds above AET, for leachables analysis should be discussed early with the Regulatory Agency and Division*.

D. Analytical Uncertainty

An AET is the concentration at or above which unknown leachables should be characterized and reported for toxicological assessment. Targeted leachables (previously characterized as potential or probable leachables from extractables or simulation studies) will have known safety profiles and previously established limits. Authentic reference compounds, if available, for previously characterized potential leachables will allow for accurate and precise quantitation of those target leachables as actual drug product leachables.

Characterization of unknown leachables requires consideration of analytical uncertainty as the determination of an AET in a given leachables profile (e.g., a gas chromatography/mass spectrometry chromatogram) must be accomplished relative to a standard that may possess a different analytical response from the unknown leachable. Uncertainty may typically include (1) uncertainty in the proposed structure and elemental composition of the unknown leachable (e.g., positional isomerism, geometric isomerism, stereoisomerism, functional groups, heteroatoms, isobaric compounds), (2) uncertainty in response of a unique, unknown leachable with regard to detection and quantitation with a particular analytical technique, (3) sample matrix effects and interference, and (4) quantification approach employed (e.g., internal or external standard). Thus, it is recommended that the estimated AET values calculated in the prior examples be adjusted for analytical uncertainty when applied to unknown leachables; adjustment of the AET for uncertainty should be achieved through a rational, scientifically justifiable approach.

By way of example, analytical uncertainty for a particular analytical technique or method may be estimated based on the analysis of a series of representative reference compounds to create a response factor database. The reference compounds included in this database should represent all known potential leachables (i.e., as determined from extractables assessments). A recommended practice for OINDP is that the estimated AET be lowered by analytical uncertainty defined as "one (1) % relative standard deviation in an appropriately constituted ad acquired Response Factor database OR a factor of 50% of the Estimated AET, whichever is greater" (e.g., AET = Est. AET * (1-RSD), or, AET = Est. AET * (1-0.50)). Examples of the OINDP recommended approach may be found in prior publications [2, 8]. Given the reduced risk profile of parenteral drug products versus OINDP [7], other methods of managing analytical uncertainty can be applied provided that a rational, scientific justification of that approach is given.

V. Conclusion

The OINDP recommendations for best practices associated with the assessment of extractables and leachables have been extended to PDP with adaptations appropriate to these dosage forms. Not only are these applied to components and finished systems but also to materials of construction for purposes of facilitating material selection. Different types of studies may be performed depending on their intended purpose. Extraction studies are used to provide a comprehensive understanding of potential leachables, while simulation studies are utilized to ascertain probable leachables. A key difference is the choice of solvents used. Extraction studies may involve aqueous solvents with extreme pH or combined with organic solvents, while simulation studies utilize solvents that are intended to mimic the extraction propensity of the drug/biologic formulation. Both types of studies can be useful to guide leachables studies in which compounds are identified and quantified for purposes of toxicological assessment.

The concept of an analytical evaluation threshold has been extended from OINDP to PDP. The AET for PDP is based on a safety concern threshold that has been established as 1.5 µg/day. Compounds above the AET are identified, and in the case of leachables, are presented for toxicological evaluation; the AET is not a control threshold above which compounds are not allowed. For some dosage forms, specifically LVP, the AET may be difficult to achieve analytically. In such cases it is recommended to discuss appropriate study designs with the Regulatory Agency and Division early in the process.

VI. References

1. Norwood, D. L; Nagao, L. M.; Stults C. L. M. Perspectives on the PQRI Extractables and Leachables "Safety Thresholds and Best Practices" Recommendations for Inhalation Drug Products. *PDA Journal of Pharmaceutical Science and Technology*, September/October **2013**, *67* (5), 413–429.

2. Ball, D. J., Norwood, D. L., Stults, C. L. M., Nagao, L. M. *Leachables and Extractables Handbook: Safety Evaluation and Best Practices Applied to Inhalation Drug Products*, Eds. John Wiley and Sons, Inc.: Hoboken, New Jersey, **2012**.

3. Jenke, D.; Castner, J.; Egert, T.; Feinberg, T.; Hendricker, A.; Houston, C.; Hunt, D. G.; Lynch, M.; Shaw, A.; Nicholas, K.; Norwood, D. L.; Paskiet, D.; Ruberto, M.; Smith, E. J.; Holcomb, F. "Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products," *PDA Journal of Pharmaceutical Science and Technology*, September/October **2013**, *67*(5), 448–511.

4. United States Pharmacopeia, <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems. 2015.

5. United States Pharmacopeia, <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems. 2015.

6. United States Pharmacopeia, <1664.1> Orally Inhaled and Nasal Drug Products. 2015.

7. Container Closure Systems for Packaging Human Drugs and Biologics; Guidance for Industry; 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); Rockville, MD, May 1999.

8. "Safety Thresholds and Best Practices For Extractables and Leachables in Orally Inhaled and Nasal Drug Products," Submitted to the PQRI Drug Product Technical Committee, PQRI Steering Committee, and U.S. Food and Drug Administration by the PQRI Leachables and Extractables Working Group, Daniel L. Norwood (Chair), Product Quality Research Institute, September 2006, https://pqri.org/wp-content/uploads/2015/08/pdf/LE_Recommendations_to_FDA_09-29-06.pdf .

9. ISO 10993-18:2020 Biological evaluation of medical devices — Part 18: Chemical characterization of materials https://www.iso.org/standard/41106.html

10. ISO/TS 21726:2019 Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents https://www.iso.org/standard/71514.html

11. United States Pharmacopeia,<659> Packaging and Storage Requirements. 2018

12. Dennis Jenke Thomas Egert, Alan Hendricker, James Castner, Tom Feinberg, Christopher Houston, Desmond G. Hunt, Michael Lynch, Kumudini Nicholas, Daniel L. Norwood, Diane Paskiet, Michael Ruberto, Edward J. Smith, and Frank Holcomb "Simulated Leaching (Migration) Study for a Model Container-closure System Applicable to Parenteral and Ophthalmic Drug Products (PODPs)" PDA Journal of Pharmaceutical Science and Technology.2016, doi:10.5731/pdajpst.2016.007229

Part 4. Special Topics: Considerations for Biological Products

I. Introduction

The safety and compatibility of the manufacturing and packaging components with biological molecules are not readily discernable. Initial chemical characterization studies can utilize the PDP safety concern threshold (SCT) of 1.5 µg total daily intake to derive the analytical evaluation threshold (AET) and identify compounds to be assessed for toxicity [1]. However, the biological product quality and safety can be affected by a nontoxic leachable or other known hazard at levels well below the SCT. Biological molecular entities are complex with the potential for leachables to reversibly or irreversibly interact and affect product quality and consequently impact patient safety.

Leachables can occur from polymer additives, processing aids, material degradation, processing residuals, and their breakdown products. Additives and processing aids are inherent to the final packaging component while, residuals and degradation products can arise over time depending on the environment. These compounds may include aldehyde, ketones, free radicals, peroxides, residual solvents, moisture, oxygen, and metal ions or salts. Well known risks to biological product quality associated with packaging systems (also referred to as container closure systems (CCS)) include silicone lubricants from packaging systems, polytungstate from syringe fabrication process, and glass lamella caused by surface corrosion [2,3,4]. Risks are also posed by highly reactive organic and inorganic compounds that can cause irreversible, covalent binding with therapeutic proteins (i.e., adducts, aggregates) or modification of residues (e.g., oxidation, deamidation), which may indirectly or directly compromise product safety. Extractable compounds that can potentially bind covalently to protein include Michael acceptors, Schiff base formers, acylating agents, aliphatic nucleophilic substitutions, aromatic nucleophilic substitutions, and transition metals [5]. Chemical information on the CCS materials and processing aids used in manufacturing along with screening of manufacturing, packaging and delivery system components for such highly reactive extractables can help to target these compounds as potential leachables in packaged biological products.

The methodology to screen for leachables should consider compounds of toxicological concern as well as impact to biological product quality attributes. The risk to quality attributes can be assessed on the basis of knowledge of primary, secondary and tertiary structure of the biological molecule(s) along with extractable profiles from chemical characterization studies using exaggerated or aggressive extractions. Simulation studies can reduce interferences and inform the propensity of chemicals to migrate and identify targets for leachable studies. Placebo studies (e.g., formulation with-out biologic product), when guided by chemical characterization studies, can assist with development and optimization of leachable methods involving complex formulations, while conserving use of expensive biologics. Leachable methods should include comprehensive screening for targeted, nontargeted, and unexpected compounds by leveraging extractable or screening methods while analyte-specific methods may be needed to target special case compounds at the appropriate sensitivity. Extractable knowledge, together with biological product characterization data from clinical studies, is an important aspect to understand potential risk to product quality and provide evidence of the safety and compatibility for manufacturing packaging systems and delivery devices.

II. Context of Biological Products

The extractables from materials, components and systems used to manufacture, store and deliver biological products; particularly those representing potential leachables, should be understood and managed throughout development and over the product lifecycle. A biological product is officially defined as ‘‘a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. A protein is any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer will be based on the total number of amino acids in those chains, and not limited to the number of amino acids in a contiguous sequence [6]. Through a greater understanding of critical disease relevant targets, new chemical modalities continue to emerge e.g., RNA therapeutics, macrocycles and cyclopeptides for protein–protein interactions, antibody drug conjugates, and gene therapies [7].

Biological products may be comprised of more than one molecular entity produced by biotechnology or isolated from biological specimens. Many biological products involve one or more therapeutic proteins in a complex matrix. Advances in protein engineering have resulted in several forms of complex therapeutic proteins that include protein conjugates (e.g., Fc fusion, antibody-drug), derivatives (PEGylated) and genetic alterations (e.g., chimeric or humanized mAbs). Due to the origin of biological products and their complex manufacturing processes, a broad range of process- and product-related impurities can exist. It is estimated that more than 5000 critical process steps may be associated with manufacturing and production of a therapeutic protein [8].

Interactions between biological products and primary packaging systems may negatively affect product quality, stability, purity and safety. The effects of the manufacturing processes and CCS on the biological product may not be well understood depending on the phase of development and degree of product characterization. Products are characterized by a wide array of analytical techniques to determine the physicochemical properties, biological activity, contaminants, purity and impurities. Biological purity is the relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. This includes but is not limited to relative freedom from residual moisture, particulates, volatile substances, viruses and pyrogenic substances [9]. Risks to biological quality related to CCS (e.g., aggregation, deamidation, oxidation, formation of clipped variants) can have an impact on product safety and efficacy or potentially induce immunogenic effects.

Therapeutic protein products can generate immune responses to itself and to related proteins or induce immunologically related adverse clinical events. Physical degradation of the proteins as well as chemical decomposition may enhance the immune response [10]. The consequences of immune responses to therapeutic protein products can range from no apparent effect to serious adverse events, including life-threatening complications. Interactions between therapeutic protein products and the CCS may negatively affect product quality, and in some cases provoke or increase immunogenicity. Examples of protein product CCS interaction

include the release of organic compounds with immunomodulatory activity based on polysorbate-containing formulations; and oxidized metals causing aggregates or activation of metalloproteinases. Interaction would be specific to each therapeutic protein product and is the reason to evaluate leachables in the context of its storage container under real-time storage conditions [11].

Characterization of the diverse inherent properties of biological products and therapeutic proteins become more challenging as new modalities are being introduced with gene replacement therapy, gene editing, and CAR-T cells [12]. Due to the advancement of gene-cell based therapies, FDA has updated the gene therapy guidance to reflect current recommendations regarding the format and content of chemistry manufacturing and control (CMC) information for investigational new drug applications (IND) [13,14]. The information considers products in combination with a drug and/or device and is organized according to the common technical document (CTD) structure [15,16]. Information that is needed for CCS is incorporated by reference to the FDA container closure/packaging guidance for drugs and biologics [17]. The premise of the guidance is to choose materials and components that will be safe, perform appropriately, be compatible with the product formulation and that will protect the product from moisture, gases and light. Suitability encompasses risk associated with: i) chemical substances that have potential to leach harmful substances, ii) safety of materials and components, iii) potential adsorption of the product onto container/closure surfaces, iv) functionality of the system for intended use and v) in-use performance of the final system. Essential information for INDs also includes comparability studies, acceptable limits, and assurance of product stability and in-device stability associated with clinical treatments. The process for gene therapy product development advocates a quality by design (QbD) approach that will establish critical quality attributes (CQA) based on product and process knowledge to ensure the desired quality. It is recommended to carefully control and assess product compatibility and the final steps of product preparation and administration [13,18]. One aspect that can be a particular challenge for gene therapies is final product release due to small lot sizes. Availability of multiple products for stability assessments may not be feasible for final storage and transport steps. Due to the diversity of biological products and end use, a strategy for extractables and leachables should be justified case-by-case to demonstrate suitability of materials and components used in the manufacture, storage and final delivery to patients.

Note: Due to the increasing complexity and diversity of pharmaceutical and biological products, manufacturing systems, drug delivery devices and CCS, justifications for the AET, extraction conditions, extraction solvents and analysis should be discussed early with the Regulatory Agency/Division.

III. Quality Considerations for Biological Products

The final biological product quality depends on defining critical attributes and the extent to which they can vary without affecting the safety or efficacy. Biological molecules have numerous quality attributes and are very sensitive to physical and chemical stressors, including freeze-thaw cycles, agitation, light, pH, and other environmental effects. The impurities or contaminants can be of a known structure, partially characterized, or unidentified. Process-related impurities encompass those that are derived from starting materials and equipment used in the manufacturing process or downstream processing. Product-related impurities are

molecular variants that arise during manufacture and/or storage and that do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety. If process or product-related impurities are known to be introduced or formed during the production and/or storage of the biological product, the levels should be determined, and acceptance criteria should be established [19]. Leachables in the final drug product may originate from the manufacturing process or from packaging and delivery systems. Leachables may compromise patient safety as a result of their direct inherent toxicity as well as their potential to interact with the protein and thereby indirectly modifying product quality [20]. The abundance of both hydrophilic and hydrophobic sites and extensive surface area of a protein can serve as potential interaction sites. Particulates can arise from interactions with leachables or environmental changes that lead to aggregation due to surface chemistry, morphology, and system interfaces. Particulates are also inherent to protein products and critical to the control of biological product quality having potential to cause immunogenicity [21].

A CCS and its individual components must be proven chemically and physically compatible to ensure patient safety and product quality. The correlation of extractables to leachables and the impact on biological product quality is a dynamic process that involves understanding changes in quality attributes with respect to CCS component extractability, physicochemical compatibility, and safety. Evaluation of the manufacturing process and intended marketed package should be considered from early development stages through commercialization to avoid possible unexpected negative effects on the product quality. The manufacturing, CCS and delivery system components need to be qualified for specific use with consideration of changes that may occur at any time over the product lifecycle. Qualification of the entire system with respect to extractables and leachables is an iterative process starting with leveraging any/all prior physicochemical knowledge and obtaining chemical characterization information from individual CCS components (e.g., extractables studies) followed by simulation and/or leachables studies of the packaged product. The packaging systems should also be evaluated as part of biological product stability studies (accelerated and real time) and during clinical phases to understand if any critical product attributes have been impacted [11]. The compatibility of the biological product with the chemical and physical properties of CCS should be investigated commensurate with the stage of development. An iterative process that is initiated early in development will allow for progressive understanding to establish CCS critical quality attributes over the product lifecycle. A high-level scheme is depicted in Figure 4-1.

Comprehensive characterization of a biological product is key to understand potential risks to product quality and safety which could be associated with materials, components and systems used during the manufacture, storage and delivery of the final product. The compatibility of delivery device is vital to biological product stability and administration to patients to ensure therapeutic effectiveness. The CCS will be qualified in the context of the biological product and any changes (e.g., product formulation, manufacturing process, or packaging components) that occur throughout the lifecycle of the product should assessed based on risk to product quality and safety [15, 22]. There is a critical balance to be maintained between the biologic molecule and systems used to manufacture, store and deliver the final therapeutic product.

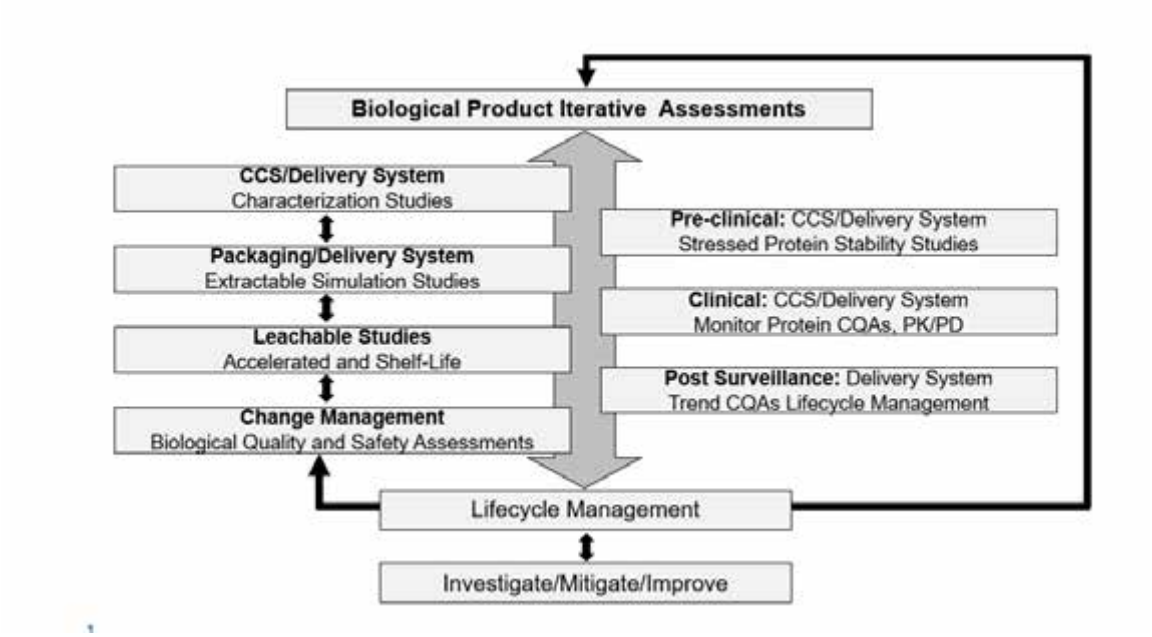


Figure 4-1 Schematic of CCS Integration Over Biological Product Lifecycle

IV. Manufacturing and Packaging Components in Contact with Biological Products

The quality and safety of biological products are linked to numerous components from the manufacturing system, CCS and delivery system from the point of development and throughout commercialization. These components must meet certain physical and mechanical performance requirements that are related to the chemical makeup of each material. Other than chemical composition, sources of potential leachables include effects from processing (mold release, lubrication, adhesives, passivation) and post-processing (e.g., sterilization, cleaning, storage) of components and assembly of the final systems. All together these factors can guide appropriate methodology for generating extractable and leachable profiles for the final packaging systems. It is important to anticipate chemical entities that could leach and or interact with a biological product to protect product quality and safety. The occurrence of leachables will be influenced by the extraction propensity of the biologic product relative to direct or even indirect contact with the CCS. CCS components that have direct contact with biological products would be considered primary packaging systems, while those with indirect contact would be secondary or tertiary systems. (e.g., labels, inks, adhesives, cartons, inserts, overwraps etc.) The probability that leachables would originate from the primary packaging system is greater due to immediate contact and longer duration compared to manufacturing systems which have a shorter, transient contact duration followed by comprehensive filtration steps.

Manufacturing and primary packaging systems can include various materials of construction that may consist of different grades of stainless steel, aluminum, glass, plastics and thermoset or thermoplastic elastomers. In many cases, fixed stainless-steel bioreactors are being replaced by single-use technologies (SUT) to overcome cleaning and maintenance issues. The materials of construction used in a single use bioreactor (SUB) can be comprised of multiple layers of polymer films to achieve strength, ductility, mechanical stability, and gas barrier as

needed. These films will have specific properties for use relative to various polymer families (e.g., polyethylene, polypropylene, polyvinyl alcohol, polyesters and polyamides). Other related manufacturing components such as connectors, tubing and filters could include other materials (e.g., polyvinyl chloride, polycarbonate, polysulfone, silicone, fluoropolymers and polystyrene). Extractables studies on manufacturing components can provide composition information to support material compatibility with product and process, change management as well as potential risks associated with product quality or cell culture operations. As an example, a cytotoxic breakdown product from a common phosphite antioxidant used in polyethylene was found to have leached into culture media resulting in detrimental cell growth [23]. Downstream processing may include similar materials in addition to anionic and cationic exchange or bind-elute resins and cellulose. Chemical or physical incompatibilities can result in failures due to harsh environments, extreme temperatures, strain, wear and tear. The user/manufacturer requirements will need to define the chemical and physical performance criteria for a given application. The physical structure of materials and associated chemistries are key for determining suitability and control of manufacturing components.

Similarly, the primary packaging materials of construction, surface finishes, and processing aids will affect suitability for use. Risk for leachables should be considered for components used during pre-formulation, final formulation, and those used during clinical and commercial use. Not all manufacturing and packaging components will require the same type or degree of assessments for qualification. Studies should be designed based on the knowledge of individual components, intended system and application relative to the level of risk. In a clinical setting the highest risk for leachables would be typically originate from the primary packaging. Typical materials include various types of glass, plastic, elastomers, stainless steel and label inks/paper/adhesives. There is potential for compounds of concern to exist in these materials as well as risk to chemical or physical interactions with the biological product which can impact safety. Biological products are often stored frozen with more than twelve months shelf life. Cold storage may minimize leachables but not necessarily overcome all compatibility issues associated with freeze thaw cycles or handling.

Diversity in materials and applications from process streams to patient use involve a wide range of contact media, manufacturing and packaging components, Table 4-1 shows typical applications from manufacturing to packaging components and considerations for various extraction propensity. Data to understand the contact media or biological product extraction propensity under conditions of use will be critical for qualifying manufacturing and packaging systems.

1 **Table 4-1 Typical Applications for Manufacturing or Packaging Components and Risk Considerations**

Process	Application	Risk Considerations	
		Components Considerations Influencing Extractability	**Media/Formulation Considerations Influencing Extraction Propensity**
Upstream Expression & Harvest	Cell Bank Cell Cultivation Fermentation Centrifugation Concentration Bioreactor Transfer	Vial/Flasks/Bottles Mixing Vessels/Bags Single Use Systems Caps/Gaskets Connectors Tubing Assemblies Bioreactors Harvest Tanks, Tank Liners	Culture/Fermentation media Nutrients: Sugars, Fats, Water Amino Acids, Electrolytes, Vitamins, Serum, Minerals Excipients: Buffer, Salts, Sugars, Additives
Downstream Isolation & Purification	Separations Viral Inactivation Purification UF/DF Filtration Viral clearance Final Concentration/Polish Sterile Filtration Formulate/Transport	Bio Containers/Carboys Modular Process Skids Chromatography Resins Filtration Systems Hoses/Tubing Systems Connectors/O-Rings Septa/Diaphragm Needles/Valves/Sensors	Fermentation Broth Cryo/Lyo Protectants Preservatives Cross Link Agents Chemical Denaturants Ion Exchange, Affinity Resins
Pre-Formulation & Formulation Process Development Preclinical	Biological Substance Thaw-Pool Pre-formulation Final Formulation Filling Assembly Sterilization Primary Packaging Final Packaging Storage Shipping	Platform Technologies Filter/Tubing Assemblies Peristaltic Pumps/Needless Connectors/Gaskets Container Closures/ Delivery Systems Secondary Containers Labels/Ink/Adhesives Cartons Shipping Cartons/Pallets	Biological Substance Thaw-Pool Excipients: Water/Buffers, Complexing Agents, polyhydric Alcohols, Surfactants, Polyhydric Alcohols, Sugars, Stabilizers, Absorption Enhancers, Preservatives, Stabilizers, Protectants Lubricating Agents Sterilization Agent

Process	Application	Risk Considerations	
		Components Considerations Influencing Extractability	**Media/Formulation Considerations Influencing Extraction Propensity**
Patient Use: Clinical & Commercialization	Route of Administration Delivery System Final Presentation Labeling Instructions for Use Post Market Surveillance	Container Closures/ Delivery Devices: Prefilled Syringe, Auto Injectors Ancillary Components: Admin Sets, Intermediate Containers Secondary Containers: Labels, Protective Packaging Tertiary Containers: Cartons, Shipping Pallets	IV Diluents/ Final Formulation: Buffers, Cosolvents, Sugars, Surfactants, Amino Acids, Complexing Agents, Stabilizers, Modified Release Agents, Absorption Enhancers, Adjuvants
Lifecycle & Change Management	Development Cycle Launch Post Market	Vendor Notifications Material changes Manufacturing -Scale-up Delivery System	Manufacturing, Storage Biologic Concentration, Administered Volume/Rate Formulation/ Excipients

2

Suitablity of the CCS and delivery device for use with a biological product relies on the component raw materials that constitute the final system. The material chemistry is fundamental to the physical and functional properties of the delivery device and ability to protect the final product and allow safe and effective dosing. Dimensional stability of components, proper fit of multiple parts, seal integrity, and performance of the final system is necessary to ensure safe and accurate dosing over time. Risk to performance of CCS and delivery system include gas permeation, component fracture/breakage, surface interaction, and material swell or outgassing. The CCS processing and use environments will impact the material's suitability. Physical and chemical properties of the packaging can be affected by multiple stressors such as exposure to sterilization and decontamination processes, fill-finish, vacuum, agitation, freeze–thaw cycles and shear forces. The extractable profiles of finished CCS components will provide information for potential leachables as well as necessary material composition information for performance. Configuration of the components and drug surface contact area will affect the potential for extractability and system interfaces (vapor, liquid, solid) that can have an impact the biological product quality. Changes in product concentration can occur due to material adsorption of product or absorption of formulation. Aggregation at product interfaces can include formation of visible particles, subvisible particles, soluble aggregates resulting from conformational changes due to interfacial stresses such as hydrophobicity, charge, and mechanical stress. [24] Material compatibility poses a multitude of risks to biological product quality and safety; chemical profiles will be key to CCS selection and control of CCS and delivery systems. Manufacturing and packaging components risk assessments should include comprehensive understanding of material chemistry and impact of the individual processes related to the following:

- Biological product quality attributes and extraction propensity of the formulation
- Type of materials and component contact area for the entire system
- Proximity of the component to the biological substance/product
- Component and system performance requirements for intended use
- Interfaces of biological product and component surfaces
- Handling conditions and in-use and storage temperatures
- Sterilization and preparation of component prior to use
- Nature of the biologic product and component contact duration

Knowledge of material chemistry, potential leachables and surface interfaces is an important aspect for qualifying manufacturing, primary packaging and delivery systems. User needs can be wide ranging and may preclude the use of certain materials based on performance requirements. Verification of materials to be suitable for every application is not practical because of broad diversity of performance requirements and grades of materials. Identification of risks followed by scientifically justified studies and clinically relevant data will lead to proper component selection and control. The degree and type of manufacturing and packaging component

assessment should be holistic with consideration of relevance to intended use, and qualification will depend upon the potential risk to biological product quality and safety.

V. Suitability of Packaging and Delivery Systems

The suitability of all packaging and delivery system components is critical to the qualification process for biological product quality and safety. There are unique factors to be considered when translating suitability of components and systems to biological molecular entities. Several functional, physical and chemical factors should be considered based on user requirements. The biological product stability and safety will be influenced by the performance of each component in a packaging and delivery system. The FDA recommends that every proposed packaging system be shown to be suitable for its intended use and i) protect the drug product; ii) be compatible with the packaging system; iii) use safe materials; and iv) meet material performance and system functional requirements [17]. Examples of representative suitability factors are listed in Table 4.2 [25].

Table 4-2 Examples of Component Suitability Factors

Protection	Compatibility	Safety	Performance
Degradation	Loss of potency	Leachable Induced	System Fit
Product loss	Product adsorption	Toxicity	Accurate Delivery
Gas Permeation	Precipitation	Toxic Impurities	Shear force Impact
Water Vapor	pH shift	Immunogenicity	Freeze-Thaw Cycles
Permeation	Aggregation	Altered Conjugated	Physical Attributes
Microbial	Impurities	Forms	Mechanical
Contamination	Surface Interfaces	Isomerization	Attributes
Leakage	Surface Morphology	Adduct Formation	Hydrophobic
Deep Cold Storage	Reducing Agents	Structural Stability	Surfaces
Agitation		Unfolding	Component Particles
Foreign Particles		Aggregates	System Shelf Life

VI. Considerations for Qualification of CCS and Delivery System Components

The SCT/AET calculation for PDP is applicable to biological products to indicate potential for toxic leachables, but nontoxic leachables and incompatible contact materials can also affect patient safety. Studies should be designed to identify the risk for potential leachables and system incompatibilities that could destabilize or interact with the final product. Stability studies should be conducted on the biological substances and product under accelerated and stress conditions and should take into consideration potential leachables that could interact with and degrade therapeutic proteins. [13,19, 26] All packaging and delivery systems combinations that will be marketed should be assessed for potential interactions with biological products as they may affect the purity or quality of the final product. Qualification studies should provide evidence that demonstrates the following: [27]

- Component materials or processing aids will not hasten the deterioration of the product or otherwise render it less suitable for the intended use.
- Final containers closures/delivery system component surfaces will be free of surface solids, harmful levels of leachable contaminants, and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use.
- Filling and sealing and terminal sterilization processes will be performed in a manner that will maintain the integrity of the product during the dating period.

Considerations for evaluating the safety of biological products requires a complete assessment of final packaging that can be correlated to the product's quality attributes and the potential for immunogenicity. The presence of a leachable could exceed a safe limit or induce conformational changes or modifications that could result in harm to a patient. The final biological product formulation is the vehicle that delivers the biological substance to the targeted location and will have a major impact on the likelihood for leachables. The bulk of the biological product is made up of a variety of excipients intended to enhance solubility of the active molecular entities, maintain stable conformations, prevent aggregation, and control pH and tonicity. Examples of common formulation agents and their functions are listed in Table **4-3.**

Table 4-3 Examples of Common Formulation Excipients and Impact to Biological Products

Formulation Agents	**Function**	**Examples of agents**
Buffer	Maintain pH, prevent aggregation and improve conformational and colloidal stability	Citrate, Histidine, Acetate, Succinate, Phosphate
Tonicity	Enhance solubility, conformational and colloidal stability and minimize intermolecular attraction, tonicity, storage	Sodium Chloride, Potassium Chloride, Mannitol, Sorbitol
Stabilizer	Minimize aggregation and enhance conformational and colloidal stability, tonicity, reducing viscosity	Sugar Based Excipients, Sucrose, Trehalose, Glycerol, Polyethylene Glycol, Amino Acid Based Excipients, Cryo Protectants
Surfactants	Minimize aggregation, interfacial stress and improve conformational and colloidal stability	Polysorbate 20, Polysorbate 80, Poloxamer 188
Chelators	Minimize metal impact on biologics	Metal Ions, ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA)

Detection and identification of leachables in biological products may be difficult as the formulations are often complex and may contain nonionic surfactant mixtures (e.g., poloxamers

or polysorbates) or other excipients that can obscure known or unknown chemical entities, labile compounds or degrade (autoxidize), interact with other excipients, other leachables or the active molecular entities. Studies for targeted (known) and non-targeted (unanticipated) leachables should be designed and performed using knowledge acquired through the initial establishment of a comprehensive extractable profile and thorough understanding of the biological product. When a biologic liquid formulation contains cosolvents or surfactants, there is greater potential for organic leachables from uncoated stoppers [28]. Biological formulations containing ethylenediaminetetraacetic acid complexing agents and phosphate buffers can facilitate the migration of metal ions into solution. Alkali and alkaline earth metals will bind proteins predominantly through electrostatic interactions, and transition metals will covalently bind to proteins depending on the pH and ionization state of amino acid residues [29].

A properly conducted chemical characterization study should provide a robust and comprehensive profile of organic and inorganic extractables as a starting point, without compromising the surface integrity or shape of the component. Use of simulation studies with the final packaging and delivery system can facilitate identification and quantification of probable leachables to be toxicologically assessed. Chemical composition information and toxicological assessment of chemical profiles can indicate compounds of concern representing leachables for which to develop, optimize and validate targeted analyte methods. Non-targeted leachable screening methods may be useful for detection of unanticipated leachables but may not have the proper sensitivity or specificity for critical targets, which should be monitored by optimized and fully validated methods. The correlation of extractables to leachables with product quality is a process that involves understanding changes in the product attributes with respect to leachables, and safety throughout the biological product lifecycle.

VII. Lifecycle Management Example - Injectable Delivery Systems

Many biological products are sterile injectables that may be administered frequently and at relatively high volumes, or concentrated doses. These products are often marketed in single or multidose vials; however, delivery devices such as a prefilled syringe or auto injector are becoming more prevalent with provision of a more simplified procedure for patient administration. When injectors are combined, co-packaged, or labeled for use with a specific biological product, they are designated as a combination product [15,30]. A biologic-device combination product will be assigned a lead FDA Center (drugs, biologics or devices) based on the biological primary mode of action, technological characteristics, proposed labeling, and packaging. This will lead to different legal, regulatory and scientific approaches for CCS qualification. Combination product CCSs should be qualified with-in the context of use and according to combined requirements from both biologics and devices. The CCS must protect product safety, identity, strength, quality, and purity to ensure safe delivery of finished pharmaceutical [31]. Quality assessments for biological products should include identifying and mitigating risks related to the following:

- Changes in the dosage form purity, safety, stability
- Changes in the product appearance, molecular structure, physical, chemical characteristics.

- Loss of potency due to absorption or adsorption of the active biological substance
- Degradation of the active biological substance induced by a leachable
- Reduced concentration of active biological substance due to physical/chemical changes
- Leachable-induced changes in formulation pH, product degradation, precipitation, aggregation
- Changes in the packaging and delivery device component(s) or system (discoloration, surface, function, brittleness etc.)

Examples of leachables affecting biologic quality include:

- A change in formulation from a lyophilized to a liquid formulation resulted in product degradation at the N-terminal site due to a divalent cation that leached from a rubber stopper causing activation of metalloprotease. [32]
- A change in formulation excipients from human serum albumin to a polysorbate caused pure red cell aplasia (PRCA) in chronic kidney disease patients treated with epoetin. The source was suspected to be related to a vulcanizing agent that leached from a plunger. PCRA was mitigated by modifying the plunger with a barrier film. [28]
- A prefilled syringe system for subcutaneous delivery induced protein denaturation and aggregation and elicited immunogenicity. This was correlated to the presence of covalent dimers. The cause was traced to tungsten oxide and salts that leached from the tip of the prefilled syringe due to insertion of the needle into glass with tungsten filaments. [33]
- A change in the forming of glass vials from molding to tubing glass caused formation of visible particulates after 12 months storage. Aluminum leached from the glass and reacted with the sodium phosphate buffer creating aluminum phosphate crystals. [34]

Critical packaging components should not cause unacceptable changes in product quality, safety, or delivery to patients. The suitability of a final packaging system covers a wide range of interrelated factors that may not always be evident during the initial component qualification studies. Incompatibilities between the CCS and biological product often occur over time and can result in serious consequences if risks are not identified and mitigated in advance.

VIII. Conclusion

Packaging system and delivery devices are an integral part of a biological product ensuring protection and quality of the product and safety throughout the labelled shelf-life. Biological products pose a unique set of safety risks due to the inherent capacity of the product to become unstable, adopt multiple conformations, interact with other large or small chemical entities in the formulation, or undergo alterations in the primary structure. Safety thresholds and best practices for extractables and leachables in PDP intravenous, subcutaneous, and

intramuscular routes of administration is a risk and science-based approach that can be utilized for biological products. The PDP-SCT is relevant for biological products as it relates to direct toxicity; however, reactive species at much lower concentrations can have a negative impact on biological product quality, thereby effect patient safety and risks for immunogenicity. Extractables and leachables studies should be performed to evaluate the capacity of packaging container closure materials to interact with and modify the biological product [11]. Comprehensive extractable studies should be designed to develop material characterization profiles for CCS, delivery device and manufacturing systems as appropriate. These should employ robust methodology and consider use of simulated potential leachable profiles to support detection and identification of probable leachables. Materials composition, prior knowledge and extractables information can guide investigation and assessment of leachables and augment understanding of potential risk to the quality of biological products.

IX. References

1. Paskiet, D., et al., The Product Quality Research Institute Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP). PDA Journal of Pharmaceutical Science and Technology, 2013, 67 (5), 430–447.

2. Gerhardt, A., et al., Protein aggregation and particle formation in prefilled glass syringes. J Pharm Sci, 2014, 103 (6), 1601–1612.

3. Liu.Wei et.al., Root Cause Analysis of Tungsten-Induced Protein Aggregation in Pre-filled Syringes. PDA Journal of Pharmaceutical Science and Technology, 31 Dec 2009, 64(1):11-19

4. Rx-360 Highlights from Glass Container Delamination Scientific Symposium June 2011. Report on glass delamination meeting summary, https://rx-360.org/

5. Li, K., et al., Creating a holistic extractables and leachables (E&L) program for biotechnology products. PDA Journal of Pharmaceutical Science and Technology, 2015, 69 (5), 590–619.

6. 21 CFR Subpart A, Sec 600.3 (h);(h)(6)), Biological Products General Provisions, Definitions, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.3

7. Jesus-Blanko, M. Gardiner, KM New Chemical Modalities and Strategic Thinking in Early Drug Discovery https://pubs.acs.org/doi/10.1021/acsmedchemlett.9b00582#

8. Lagasse, HA, et.al., Recent advances in (therapeutic protein) drug development, https://www.accessdata.fda.gov/scripts/publications, DOI: 10.12688/f1000research.9970.1,

9. 21 CFR Subpart A, Sec 600.3 (h)(5), Biological Products General Provisions, Definitions, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.3

10. Hermeling, S., et al., Structure-immunogenicity relationships of therapeutic proteins. Pharmaceutical Research, 2004, 21, 897–903

11. FDA, Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products. 2014. (link)

12. Plenge R. Drug Discovery, Celebrating New Therapeutic modalities, September 27, 2017 https://www.plengegen.com/blog/modalities/

13. FDA Guidance for Industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), January 2020 https://www.fda.gov/media/113760/download

14. 21 CFR Subpart B Sec. 312 23(a)(7)(iv)(b) Investigational New Drug Content and Format https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.23

15. Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products, January 2017. https://www.fda.gov/media/90425/download

16. Guidance for Industry: M4Q: The CTD – Quality, August 2001. https://www.fda.gov/media/71581/download.

17. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, May 1999. https://www.fda.gov/media/70788/download.

18. Guidance for Industry: Q8(R2) Pharmaceutical Development, November 2009, https://www.fda.gov/media/71535/download

19. ICH Q6B, Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. 1999.Link

20. Markovic, I., Challenges Associated with Extractable and/or Leachables Substances in Therapeutic Biologic Protein Products, American Pharmaceutical Review, 2006

21. Markovic, I., Regulatory perspective on Extractables & Leachables in Biologics: Quality considerations. Presentation at USP/PQRI Extractables & Leachables Workshop, Rockville, MD. 2014. Link

22. ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, 2019 https://www.ich.org/page/quality-guidelines

23. Hammond M. et.al., dentification of a leachable compound detrimental to cell growth in single-use bioprocess containers, J Pharm Sci Technol. Mar-Apr 2013;67(2):123-34

24. Li, J., et al., Interfacial Stress in the Development of Biologics: Fundamental Understanding, Current Practice, and Future Perspective. AAPS J 21, 44 (2019). https://doi.org/10.1208/s12248-019-0312-3

25. Paskiet D. PQRI Workshop Considerations for Biologics: Safety and Compatibility of Container Closure Systems 2018 Link

26. ICH guidance for industry Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (ICH Q5C) (July 1996). Link

27. 21CFR Part 600 Biological Products Subpart B section 600.11 (h) Containers Closures. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=600.11

28. Boven, K., et al., The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney International, 2005, 67, 2346–2353.

29. Zhou, S., et.al, Biologics Formulation Factors Affecting Metal Leachables from Stainless Steel, AAPS PharmSciTech. 2011 Mar; 12(1): 411–421.

30. Code of Federal Regulations, 21CFR3.2(e). Product Jurisdiction. Definitions. Link

31. Code of Federal Regulations, 21CFR211.94(a). Current Good Manufacturing Practice for Finished Pharmaceuticals. Drug Product Containers and Closures. Link

32. Markovic, PQRI Workshop on Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products (PODP) Bethesda, MD, February 22-23, 2011 Link

33. Bee, J. S., S. A. Nelson, et al. (2009). "Precipitation of a monoclonal antibody by soluble tungsten." J Pharm Sci 98(9): 3290-3301.

34. E. Milano et al. The Formation of an Aluminum-Epinephrine Complex and Its Effect on the Addition of Bisulfite to Epinephrine, PDA Journal Sci-tech vol. 37 no. 5 165169, 1983

Part 5. Appendices

Appendix 1 List of Extractables and Leachables in the Database

CAS #	CAS Primary Name 2021
100-21-0	Terephthalic acid
10024-58-5	1,1′-[1,2-Ethanediylbis(oxy-2,1-ethanediyl)] didecanoate
1002-84-2	Pentadecanoic acid
100-41-4	Ethylbenzene
100-51-6	Benzyl alcohol
100-52-7	Benzaldehyde
1014-60-4	1,3-Di-*tert*-butylbenzene
103-09-3	2-Ethylhexyl acetate
103-23-1	Bis(2-ethylhexyl) adipate
103-65-1	Propylbenzene
103-79-7	Phenylacetone
10385-78-1	2-Bornanol
507-70-0	Borneol
103982-58-7	2,4,4,6-Tetramethyl-2-heptene
104-76-7	2-Ethylhexanol
104-87-0	4-Methylbenzaldehyde
105-57-7	Diethyl acetal
105-75-9	Dibutyl fumarate
16062-88-7	Monobutyl fumarate
106-35-4	3-Heptanone
106575-31-9	19,22,25,28-Tetratriacontatetraenoic acid, methyl ester, (*all-Z*)-
106-68-3	3-Octanone
1069-53-0	2,3,5-Trimethylhexane
106-97-8	Butane
107-21-1	Ethylene glycol
107-39-1	2,4,4-Trimethyl-1-pentene
107-83-5	2-Methylpentane
107-87-9	2-Pentanone
107-92-6	Butyric acid
108-08-7	2,4-Dimethylpentane
108-10-1	Methyl isobutyl ketone

CAS #	CAS Primary Name 2021
108-83-8	Isobutyl ketone
109-52-4	Pentanoic acid
109-60-4	Propyl acetate
110-27-0	Isopropyl myristate
110-43-0	2-Heptanone
110-54-3	Hexane
110-62-3	Pentanal
110-63-4	1,4-Butanediol
110-82-7	Cyclohexane
111-02-4	Squalene
111-06-8	Butyl palmitate
111-13-7	2-Octanone
1113-92-4	1,3-Dibutyl 2-ethylpropanedioate
111-46-6	Diethylene glycol
111-61-5	Ethyl stearate
111-65-9	Octane
111-66-0	1-Octene
111-71-7	Heptanal
111-76-2	2-Butoxyethanol
111-84-2	Nonane
1120-21-4	Undecane
112-10-7	Isopropyl stearate
112-27-6	Triethylene glycol
112-34-5	Diethylene glycol monobutyl ether
1123-85-9	2-Phenyl-1-propanol
112-40-3	Dodecane
112-42-5	1-Undecanol
112-61-8	Methyl stearate
112-79-8	Elaidic acid
112-80-1	Oleic acid
112-84-5	Erucamide
112-88-9	1-Octadecene
112-92-5	Stearyl alcohol
112-95-8	Eicosane

CAS #	CAS Primary Name 2021
115-07-1	Propylene
115-11-7	Isobutylene
117-81-7	Dioctyl phthalate or 1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester
117-82-8	Bis(2-methoxyethyl) phthalate
120-55-8	Di-*O*-benzoyldiethylene glycol
120-61-6	Dimethyl terephthalate
121-91-5	Isophthalic acid
122-00-9	*p*-Methylacetophenone
122-20-3	Triisopropanolamine
122-62-3	Bis(2-ethylhexyl) sebacate
122-78-1	Phenylacetaldehyde
123-28-4	Dilauryl thiodipropionate
123-38-6	Propanal
123-72-8	Butanal
123-79-5	Dioctyl adipate
123-86-4	Butyl acetate
123-95-5	Butyl stearate
123-99-9	Azelaic acid
124-07-2	Octanoic acid
124-17-4	Diethylene glycol monobutyl ether acetate
124-18-5	Decane
124-19-6	Nonanal
124-26-5	Stearamide
126-30-7	Neopentyl glycol
131-11-3	Dimethyl phthalate
13269-52-8	*trans*-3-Hexene
1330-86-5	Diisooctyl adipate
13323-81-4	1-Phenylethanol
13475-82-6	2,2,4,6,6-Pentamethylheptane
136-36-7	Resorcinol, monobenzoate
138-86-3	Limonene
13926-69-7	1,8-Dioxacyclotetradecane-2,7-dione
141-04-8	Diisobutyl adipate
14167-59-0	Tetratriacontane

CAS #	CAS Primary Name 2021
141-78-6	Ethyl acetate
142-62-1	Hexanoic acid
142-82-5	Heptane
142-91-6	Isopropyl palmitate
143-07-7	Lauric acid
123250-74-8 (143925-92-2)	*N*-Hydroxy-*N*-octadecyl-1-octadecanamine (Irgastab FS 042)
149-57-5	2-Ethylhexanoic acid
1563-90-2	*N*,*N*-Dibutylacetamide
1569-02-4	1-Ethoxy-2-propanol
16545-54-3	Dimyristyl thiodipropionate
17301-27-8	2,10-Dimethylundecane
17301-32-5	4,7-Dimethylundecane
17302-28-2	2,6-Dimethylnonane
1732-10-1	Dimethyl azelate
17453-94-0	5-Ethylundecane
17699-14-8	alpha-Cubebene
17851-53-5	Butyl isobutyl phthalate
1921-70-6	Pristane
19549-80-5	4,6-Dimethyl-2-heptanone
19549-87-2	2,4-Dimethyl-1-heptene
19550-59-5	1,6-Dimethyl 2,5-dimethyl-2-hexenedioate
2104-19-0	Monomethyl azelate
22041-23-2	Butanoic acid, 4-(dimethylamino)-, ethyl ester
2213-23-2	(±)-2,4-Dimethylheptane
2216-34-4	(±)-4-Methyloctane
22163-52-6	1,4-Benzenedicarboxylic acid, 1-ethyl 4-methyl ester
2365-48-2	Methyl thioglycolate
24634-95-5	Ethyl tetracosanoate
2500-88-1	Dioctadecyl disulfide
112-41-4	1-Dodecene
27138-31-4	Dipropylene glycol, dibenzoate
27554-26-3	Diisooctyl phthalate
2756-56-1	Isobornyl propionate
2785-89-9	4-Ethylguaiacol

CAS #	CAS Primary Name 2021
2807-30-9	Glycol monopropyl ether
2847-72-5	(±)-4-Methyldecane
2885-00-9	1-Octadecanethiol
29058-99-9	Dioctyl azelate
292-64-8	Cyclooctane
29387-86-8	Propylene glycol butyl ether
293-96-9	Cyclodecane
294-62-2	Cyclododecane
295-65-8	Cyclohexadecane
296-56-0	Cycloeicosane
300-85-6	3-Hydroxybutyric acid
301-02-0	Oleamide
334-48-5	Decanoic acid
36443-68-2	Antioxidant 245 or Benzenepropanoic acid, 3-(1,1-dimethylethyl)-4-hydroxy-5-methyl-, 1,1′-[1,2-ethanediylbis(oxy-2,1-ethanediyl)] ester
13945-76-1	Lauryl laurate
3892-00-0	Norpristane
4181-95-7	Tetracontane
4376-20-9	Mono(2-ethylhexyl) phthalate
464-07-3	3,3-Dimethyl-2-butanol
487-68-3	2,4,6-Trimethylbenzaldehyde
502-26-1	γ-Stearolactone
502-69-2	6,10,14-Trimethyl-2-pentadecanone
513-35-9	2-Methyl-2-butene
51360-63-5	Eicosanamide
529-20-4	2-Methylbenzaldehyde
5345-01-7	3-Ethyl-3-methylpentanedioic acid
540-84-1	2,2,4-Trimethylpentane
544-63-8	Myristic acid
544-76-3	Hexadecane
544-85-4	Dotriacontane
54932-78-4	4-(2,2,3,3-Tetramethylbutyl)phenol
5578-82-5	Ethylene sebacate
57-10-3	Palmitic acid
57-11-4	Stearic acid

CAS #	CAS Primary Name 2021
57-55-6	(±)-Propylene glycol
577-11-7	Sodium bis(2-ethylhexyl) sulfosuccinate
589-38-8	3-Hexanone
589-53-7	4-Methylheptane
592-13-2	2,5-Dimethylhexane
592-27-8	2-Methylheptane
592-41-6	1-Hexene
592-76-7	1-Heptene
593-45-3	Octadecane
593-49-7	Heptacosane
5989-54-8	(*S*)-Limonene
60-32-2	6-Aminohexanoic acid
60-33-3	Linoleic acid
61461-81-2	*N*,*N*-Dimethylstearamide
619-99-8	3-Ethylhexane
624-17-9	Diethyl azelate
626-19-7	1,3-Benzenedicarboxaldehyde
626-93-7	(±)-2-Hexanol
628-97-7	Ethyl palmitate
629-11-8	1,6-Hexanediol
629-50-5	Tridecane
629-54-9	Hexadecanamide
629-59-4	Tetradecane
629-62-9	Pentadecane
629-73-2	1-Hexadecene
629-76-5	1-Pentadecanol
629-78-7	Heptadecane
629-92-5	Nonadecane
629-94-7	Heneicosane
629-96-9	1-Eicosanol
629-97-0	Docosane
629-99-2	Pentacosane
630-01-3	Hexacosane
630-02-4	Octacosane

CAS #	CAS Primary Name 2021
630-06-8	Hexatriacontane
636-09-9	Diethyl terephthalate
637-92-3	Ethyl *tert*-butyl ether
638-36-8	Phytane
638-58-4	Tetradecanamide
638-67-5	Tricosane
638-68-6	Triacontane
64-17-5	Ethanol
64-18-6	Formic acid
64-19-7	Acetic acid
6422-86-2	Dioctyl terephthalate or 1,4-Benzenedicarboxylic acid, 1,4-bis(2-ethylhexyl) ester
646-31-1	Tetracosane
6482-34-4	Diisopropyl carbonate
65-85-0	Benzoic acid
66-25-1	Hexanal
67-56-1	Methanol
67-63-0	Isopropanol
67-64-1	Acetone
693-36-7	Distearyl thiodipropionate
71-23-8	1-Propanol
71-36-3	1-Butanol
71850-09-4	Diisohexyl phthalate
7194-85-6	Octatriacontane
7346-78-3	2-[2-[2-[(1-Oxooctyl)oxy]ethoxy]ethoxy]ethyl decanoate
73513-30-1	Methylpentanal
7397-62-8	Butyl glycolate
4277-06-9	1,9-Cyclohexadecadiene
74381-40-1	1,1′-[1-(1,1-Dimethylethyl)-2-methyl-1,3-propanediyl] bis(2-methylpropanoate)
7443-25-6	1,3-Dimethyl 2-[(4-methoxyphenyl)methylene]propanedioate
74-98-6	Propane
75-04-7	Ethylamine
75-07-0	Acetaldehyde
75-28-5	Isobutane

CAS #	CAS Primary Name 2021
763-29-1	2-Methyl-1-pentene
7659-86-1	2-Ethylhexyl thioglycolate
592-43-8	2-Hexene
78-78-4	Isopentane
78-83-1	Isobutanol
78-84-2	Isobutyraldehyde
78-93-3	Methyl ethyl ketone
79-09-4	Propionic acid
79-29-8	2,3-Dimethylbutane
79-92-5	(±)-Camphene
80-46-6	4-*tert*-Pentylphenol
821-95-4	1-Undecene
822-20-8	1-Heptadecanol, 1-acetate
822-23-1	Octadecyl acetate
84-66-2	Diethyl phthalate
84-69-5	Diisobutyl phthalate
84-74-2	Dibutyl phthalate
84-78-6	Butyl octyl phthalate
85-69-8	Butyl 2-ethylhexyl phthalate
872-05-9	1-Decene
87-26-3	2-(1-Methylbutyl)phenol
88-99-3	Phthalic acid
931-87-3	*cis*-Cyclooctene
931-88-4	Cyclooctene
93-89-0	Ethyl benzoate
93-99-2	Phenyl benzoate
94113-47-0	3,3-Dimethyl-1,5-dioxacycloundecane-6,11-dione
94113-50-5	3,3-Dimethyl-1,5-dioxacyclopentadecane-6,15-dione
94-60-0	Dimethyl 1,4-cyclohexanedicarboxylate
959-26-2	Bis(2-hydroxyethyl) terephthalate
96-14-0	3-Methylpentane
96-22-0	Ethyl ketone
96-37-7	Methylcyclopentane
96-76-4	2,4-Di-*tert*-butylphenol

CAS #	CAS Primary Name 2021
98-82-8	Cumene
98-83-9	α-Methylstyrene
98-86-2	Acetophenone
99-87-6	*p*-Cymene
108-95-2	Phenol
109-16-0	Triethylene glycol dimethacrylate
109-17-1	Tetraethylene glycol, dimethacrylate
1189-08-8	1,3-Butyleneglycol dimethacrylate
3290-92-4	Trimethylolpropane trimethacrylate
576-26-1	2,6-Dimethylphenol
80-62-6	2-Propenoic acid, 2-methyl-, methyl ester
868-77-9	2-Hydroxyethyl methacrylate
95-47-6	*o*-Xylene
97-88-1	Butyl methacrylate
97-90-5	Ethylene glycol dimethacrylate
1011-12-7	2-Cyclohexylidenecyclohexanone
10191-41-0	DL-α-Tocopherol
104-40-5	4-Nonylphenol
104-61-0	(±)-γ-Nonalactone
104-68-7	Diethylene glycol monophenyl ether
104-72-3	Decylbenzene
107-88-0	1,3-Butanediol
108-94-1	Cyclohexanone
1120-73-6	2-Methyl-2-cyclopenten-1-one
122-99-6	Phenoxyethanol
1235-74-1	Methyl dehydroabietate
146598-26-7	Irganox 1135 or Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, isooctyl ester
2607-52-5	BHT-quinone methide
128-39-2	2,6-Di-*tert*-butylphenol
1459-09-2	Hexadecylbenzene
1620-98-0	3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde
20170-32-5	3-(3′,5′-Di-*tert*-butyl-4′-hydroxyphenyl)propionic acid
2082-79-3	Antioxidant 1076 or Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, octadecyl ester

CAS #	CAS Primary Name 2021
23676-09-7	Ethyl 4-ethoxybenzoate
2398-68-7	Eicosylbenzene
2455-14-3	4-[3,5-Bis(1,1-dimethylethyl)-4-oxo-2,5-cyclohexadien-1-ylidene]-2,6-bis(1,1-dimethylethyl)-2,5-cyclohexadien-1-one
25154-52-3	Nonylphenol
2607-52-5	BHT-quinone methide
36913-60-7	1,1′-[2,2-Bis(hydroxymethyl)-1,3-propanediyl] bis[3,5-bis(1,1-dimethylethyl)-4-hydroxybenzenepropanoate]
4130-42-1	2,6-Di-*tert*-butyl-4-ethylphenol
41484-35-9	Thiodiethylene bis(3,5-di-*tert*-butyl-4-hydroxyhydrocinnamate)
4221-80-1	2,4-Di-*tert*-butylphenyl 3′,5′-di-*tert*-butyl-4′-hydroxybenzoate
4445-07-2	Octadecylbenzene
489-01-0	2,6-Di-*tert*-butyl-4-methoxyphenol
502-49-8	Cyclooctanone
51175-35-0	Cyclooctylideneoctahydrocyclooctane
57213-26-0	2-(1-Hydroxycyclohexyl)-1-phenylethanone
591-78-6	2-Hexanone
6386-38-5	Methyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate
6683-19-8	Antioxidant 1010 or Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, 1,1′-[2,2-bis[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxopropoxy]methyl]-1,3-propanediyl] ester
67845-93-6	Hexadecyl 3,5-di-*tert*-butyl-4-hydroxybenzoate
69310-20-9	Butanedioic acid, 2,3-bis[[3,5-bis(1,1-dimethylethyl)-4-oxo-2,5-cyclohexadien-1-ylidene]methyl]-, dioctadecyl ester, (*R**,*S**)-
69310-21-0	*rel*-1,4-Dioctadecyl (2*R*,3*R*)-2,3-bis[[3,5-bis(1,1-dimethylethyl)-4-oxo-2,5-cyclohexadien-1-ylidene]methyl]butanedioate
343933-08-4	1,4-Dioctadecyl 2,3-bis[[3,5-bis(1,1-dimethylethyl)-4-oxo-2,5-cyclohexadien-1-ylidene]methyl]butanedioate
719-22-2	2,6-Di-*tert*-butyl-1,4-benzoquinone
719-49-3	2,4-Dimethyl-6-(2-methylcyclohexyl)phenol
7204-16-2	2-[2-(2-Phenoxyethoxy)ethoxy]ethanol
732-26-3	2,4,6-Tri-*tert*-butylphenol
78-59-1	Isophorone
78-92-2	(±)-2-Butanol
809-73-4	4,4′-(1,2-Ethanediylidene)bis[2,6-bis(1,1-dimethylethyl)-2,5-cyclohexadien-1-one
825-25-2	2-Cyclopentylidenecyclopentanone
83-48-7	Stigmasterol

CAS #	CAS Primary Name 2021
84633-54-5	1,1′-[2-[[3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxopropoxy]methyl]-2-(hydroxymethyl)-1,3-propanediyl] bis[3,5-bis(1,1-dimethylethyl)-4-hydroxybenzenepropanoate]
85851-44-1	Cyclopropane, 1-(1,1-dimethylethyl)-2-(1,2,2-trimethylpropylidene)-, (*E*)-
2129-93-3	Propylidenecyclohexane
88-26-6	3,5-Di-*tert*-butyl-4-hydroxybenzyl alcohol
9016-45-9	Polyethylene glycol nonylphenyl ether
947-19-3	1-Hydroxycyclohexyl phenyl ketone
1006-94-6	5-Methoxyindole
10081-67-1	4,4′-Bis(α,α-dimethylbenzyl)diphenylamine
101-84-8	Diphenyl ether
102-06-7	Diphenylguanidine
103-49-1	Dibenzylamine
103-83-3	*N*,*N*-Dimethylbenzylamine
104-90-5	5-Ethyl-2-methylpyridine
10544-50-0	S8 or Cyclic octaatomic sulfur
105-60-2	Caprolactam
106001-67-6	α2-2-Furanyl-2,5-furandimethanol
106-62-7	2-(2-Hydroxypropoxy)-1-propanol
1066-40-6	Trimethylsilanol
106917-30-0	3-Dodecyl-1-(1,2,2,6,6-pentamethyl-4-piperidyl)pyrrolidine-2,5-dione
106990-43-6	Chimassorb 119 or 1,3,5-Triazine-2,4,6-triamine, N2,N2′-1,2-ethanediylbis[N2-[3-[[4,6-bis[butyl(1,2,2,6,6-pentamethyl-4-piperidinyl)amino]-1,3,5-triazin-2-yl]amino]propyl]-N4,N6-dibutyl-N4,N6-bis(1,2,2,6,6-pentamethyl-4-piperidinyl)-
107-51-7	Octamethyltrisiloxane
107-98-2	1-Methoxy-2-propanol
1081-75-0	1,3-Diphenylpropane
108-48-5	2,6-Lutidine
108-65-6	1-Methoxy-2-propyl acetate
108-91-8	Cyclohexylamine
109-89-7	Diethylamine
109-99-9	Tetrahydrofuran
110553-27-0	2-Methyl-4,6-Bis[(octylthio)methyl]phenol
110-91-8	Morpholine
110-98-5	Bis(2-hydroxypropyl) ether

CAS #	CAS Primary Name 2021
1121-55-7	3-Vinylpyridine
1123-07-5	4,4,6-Trimethyl-1,3-dioxane
1124-53-4	*N*-Cyclohexylacetamide
115-86-6	Triphenyl phosphate
38613-77-3	Tetrakis(2,4-di-tert-butylphenyl)-4,4′-biphenylenediphosphonite
119-47-1	2,2′-Methylenebis[4-methyl-6-*tert*-butylphenol]
119-61-9	Benzophenone
120-40-1	Lauric acid diethanolamide
1212-08-4	*S*-Phenyl benzenesulfonothioate
122-39-4	Diphenylamine
123-42-2	Diacetone alcohol
1241-94-7	2-Ethylhexyl diphenyl phosphate
122586-52-1	Tinuvin 123 or Decanedioic acid, 1,10-bis[2,2,6,6-tetramethyl-1-(octyloxy)-4-piperidinyl] ester
131-53-3	2,2′-Dihydroxy-4-methoxybenzophenone
131-56-6	2,4-Dihydroxybenzophenone
135861-56-2	Bis(3,4-dimethylbenzylidene) sorbitol
136-95-8	2-Aminobenzothiazole
13798-23-7	Sulfur, mol. (S6) or Cyclohexasulfur
138370-64-6	5-(1,2-Dihydroxyethyl)-3(2*H*)-furanone
142-78-9	Lauric acid monoethanolamide
147315-50-2	Tinuvin 1577 or Phenol, 2-(4,6-diphenyl-1,3,5-triazin-2-yl)-5-(hexyloxy)-
147-47-7	2,2,4-Trimethyl-1,2-dihydroquinoline
14808-79-8	Sulfate
150-11-8	Dibutyldithiocarbamic acid
15045-43-9	2,2,5,5-Tetramethyltetrahydrofuran
1516-94-5	4,4′-(1,2-Ethanediyl)bis[2,6-bis(1,1-dimethylethyl)phenol
15571-58-1	2-Ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate
1565-94-2	Bisphenol A diglycidyl ether dimethacrylate
1634-04-4	*tert*-Butyl methyl ether
16887-00-6	Chloride
1709-70-2	1,3,5-Trimethyl-2,4,6-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzene
1806-29-7	[1,1′-Biphenyl]-2,2′-diol
1843-05-6	2-Hydroxy-4-octoxybenzophenone

CAS #	CAS Primary Name 2021
18600-59-4	UV 3638 or 4H-3,1-Benzoxazin-4-one, 2,2′-(1,4-phenylene)bis-
18928-62-6	*N*1,*N*4-Bis(2-hydroxyethyl)-1,4-benzenedicarboxamide
18966-64-8	2-Bromo-4-(1,1-dimethylpropyl)phenol
20071-09-4	*trans*-1,2-Diphenylcyclobutane
2014-58-6	6-[(6-Amino-1-oxohexyl)amino]hexanoic acid
208-96-8	Acenaphthylene
145849-89-4	Poly[[6-(4-morpholinyl)-1,3,5-triazine-2,4-diyl][(1,2,2,6,6-pentamethyl-4-piperidinyl)imino]-1,6-hexanediyl[(1,2,2,6,6-pentamethyl-4-piperidinyl)imino]]
2201-15-2	*N*-Ethyl-1-phenylcyclohexanamine
4384-82-1	Dithiocarbamate
22122-36-7	3-Methyl-2(5*H*)-furanone
22759-34-8	*rel*-(1*R*,3*S*,4*S*)-3-Hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one
22796-14-1	1-(1,1-Dimethylethyl)-4-(methylsulfonyl)benzene
2304-58-7	5-Cyanopentanamide
23128-74-7	Antioxidant 1098 or Benzenepropanamide, N,N′-1,6-hexanediylbis[3,5-bis(1,1-dimethylethyl)-4-hydroxy-
24157-81-1	2,6-Diisopropylnaphthalene
24295-03-2	2-Acetylthiazole
2440-22-4	Drometrizole
24650-42-8	2,2-Dimethoxy-2-phenylacetophenone
1333-16-0	Bisphenol F or Methylenebis[phenol]
620-92-8	Bisphenol F or 4,4′-Methylenebis[phenol]
2467-02-9	Bisphenol F or 2,2′-Methylenebis[phenol]
24959-67-9	Bromide
25038-59-9	Poly(ethylene terephthalate)
2591-86-8	*N*-Formylpiperidine
25973-55-1	UV 328 or Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)-
26523-78-4	Phenol, nonyl-, 1,1′,1″-phosphite
32258-84-7	Phenol, 4-nonyl-, phosphate (3:1) or Tris(p-nonylphenyl) phosphate
26741-53-7	Bis(2,4-di-*tert*-butylphenyl) pentaerythritol diphosphite
27107-89-7	Octyltin tris(2-ethylhexylthioglycolate)
2725-22-6	2-[4,6-Bis(2,4-dimethylphenyl)-1,3,5-triazin-2-yl]-5-(octyloxy)phenol
27676-62-6	Tris(3,5-di-*tert*-butyl-4-hydroxybenzyl) isocyanurate
2782-91-4	Tetramethylthiourea

CAS #	CAS Primary Name 2021
28291-69-2	*N*-Ethyl-2-benzothiazolamine
2985-59-3	2-Hydroxy-4-dodecyloxybenzophenone
3018-20-0	1-Phenyltetralin
3147-75-9	2-(2-Hydroxy-5-*tert*-octylphenyl)benzotriazole
31570-04-4	Tris(2,4-di-*tert*-butylphenyl) phosphite
19046-64-1	Dibenzylidene sorbitol
3333-52-6	2,2,3,3-Tetramethylbutanedinitrile
3386-33-2	1-Chlorooctadecane
34137-09-2	1,3,5-Tris[2-(3,5-di-*tert*-butyl-4-hydroxyhydrocinnamoyloxy)ethyl] isocyanurate
3622-84-2	*N*-Butylbenzenesulfonamide
3806-34-6	Distearyl pentaerythritol diphosphite
3846-71-7	2-(2′-Hydroxy-3′5-di-*tert*-butylphenyl) benzotriazole
3864-99-1	UV 327 or Phenol, 2-(5-chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-
38940-67-9	Methyl 5-vinylnicotinate
3896-11-5	2-(2-Hydroxy-3-*tert*-butyl-5-methylphenyl)-5-chlorobenzotriazole
40029-70-7	3-Ethyl-2(5*H*)-furanone
40601-76-1	Cyanox 1790 or 1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris[[4-(1,1-dimethylethyl)-3-hydroxy-2,6-dimethylphenyl]methyl]-
41556-26-7	Bis(1,2,2,6,6-pentamethyl-4-piperidyl) decanedioate
41981-68-4	4-Ethyl-2-propylthiazole
4266-66-4	1,8-Diazacyclotetradecane-2,7-dione
4520-29-0	1,3-Bis(trimethylsiloxy)benzene
46055-91-8	2-Benzothiazoleethanol
10373-78-1	Camphorquinone
4665-63-8	2-(2-Benzothiazolylthio)ethanol
474-62-4	Campesterol
497-26-7	2-Methyl-1,3-dioxolane
498-66-8	Norbornene
50598-50-0	3,5,5-Trimethyl-2(5*H*)-furanone
124-40-3	Dimethylamine
50-84-0	2,4-Dichlorobenzoic acid
514-10-3	Abietic acid
52829-07-9	Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate
5323-65-9	2-Chloro-4-(1,1-dimethylpropyl)phenol

CAS #	CAS Primary Name 2021
540-97-6	Dodecamethylcyclohexasiloxane
541-02-6	Decamethylcyclopentasiloxane
541-05-9	Hexamethylcyclotrisiloxane
542-85-8	Ethyl isothiocyanate
556-67-2	Octamethylcyclotetrasiloxane
5581-32-8	Bisphenol A bis(2,3-dihydroxypropyl) ether
56403-08-8	1,8,15-Triazacycloheneicosane-2,9,16-trione
56403-09-9	1,8-Diazacyclotetradecane-2,9-dione
57-13-6	Urea
57472-50-1	1,1′-[Methylenebis(hydroxymethoxyphenylene)]bis[1-phenylmethanone]
5776-78-3	6-[[6-[(6-Amino-1-oxohexyl)amino]-1-oxohexyl]amino]hexanoic acid
5834-63-9	1,8,15,22-Tetraazacyclooctacosane-2,9,16,23-tetrone
58392-22-6	2-Hydroxy-4-methoxybenzophenone
591-50-4	Iodobenzene
599-64-4	4-Cumylphenol
599-69-9	*N*,*N*-Dimethyl-*p*-toluenesulfonamide
601-58-1	Stigmastane
603-36-1	Triphenylantimony
613-93-4	*N*-Methylbenzamide
615-22-5	2-(Methylthio)benzothiazole
617-94-7	2-Phenyl-2-propanol
6267-02-3	9,9-Dimethyl-9,10-dihydroacridine
63843-89-0	Bis(1,2,2,6,6-pentamethyl-4-piperidyl) 2-(3,5-di-*tert*-butyl-4-hydroxybenzyl)-2-*n*-butylmalonate
646-06-0	1,3-Dioxolane
65140-91-2	Irganox 1425 or C17H29O4P.1/2Ca (66165-37-5)
66165-37-5	Ethyl hydrogen *P*-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]phosphonate
65447-77-0	Butanedioic acid, 1,4-dimethyl ester, polymer with 4-hydroxy-2,2,6,6-tetramethyl-1-piperidineethanol
15721-78-5	4,4′-Di-*tert*-octyldiphenylamine
6911-45-1	2,5-Dibutylthiophene
70321-86-7	2-(2*H*-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol
70331-94-1	2,2′-Oxamidobis[ethyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate]
7128-64-5	2,5-Bis(5′-*tert*-butyl-2-benzoxazolyl)thiophene
7390-81-0	1,2-Epoxyoctadecane

CAS #	CAS Primary Name 2021
7429-90-5	Aluminum
7439-95-4	Magnesium
7440-21-3	Silicon
7440-32-6	Titanium
7440-66-6	Zinc
7440-70-2	Calcium
7473-98-5	2-Hydroxy-2-methyl-1-phenylpropan-1-one
75-15-0	Carbon disulfide
75-65-0	*tert*-Butanol
75908-77-9	2,6-Dichloro-4-(1,1-dimethylpropyl)phenol
761-65-9	*N*,*N*-Dibutylformamide
765-09-3	1-Bromotridecane
766-93-8	Cyclohexylformamide
768-66-1	2,2,6,6-Tetramethylpiperidine
7704-34-9	Sulfur
77-73-6	Dicyclopentadiene
78-51-3	Tris(2-butoxyethyl) phosphate
78-67-1	Azobisisobutyronitrile
791-28-6	Triphenylphosphine oxide
79720-19-7	3-Dodecyl-1-(2,2,6,6-tetramethyl-4-piperidyl)pyrrolidine-2,5-dione
80-05-7	2,2-Bis(4-hydroxyphenyl)propane
80-39-7	*N*-Ethyl-4-methylbenzenesulfonamide
80410-33-9	2-[[2,4,8,10-Tetrakis(1,1-dimethylethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yl]oxy]-*N*,*N*-bis[2-[[2,4,8,10-tetrakis(1,1-dimethylethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yl]oxy]ethyl]ethanamine
80693-00-1	PEP 36 or 2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[2,6-bis(1,1-dimethylethyl)-4-methylphenoxy]-
81541-12-0	1,3:2,4-Di(*p*-methylbenzylidene)sorbitol
82304-66-3	7,9-Di-*tert*-butyl-1-oxaspiro[4,5]deca-6,9-diene-2,8-dione
83237-15-4	3,5-Bis(1,1-dimethylethyl)-1-hydroxy-4-oxo-2,5-cyclohexadiene-1-propanoic acid
83-32-9	Acenaphthene
83-46-5	(-)-β-Sitosterol
85209-91-2	12*H*-Dibenzo[*d*,*g*][1,3,2]dioxaphosphocin, 2,4,8,10-tetrakis(1,1-dimethylethyl)-6-hydroxy-, 6-oxide, sodium salt (1:1)
85-44-9	Phthalic anhydride

CAS #	CAS Primary Name 2021
864-90-4	1,8,15,22,29-Pentaazacyclopentatriacontane-2,9,16,23,30-pentone
865-14-5	1,8,15,22,29,36-Hexaazacyclodotetracontane-2,9,16,23,30,37-hexone
86-73-7	Fluorene
88-24-4	2,2′-Methylenebis[4-ethyl-6-*tert*-butylphenol]
90-04-0	2-Methoxyaniline
9016-00-6	Poly(dimethylsiloxane)
90-43-7	[1,1′-Biphenyl]-2-ol
90-66-4	2,2′-Thiobis(4-methyl-6-*tert*-butylphenol)
90751-07-8	UV 3346 or Poly[[6-(4-morpholinyl)-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]]
931-53-3	Cyclohexyl isocyanide
934-34-9	2-Benzothiazolinone
93968-78-6	2-(2-Benzothiazolyloxy)ethanol
95-16-9	Benzothiazole
95906-11-9	Tris(2,4-di-*tert*-butylphenyl) phosphate
96-69-5	4,4′-Thiobis(3-methyl-6-tert-butylphenol)
98185-21-8	4-Methyl-2,6-bis(2-phenylethenyl)phenol
98-94-2	*N*,*N*-Dimethylcyclohexylamine
991-84-4	2,4-Bis-(*n*-octylthio)-6-(4-hydroxy-3′,5′-di-*tert*-butylanilino)-1,3,5-triazine
100-42-5	Styrene
100-75-4	*N*-Nitrosopiperidine
101-68-8	Diphenylmethane diisocyanate
101-77-9	4,4-Diaminodiphenylmethane
106-46-7	1,4-Dichlorobenzene
106-74-1	2-Ethoxyethyl acrylate
106-99-0	1,3-Butadiene
107-13-1	Acrylonitrile
108-45-2	*m*-Phenylenediamine
120-12-7	Anthracene
120-78-5	Accelerator DM or Benzothiazole, 2,2′-dithiobis-
127-18-4	Tetrachloroethylene
129-00-0	Pyrene
137-26-8	Tetramethylthiuram disulfide
149-30-4	2-Mercaptobenzothiazole

CAS #	CAS Primary Name 2021
150-76-5	4-Methoxyphenol
163405-36-5	4-[1-(4-Hydroxyphenyl)-1-methylethyl]-3,5-cyclohexadiene-1,2-dione
1675-54-3	Bisphenol A diglycidyl ether
18984-88-8	Zinc dithiocarbamate
191-24-2	Benzo[*ghi*]perylene
192-97-2	Benzo[*e*]pyrene
193-39-5	Indeno[1,2,3-*cd*]pyrene
205-99-2	Benz[*e*]acephenanthrylene
206-44-0	Fluoranthene
207-08-9	Benzo[*k*]fluoranthene
2091-51-2	4-(Bromomethyl)-2,6-bis(1,1-dimethylethyl)phenol
2156-97-0	Lauryl acrylate
218-01-9	Chrysene
2346-81-8	3-Chlorohexane
25013-16-5	*tert*-Butylhydroxyanisole
26603-40-7	1,3,5-Tris(3-isocyanatomethylphenyl)-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione
26747-90-0	1,3-Bis(3-isocyanatomethylphenyl)-1,3-diazetidine-2,4-dione
28213-80-1	Ethenylbenzene trimer
3021-89-4	2-Pentyl-2-nonenal
3077-12-1	*N*,*N*-Bis(2-hydroxyethyl)-*p*-toluidine
3101-60-8	*p*-*tert*-Butylphenyl glycidyl ether
32687-78-8	*N*,*N*′-Bis[3-(3′,5′-di-*tert*-butyl-4′-hydroxyphenyl)propionyl]hydrazine
48145-04-6	Phenoxyethyl acrylate
497-23-4	2(5*H*)-Furanone
50-00-0	Formaldehyde
50-32-8	Benzo[*a*]pyrene
532-55-8	Benzoyl isothiocyanate
53-70-3	Dibenz[*a*,*h*]anthracene
55-18-5	Diethylnitrosamine
56-55-3	Benzanthracene
584-84-9	Toluene 2,4-diisocyanate
5888-33-5	Isobornyl acrylate
59-89-2	Nitrosomorpholine
624-20-4	1,2-Dibromohexane

CAS #	CAS Primary Name 2021
62-53-3	Aniline
62-75-9	*N*-Nitrosodimethylamine
67580-72-7	1-(4-Methylphenyl)-3-phenyl-2-propen-1-one oxime
71-43-2	Benzene
75-25-2	Bromoform
76002-91-0	2-[4-(2,3-Dihydroxypropoxy)phenyl]-2-[4-(2,3-epoxypropoxy)phenyl]propane
79-34-5	1,1,2,2-Tetrachloroethane
823-40-5	2,6-Diaminotoluene
85-01-8	Phenanthrene
87-66-1	Pyrogallol
91-20-3	Naphthalene
924-16-3	*N*-Nitrosodibutylamine
930-55-2	*N*-Nitrosopyrrolidine
95-53-4	*o*-Toluidine
95-68-1	2,4-Dimethylaniline
95-80-7	2,4-Diaminotoluene
96-09-3	Styrene oxide
97-39-2	Di-*o*-tolylguanidine
99-97-8	Dimethyl-*p*-toluidine
108-88-3	Toluene

Appendix 2: Method for Establishing the PDE

Permitted Daily Exposure values were calculated according to the procedures outlined in ICH Q3C and ICH Q3D. These procedures were developed based on the approaches outlined for setting exposure limits in pharmaceuticals (*Pharmacopeial Forum*, Nov–Dec 1989), and the method adopted by the International Programme on Chemical Safety for Assessing Human Health Risk of Chemicals (Environmental Health Criteria [EHC] 170, WHO, 1994). These methods are similar to those used by the US EPA (IRIS) and the FDA Red Book and others. The method is outlined here to give a better understanding of the origin of the PDE values.

A PDE is derived from the NOEL or NOAEL:

PDE = NO(A)EL x Mass Adjustment/[F1 x F2 x F3 x F4 x F5 x F6]

PDEs are derived from the no-observed-effect level (NOEL), or the lowest observed effect level (LOEL) in the most relevant animal study. NOEL refers to the highest exposure level at which no effects (adverse or nonadverse) are observed in the exposed population distinguishable from an appropriate control; likewise, LOEL corresponds to the lowest exposure level at which effects (adverse or nonadverse) are observed in the exposed population distinguishable from an appropriate control. The no observed adverse effect level (NOAEL) refers to the highest exposure level at which no biologically (or statistically) significant increases in frequency or severity of adverse effects are observed between the exposed population and an appropriate control. Likewise, the lowest observed adverse effect level (LOAEL) corresponds to the lowest exposure level at which biologically (or statistically) significant increases in frequency or severity of adverse effects are observed between the exposed population and an appropriate control. [1] The terms NOAEL and LOAEL as used in this discussion are considered to appropriately represent a meaningful health risk evaluation.

The PDE is derived preferably from a NOAEL. If no NOAEL is obtained, the LOAEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of "uncertainty factors" used in EHC (EHC 170, World Health Organization, Geneva, 1994), and "modifying factors" or "safety factors" in Pharmacopeial Forum. The assumption of 100% systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

F1: A factor to account for extrapolation between species. F1 takes into account the comparative surface area: body mass ratios for the species concerned and for man. Surface area (S) is calculated as $S = kM^{0.67}$, in which M = body mass and the constant k has been taken to be 10. The body masses used in the equation are those shown below in Table 5-1.

F1 = 5 for extrapolation from rats to humans

F1 = 12 for extrapolation from mice to humans

F1 = 2 for extrapolation from dogs to humans

F1 = 2.5 for extrapolation from rabbits to humans

F1 = 3 for extrapolation from monkeys to humans

F1 = 10 for extrapolation from other animals to humans

Table 5-1 Values Used in the Calculations in this Document (from the ICH Q3D Guidance)

Rat body weight	425 g	Mouse respiratory volume	43 L/day
Pregnant rat body weight	330 g	Rabbit respiratory volume	1440 L/day
Mouse body weight	28 g	Guinea pig respiratory volume	430 L/day
Pregnant mouse body weight	30 g	Human respiratory volume	28,800 L/day
Guinea pig body weight	500 g	Dog respiratory volume	9,000 L/day
Rhesus monkey body weight	2.5 kg	Monkey respiratory volume	1,150 L/day
Rabbit body weight (pregnant or not)	4 kg	Mouse water consumption	5 mL/day
Beagle dog body weight	11.5 kg	Rat water consumption	30 mL/day
Rat respiratory volume	290 L/day	Rat food consumption	30 g/day

F2: A factor of 10 to account for variability between individuals

A factor of 10 is generally given for chemicals, and 10 is used consistently in this guideline

F3: A variable factor to account for toxicity studies of short-term exposure

F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys)

F3 = 1 for reproductive studies in which the whole period of organogenesis is covered

F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents

F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents

F3 = 10 for studies of a shorter duration

In all cases, the higher factor has been used for study durations between the time points, e.g., a factor of 2 for a 9-month rodent study.

F4: A factor that may be applied in cases of severe toxicity, e.g., nongenotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used:

F4 = 1 for fetal toxicity associated with maternal toxicity

F4 = 5 for fetal toxicity without maternal toxicity

F4 = 5 for a teratogenic effect with maternal toxicity

F4 = 10 for a teratogenic effect without maternal toxicity

F5: A variable factor that may be applied if the no-effect level was not established

When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

F6: A variable factor to account for route of exposure difference (e.g., oral to parenteral).

The ICH Q3D Guidance suggests that F6 may be assigned as follows:
In the absence of data and/or where data are available but not considered sufficient for a safety assessment for the parenteral and or inhalation route of administration, modifying factors based on oral bioavailability can be used to derive the PDE from the oral PDE:

• Oral bioavailability <1%: divide by a modifying factor of 100;

• Oral bioavailability ≥ 1% and <50%: divide by a modifying factor of 10;

• Oral bioavailability ≥50% and <90%: divide by a modifying factor of 2; and

• Oral bioavailability ≥ 90%: divide by a modifying factor of 1.

Where oral bioavailability data or occupational inhalation exposure limits are not available, a calculated PDE can be used based on the oral PDE divided by a modifying factor of 100.

The mass adjustment assumes an arbitrary adult human body mass for either sex of 50 kg. This relatively low mass provides an additional safety factor against the standard masses of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine the PDE.

[1] Richard W. Lewis, Richard Billington, Eric Debryune, Armin Gamer, B. Lang, Francis Carpanini. TOXICOLOGIC PATHOLOGY, vol 30, no 1, pp 66–74, 2002.

Appendix 3: Links to Publications by the PODP Working Group

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

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

Simulated Leaching (Migration) Study for a Model Container Closure System Applicable to Parenteral and Ophthalmic Drug Products (PODP)

Principles for Management of Extractables and Leachables in Ophthalmic Drug Products

Appendix 4: Glossary of Acronyms and Abbreviations

Abbreviation/Acronym	Meaning
ADI	Acceptable Daily Intake
ADME	Absorption Distribution Metabolism Excretion
AET	Analytical Evaluation Threshold
CAS	Chemical Abstracts Service
CCS	Container Closure Systems
CDER	The Center for Drug Evaluation and Research
cGMP or CGMP	Current Good Manufacturing Practice
COC	Cyclic Olefin Copolymer
DEREK	Deductive Estimation of Risk from Existing Knowledge (a Computer Program)
DNA	Deoxyribonucleic Acid
DPI	Dry Powder Inhaler
ECH	Environmental Health Criteria
EFD	Embryo-Fetal Development
EFSA	European Food Safety Authority
ELSIE Consortium	Extractables and Leachables Safety Information Exchange
EMA	European Medicines Agency
EPA	Environmental Protection Agency
EPA IRIS	Environmental Protection Agency Integrated Risk Information System Database
FALCPA	Food Allergen Labeling and Consumer Protection Act of 2004
FAO	Food and Agriculture Organization of The United Nations
FDA	Food and Drug Administration
IARC	International Agency for Research on Cancer
ICH	The International Council for Harmonisation of Technical Requirements For Pharmaceuticals For Human Use
IRIS	Integrated Risk Information System of the EPA
ISO	International Organization for Standardization
JMPR	Joint (FAO/WHO) Meeting on Pesticide Residues
JRC	European Commission's Joint Research Centre
LDPE	Low-Density Polyethylene
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
LVP	Large Volume Parenterals
MDI	Metered Dose Inhaler
MMA	Monomeric Methyl Methacrylate
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NSF	National Science Foundation
NTP	National Toxicology Program
ODP	Ophthalmic Drug Products

Abbreviation/Acronym	Meaning
OINDP	Orally Inhaled and Nasal Drug Products
PDE	Permissible Daily Exposure
PDP	Parenteral Drug Product
PFS	Prefilled Syringes
PODP	Parenteral and Ophthalmic Drug Products
PQRI	Product Quality Research Institute
QSAR	Quantitative Structure-Activity Relationship
QT	Qualification Threshold
RfD	Reference Dose
SAR	Structure Activity Relationship
SCCS	Scientific Committee on Consumer Safety
SCT	Safety Concern Threshold
SVP	Small Volume Parenterals
TD_{50}	Median Toxic Dose
TD_{Lo}	Toxic Dose, Low
TTC	Threshold of Toxicological Concern
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization