PDA Training Course Extractables & Leachables

31 May 2022

The PDP and ODP Best Demonstrated Practice Recommendations – Chemistry and Toxicology

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Nelson Labs A Sotera Health company

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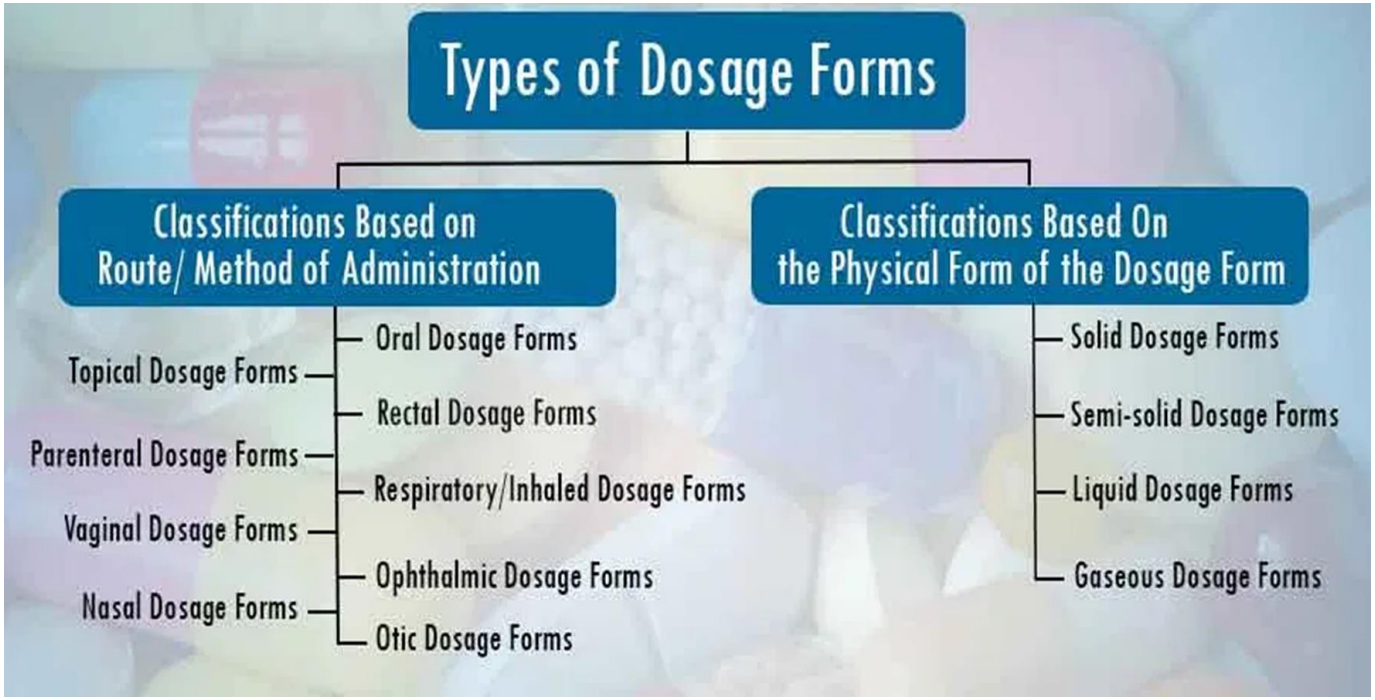
Training Outline

1. Introduction to the PQRI Recommendations.
2. Recommendations for Parenteral Drug Products (PDP).
3. Recommendations for Ophthalmic Drug Products (ODP).

The Product Quality Research Institute (PQRI) was established in 1999, and brings together members of the pharmaceutical industry, academia and regulatory agencies to develop science-based approaches to regulation.

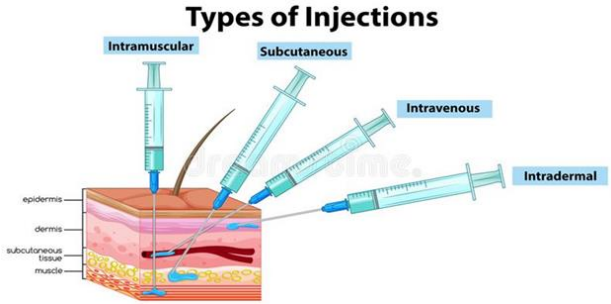
Pharmaceutical Dosage Forms



Pharmaceutical Dosage Forms and the PQRI

Orally Inhaled and Nasal Drug Products (**OINDP**)

Parenteral Drug Products (**PDP**)



Ophthalmic Drug Products (**ODP**)

Why These Dosage Forms?

Table 1

Examples of Packaging Concerns for Common Classes of Drug Products

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

From the 1999 FDA Container-Closure Guidance

The PQRI Initiatives

2006: The Product Quality Research Institute (PQRI) issued a Recommendation entitled “Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products”. The recommendation provided a scientific rationale and process to identify, quantify and establish the biological safety of leachables and/or extractables in OINDP, including performing Controlled Extraction Studies.

2008: The PQRI initiated an effort to extend the OINDP Recommendations to a additional dosage forms, Parenteral and Ophthalmic Drug Products (PODP), hypothesizing that the “good science” best demonstrated practices established for OINDPs can be extrapolated to PODPs.

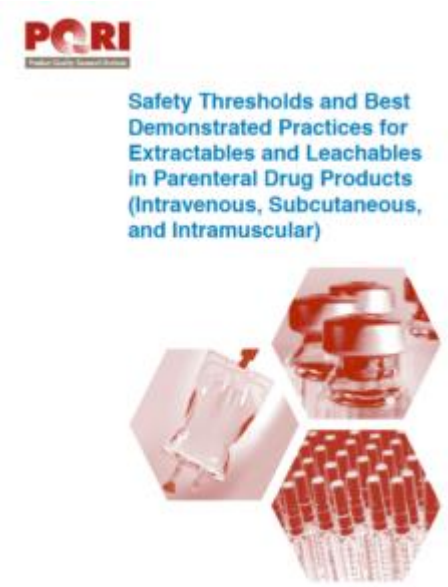
2013: The PQRI PODP Chemistry Team publishes the results of a chemical characterization of 5 plastics commonly used in pharmaceutical applications.

2016: The PQRI PODP Chemistry Team publishes the results of a simulation (migration) study.

2019: PDP and ODPs are separated as these two dosage forms have unique considerations.

2022: The PQRI PDP and ODP Best Demonstrated Practice Recommendations are published via the PDA Journal of Pharmaceutical Science and Technology.

The PQRI Documents



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PQRI

8 SEPTEMBER 2006

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

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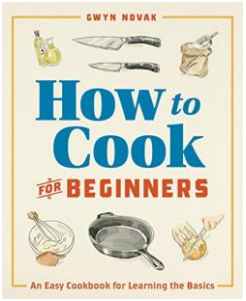
C. Houston, A.D. Rodrigues, B.B. Smith, T. Wang, M. Richardson. **Principles for Management of Extractables and Leachables in Ophthalmic Drug Products** PDA Journal of Pharmaceutical Science and Technology February 2022, pdajpst.2022.012744; DOI: https://doi.org/10.5731/pdajpst.2022.012744

What is (or is not) a Best Practice Recommendation?

A **Best Demonstrated Practice Recommendation is** a guide, made by recognized authorities in a relevant field of practice and proposed by an organization with a recognized and validated authority to do so, whose purpose is to direct and enable the practice of good science by competent practioneers in an effective, efficient, appropriate, rigorous and necessary manner.

A Best Demonstrated Practice Recommendation is not:

1. A Standard
2. A Specification
3. A Compendial Monograph
4. A Regulatory Guidance or Guideline
5. A Rule or Law
6. A Commandment
7. A Cook Book



Key Terms - Chemical

Leachables: 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) to the drug product formulation, with subsequent delivery to patients.#

Extractables: Those substances (both organic and inorganic) **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.

Other sources of leachables include:

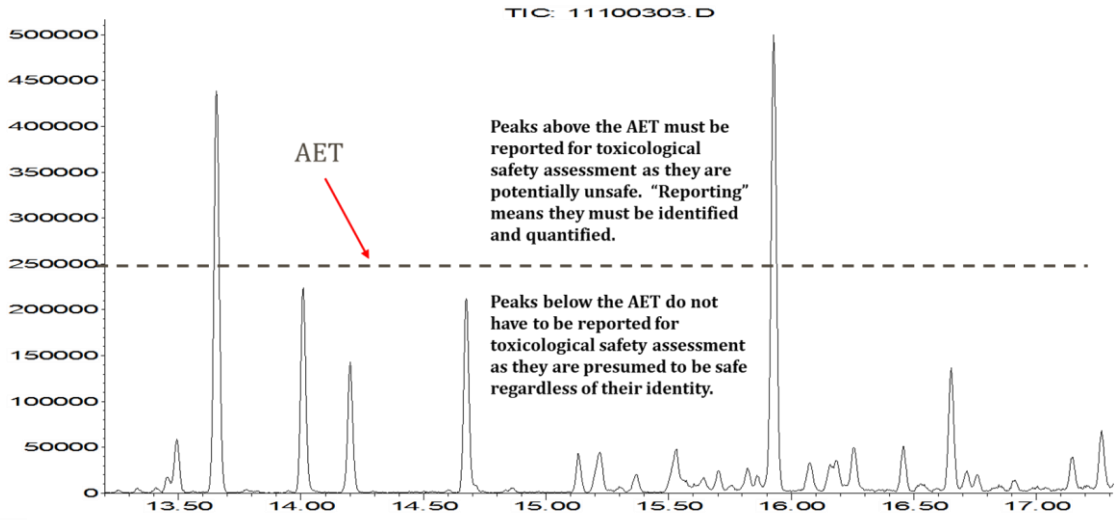
- Process-derived leachables, associated with the drug product's manufacturing system
- Environmental leachables, which are derived from the general environment that the packaged drug product encounters during shipping and storage

Key Terms - Thresholds

Safety Concern Threshold (SCT): the 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."

Qualification Threshold (QT): the threshold below which the leachable is not considered for safety qualification unless the leachable presents structure-activity relationship (SAR) or other safety concerns.

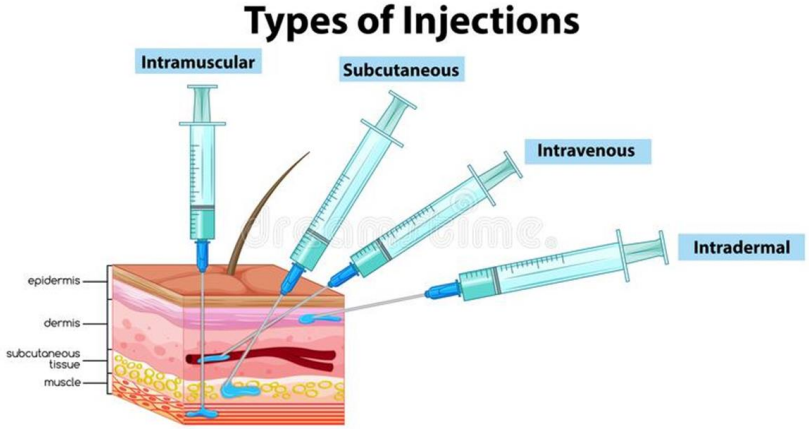
Analytical Evaluation Threshold (AET): that concentration of an extractable or leachable below which it does not have to be reported for safety assessment as its adverse effect on safety is negligible.



It does no good to report an extractable or leachable unless you can specify its identity and indicate its concentration.

Parenteral Drug Products, PDP

Parenteral drug products are injected through the skin or other external boundary tissue, or implanted within the body, **to allow the direct administration of the active drug substance**(s) into blood vessels, organs, tissues, or lesions. Parenteral dosage forms include solutions, suspensions, emulsions, sterile powders for solutions and suspensions (including liposomes), implants (including microparticles), and products that consist of both a drug and a device such as drug-eluting stents.



Parenterals = Injectables

Parenteral Drug Products, PDP

Routes of Parenteral Administration

- Intravenous injections and infusions
- Subcutaneous injections
- Intramuscular injections
- Intradermal injections
- Intra-arterial injections
- Intra-cardic injections
- Intraspinal injections
- Intra-articular injections

Classes of Parenteral Preparations

Based on Type of Packaging:

- Single dose units: ampoules, infusions, pre-filled disposable syringes
- Multiple dose units: multiple dose vials

Based on Fill Volume:

- Small volume parenteral (SVP): volume ≤ 100 mL
- Large-volume parenteral (LVP)**:** volume > 100 mL

PDP Recommendations - Thresholds

1. An SCT can be applied to leachables/extractables qualification of PDPs.
   a) Based on most PDP formulations, at **SCT of 1.5 µg/day for an individual organic leachable** can be used to calculate an AET.
   b) An SCT lower than 1.5 µg/day may be warranted for certain classes of compounds such as those within the cohort of concern.

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.

2. 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 leachables.

PDP Recommendations – Extractables and Extraction Studies

3. PDP extractables studies and assessments are appropriate for materials of construction, finished components, or complete packaging systems.
4. PDP extractables studies and assessments should include **aqueous-based extraction solvents** considering extraction pH, organic solvent content, and other appropriate extraction conditions (e.g., extraction time, extraction temperature, extraction technique, and sample-to-solvent ratio).

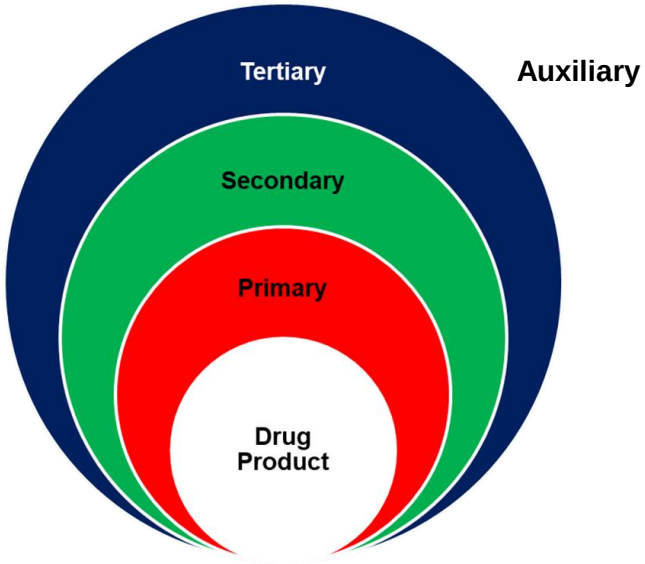
    a. Extractable studies for CCS used with **complex drug products should consider** the appropriate **solvent propensity** to establish the extractable profile to guide optimization of screening methods for leachables. Examples of complex products include:

        - 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)

PDP Recommendations – Secondary Packaging

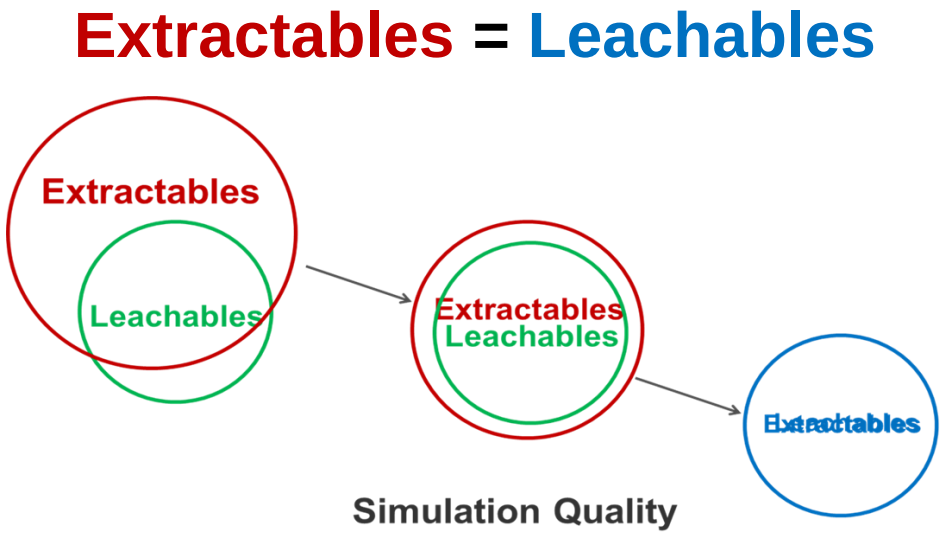
5. Where appropriate; extractables assessments, extraction studies, and leachables assessments for parenteral drug products and their packaging systems should **consider the possibility of migration across packaging barriers** (i.e., drug product labels, adhesives, inks, etc.).

"Layers" of Packaging



PDP Recommendations – Simulation Studies

6. With analytically challenging AETs (e.g., LVPs), **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. Use of a simulation study would need to be appropriately justified.



PDP Recommendations – Biologics

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 assessing leachable interactions affecting product quality attributes, i.e., degradation, oxidation, chemical modification, aggregation, immune adjuvant activity.

PDP Extractables and Leachables

For a high-risk drug products, e.g., injections, comprehensive studies of packaging components are generally required, involving:

- **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.** While most leachables are previously been identified as extractables, not all leachables correlate to 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.

A Key PDP Concept

Leachables are impurities in the drug product that are unrelated to drug substance manufacture and/or the active pharmaceutical ingredient (API).

Reaction products between a leachable and the API **ARE TECHNICALLY NOT** leachables, even though they are discovered during the screening of a drug product from leachables.

Impurities in Drug Products Potentially Surfaced in Leachables Screening#

- Expected Leachables (true leachables that were first extractables)
- Unexpected (unanticipated) Leachables
  - True leachables that were not first extractables
  - Leachables-related reaction products (e.g., MEHP formed by base hydrolysis of DEHP leached into the drug product)
  - Leachable-Drug Product interaction products (i.e., leachable + drug substance = “new” compound)
- Environmental Impurities

#Based on a differential study design that includes a comparison of a properly matched packaged drug product with a drug product blank.

PDP Recommendations – The Final Word

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.

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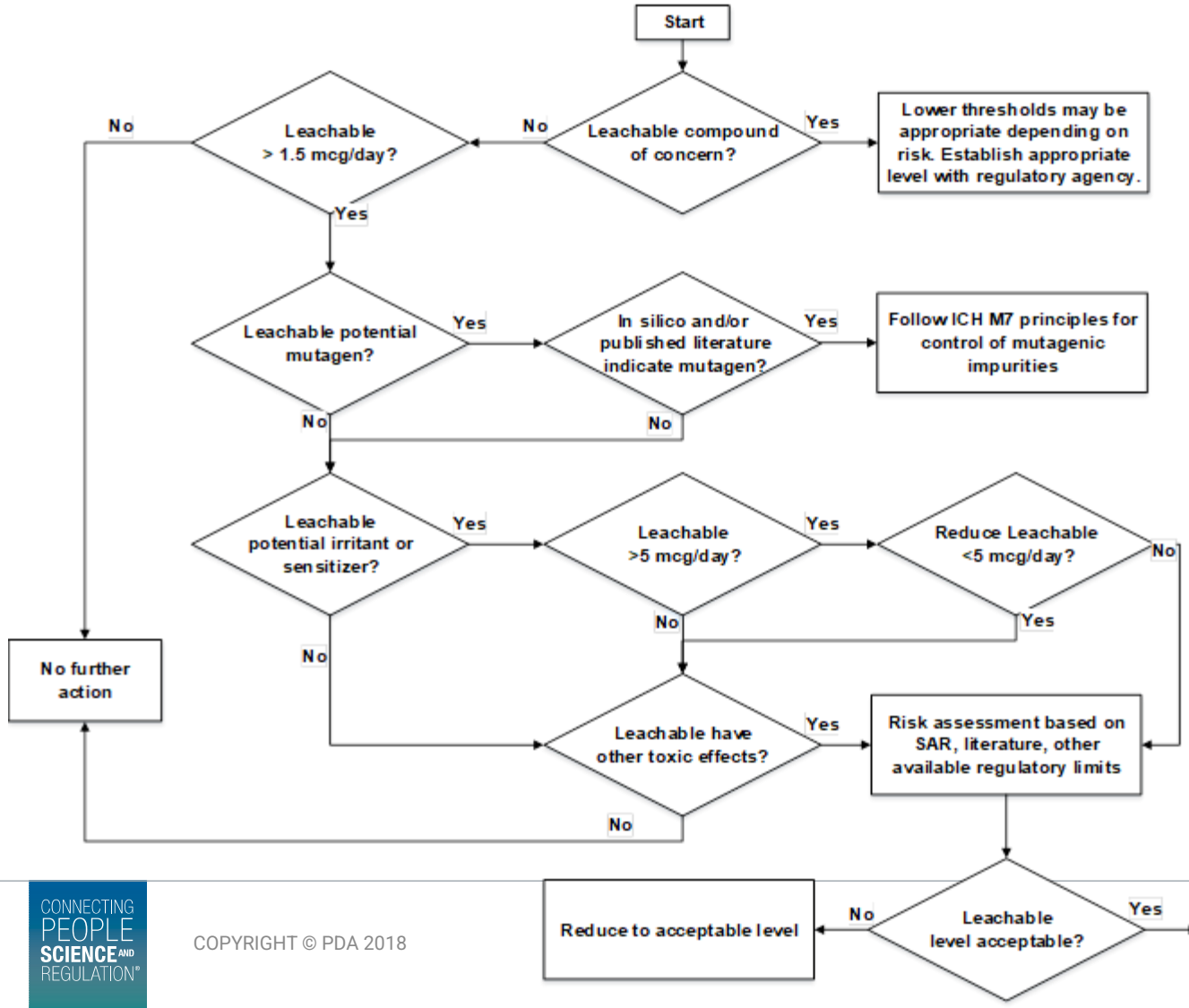
PDP E&L Safety Assessment Flowchart



E&L Requirements for PDPs

- **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**;
- **Leachables specifications including acceptance criteria**. ***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.***

PDP Controlled Extraction Studies

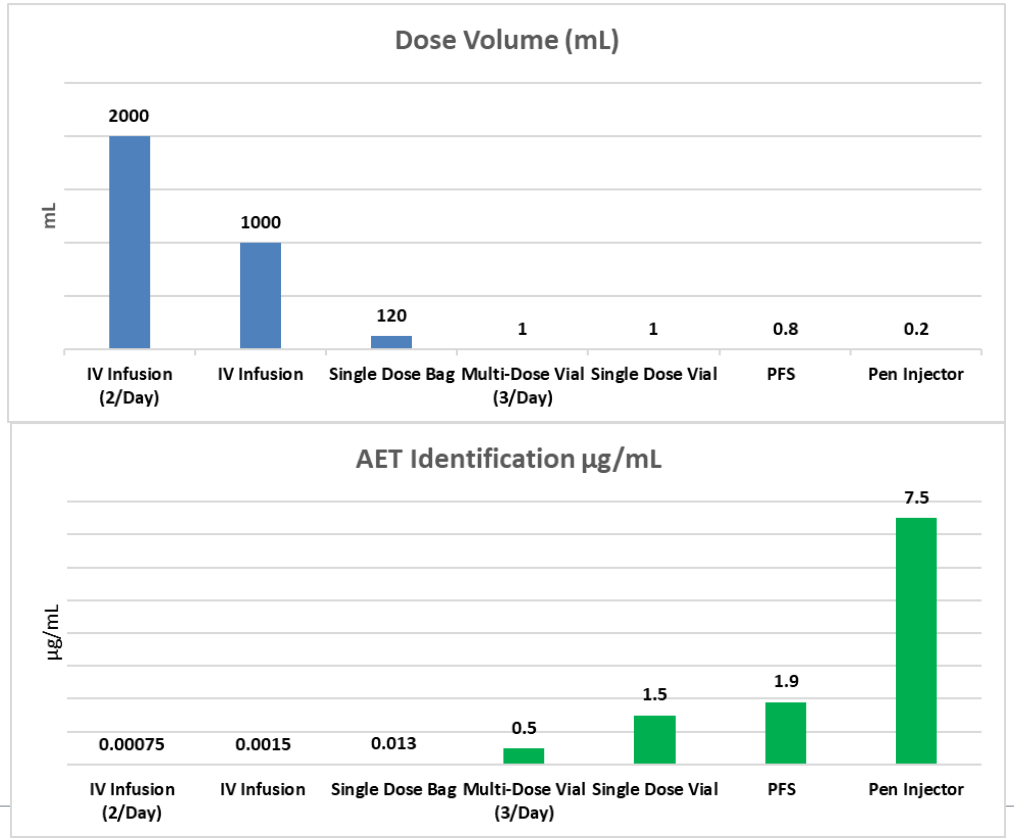
A Controlled Extraction Study is a laboratory investigation into the qualitative and quantitative nature of extractables profiles of a container/closure system, its critical components and/or assembled system with consideration of its materials of construction.

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
Justified Simulated conditions	Mimic Intend 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	

PDPs and AETs

A 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.



Uncertainty and the AET

Characterization of unknown leachables requires consideration of analytical uncertainty.

Uncertainty may typically include:

1. uncertainty in the proposed structure and elemental composition of the unknown leachable,
2. uncertainty in response of a 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 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 at the discretion of the investigator.

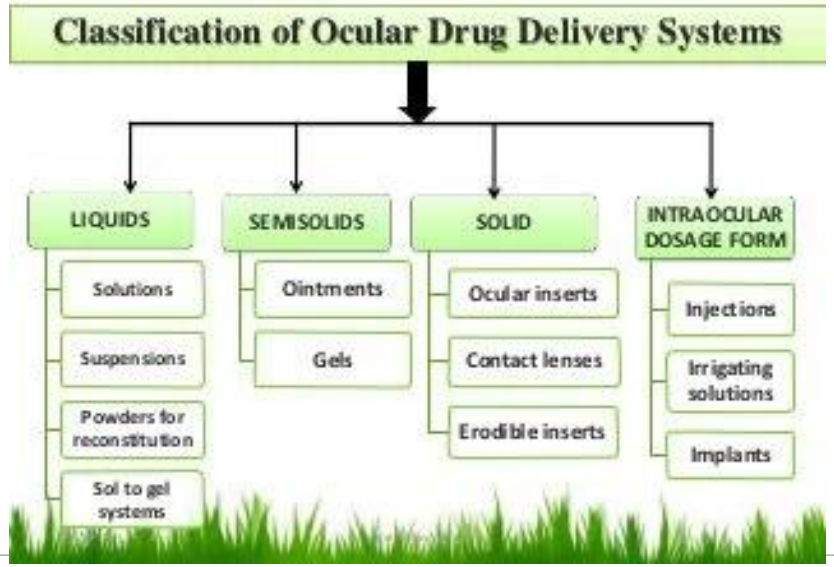
Analytical uncertainty for a particular analytical technique or method may be estimated based a response factor database that represents all known potential leachables.

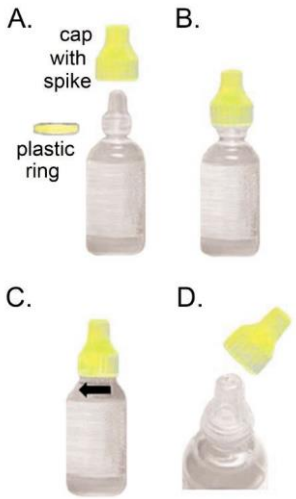
Biologics

- 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.
- The methodology to screen for leachables should consider compounds of toxicological concern as well as impact to biological product quality attributes.
- Due to the increasing complexity and diversity of 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.

Ophthalmic Drug Products, ODP

Ophthalmic preparations (eye preparations) are **sterile liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredients**. Ophthalmic products are intended for application to the conjunctiva, the conjunctival sac, or the eyelids.





ODP versus PDP

Similarities:

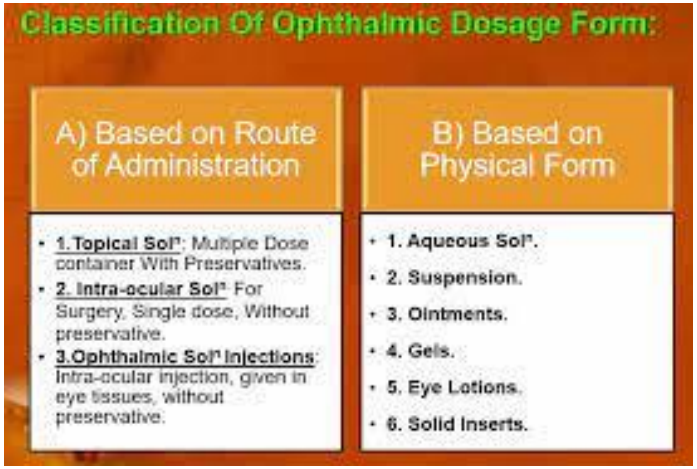
They "share the common attributes that they are generally solutions, emulsions, or suspensions, and are all required to be sterile"

Differences:

[1]. Route of administration (i.e., systemic vs. topical, respectively); thus the toxicological implications of leachables in these products are also different (e.g., systemic exposure vs. local irritation).
[2]. Dosing volumes for injections, especially LVP versus ODP, are very different.
[3]. Packaging systems for ODPs are quite different from, and generally less complicated than, those for PDP.

Therefore, ODP should be in a different category from injections when performing toxicological evaluation of leachables, thus warranting different considerations (e.g., potential for systemic exposure, toxicity endpoints, concentration- vs. TDI-based reporting)

Chemical Considerations for ODP



1. ODPs are generally aqueous (thus, extractions with non-polar vehicles are rarely appropriate).

2. ODPs are generally packaged in multi-dose packaging (thus, leachables are administered over several days in lesser quantities).

3. ODP packaging is typically semi-permeable, providing a pathway for leachables from secondary (and even tertiary) packaging and the environment.

Recommendations for ODP Extraction Studies

1. Researchers studying ODP should not restrict their attention exclusively to small, volatile or semi-volatile molecules (although different compounds migrate at different rates).
2. Sampling and shipping of secondary components for any extractable testing must always be done in a manner that minimizes loss of key extractables.
3. As leaching rates can vary significantly between specific leachables, acceleration of extraction (or leaching) studies where secondary packaging is critical must be treated cautiously.
4. Probable leachables can be determined by probing the properties of the packaging system and its associated extractables in a simulation study using a realistic solvent and realistic contact conditions.

Recommendations for ODP Extraction Studies

5. Many (but not all) ODP formulations contain polarity modifiers (e.g., demulcents, surfactants, preservatives such as benzalkonium chloride, etc.,) such that they are better sinks for leachables than straight water or simple buffered aqueous formulations.

6. A direct solvent extraction of the label, particularly a strong solvent irrelevant to the drug product such as hexane, will generate a significant number of extractables, not all of these targets will appear in the drug product as actual leachables.

7. A long term leachable study in the ODP of interest may still be required **as confirmation**.

A Holistic Approach to Minimize Leachables in ODP

1. Understand the compositions of the packaging materials (including both primary and secondary packaging) by obtaining information from the suppliers of the materials. Based on supplier information, a list of potential extractables/leachables may be compiled.

2. Conduct extractable/leachable studies on both primary and secondary packaging to evaluate the levels of the leachables. As described previously, simulation studies often work well in lieu of direct solvent extraction for profiling secondary packaging components.

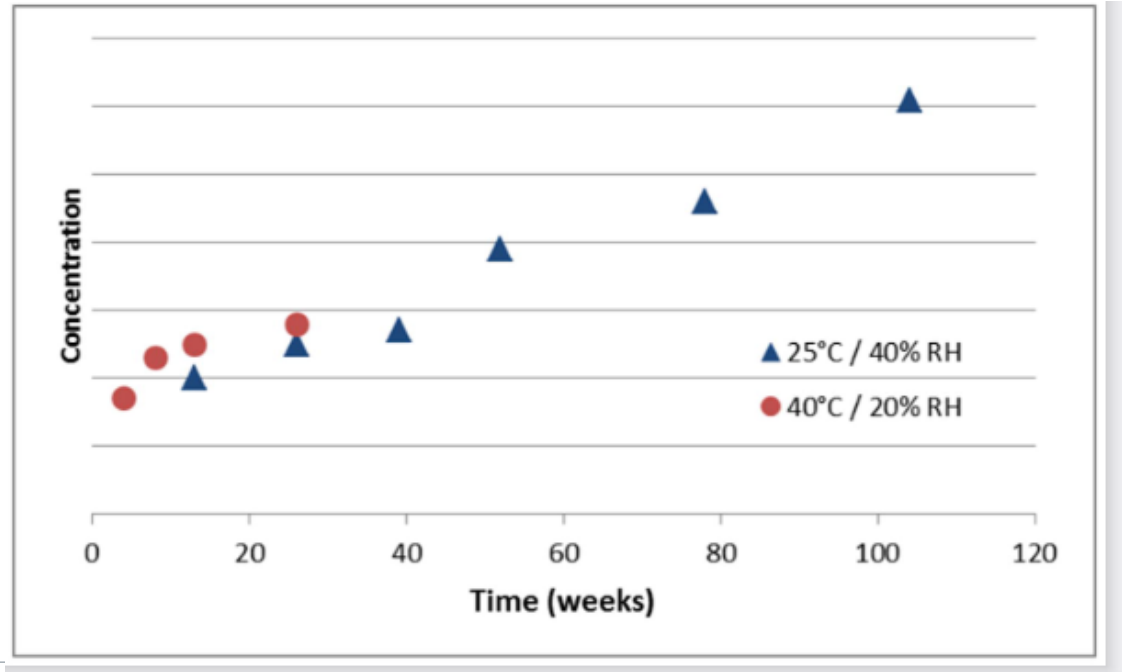
3. If certain leachables are determined to be present in the dosage form at considerable levels, the toxicological effects of these leachables should be evaluated.

4. Based on the above evaluation, select the proper packaging materials from the appropriate suppliers to limit and control the leachables at acceptable levels

Accelerated Extraction Studies

Accelerated studies are rarely predictive of long term, real time secondary packaging leachable levels. Accelerated stability studies run on products in semipermeable containers frequently underreport key secondary packaging leachables versus real time data.

Figure 1. Impact of Storage Temperature on Concentration Profiles of Secondary Packaging Leachables.



Safety Thresholds for ODP

The primary toxicological endpoints that need to be considered for qualifying leachables for topical ophthalmic products include (i) ocular irritation and toxicity; (ii) sensitization (skin) and (iii) genotoxicity.

Currently there is not a sufficient database developed on all the relevant toxicity endpoints to recommend specific safety thresholds (i.e., sensitization, ocular irritation) for ODP.

Safety Thresholds for ODP

Possible Practice for Dealing with Confirmed Leachables:

- Report in ppm concentration units, either mass per volume (µg/mL) or mass per mass (µg/g)
- At levels above 1 ppm, report that the leachable is present
- At levels of 10 ppm and above, identify the leachable
- At levels of 20 ppm and above, qualify the leachable in terms of patient safety impact

Thus, thresholds for ODP are concentration-based (and not dose based as they are for OINDP and PDP).

Ng, L. Current Regulatory Recommendations for Leachables in Ophthalmic Products, Product Quality Research Institute Workshop on Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products, Bethesda, MD, February 22–23, 2011.

If There was an AET for ODPs ...

Table 1. Comparison of Total Daily Intake to Concentration Values: Relationship to Dosing Frequency			
Total Daily Intake (µg/day)	**Number of Eyes Treated**	**Daily Dosing Frequency**	**AET Concentration (µg/mL, ppm)**
1.5	1	2	15.0
1.5	2	2	7.5
1.5	2	4	3.8
5	1	2	50.0
5	2	2	25.0
5	2	4	12.5

… it would be pretty high!

Safety Qualification of ODP Leachables

Qualification of leachables for ODP is similar to other drug types; however, the toxicological endpoints of concern would be focused on the potential for local toxicity rather than systemic effects.

Example; Summary of Leachables and Their ODP Toxicities

Compound Class	Conc. in ODP, µg/mL	Total Daily Exposure (µg/day)		Genetic Toxicity	Ocular Irritation-Toxicity	Sensitization
		Acute Indication	Chronic Indication			
Plasticizer	13	4.2	2.1	Negative genotoxicity but listed on California Proposition 65 list of hazardous substances with a recommended safe level of 9.8 µg/day (from all sources)	Non-irritant	No indication of sensitization at doses higher than its leachables level.
Antioxidant	7	2.2	1.1	No data available	Minimal reversible irritancy observed at 800x concentration on eye	No indication of sensitization at doses higher than its leachables level.
Resin Intermediate	22	7	3.5	Negative in all test systems	Strongly irritating when tested neat (10 mg) on rabbit eye; no data at lower concentrations	No indication of sensitization
Preservative	1.5	0.48	0.24	---	---	---
Unknown	< 1	Not calculated	Not calculated	---	---	---
Unknown	< 1	Not calculated	Not calculated	---	---	---

Safe Use Conclusions

- **Plasticizer:** Based on the available data and the exposure of the plasticizer relative to the recommended safe level on Prop 65, no additional testing is required for this material.
- **Antioxidant:** No additional safety testing is required.
- **Resin Intermediate:** Further evaluation/testing of ocular irritation/toxicity may be warranted.

Q&A

Thank you!

Contact the presenter at:
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