The PODP Best Demonstrated Practice Recommendations – Chemistry and Toxicology

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PODP Best Demonstrated Practice Recommendations – Chemistry: Background

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"[1]. The recommendation provided a scientific rationale and process to identify, quantify and establish the biological safety of leachables and/or extractables in OINDP. Included were Best Demonstrated Practices for performing Controlled Extraction Studies specifically for the OINDP dosage forms.

2008: The PQRI initiated an effort to extend the OINDP Recommendations to a second dosage form, Parenteral and Ophthalmic Drug Products (PODP). That organization's Chemistry Team hypothesizes that the "good science" best demonstrated practices that were established for the OINDP pharmaceutical development process can be extrapolated to container closure systems for PODP.[2]

2013: The PQRI PODP Chemistry Team is ready to talk about some of its Best Demonstrated Practice Recommendations.[3]

2016: The PQRI PODP Chemistry Team publishes the results of a simulation (migration) study.[4]

~~**2017 2018**~~ **(2019):** The PQRI PODP Best Demonstrated Practice Recommendations will be published. Training sessions were held (April 18 – 19; USP, Washington, DC)

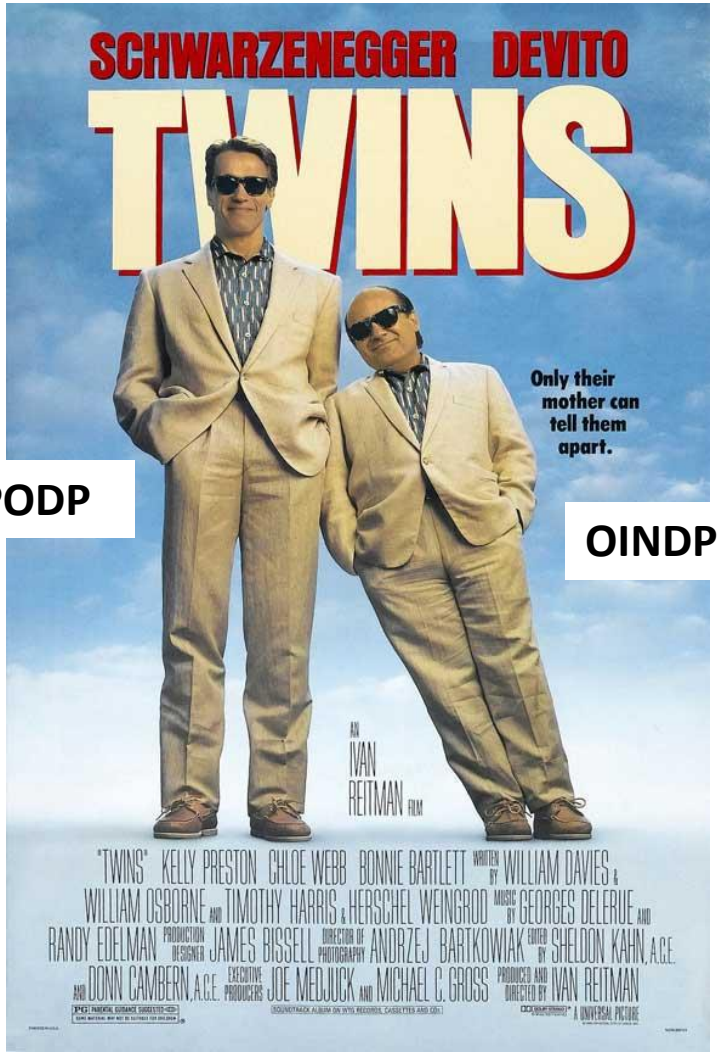
What is a Best Demonstrated Practice Recommendation?

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

The Challenge facing the PODP Team



PODP

OINDP

Attributes that OINDP and PODP Do Not Share: Daily Dose

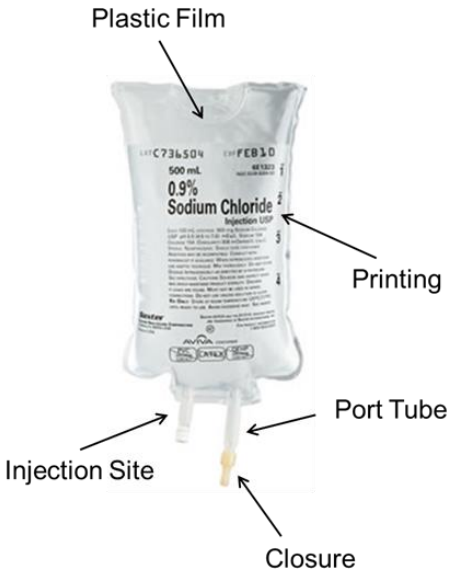
Metered Dose Inhaler
(small volume - large number of doses)

Large Volume Parenteral
(large volume - small number of doses)

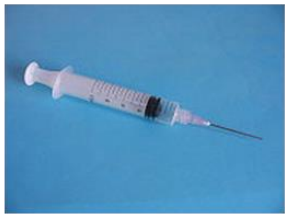
Attributes that OINDP and PODP Do Not Share: Materials of Construction

Metered Dose Inhaler

Parenteral Solution for Infusion



Prefilled Syringe



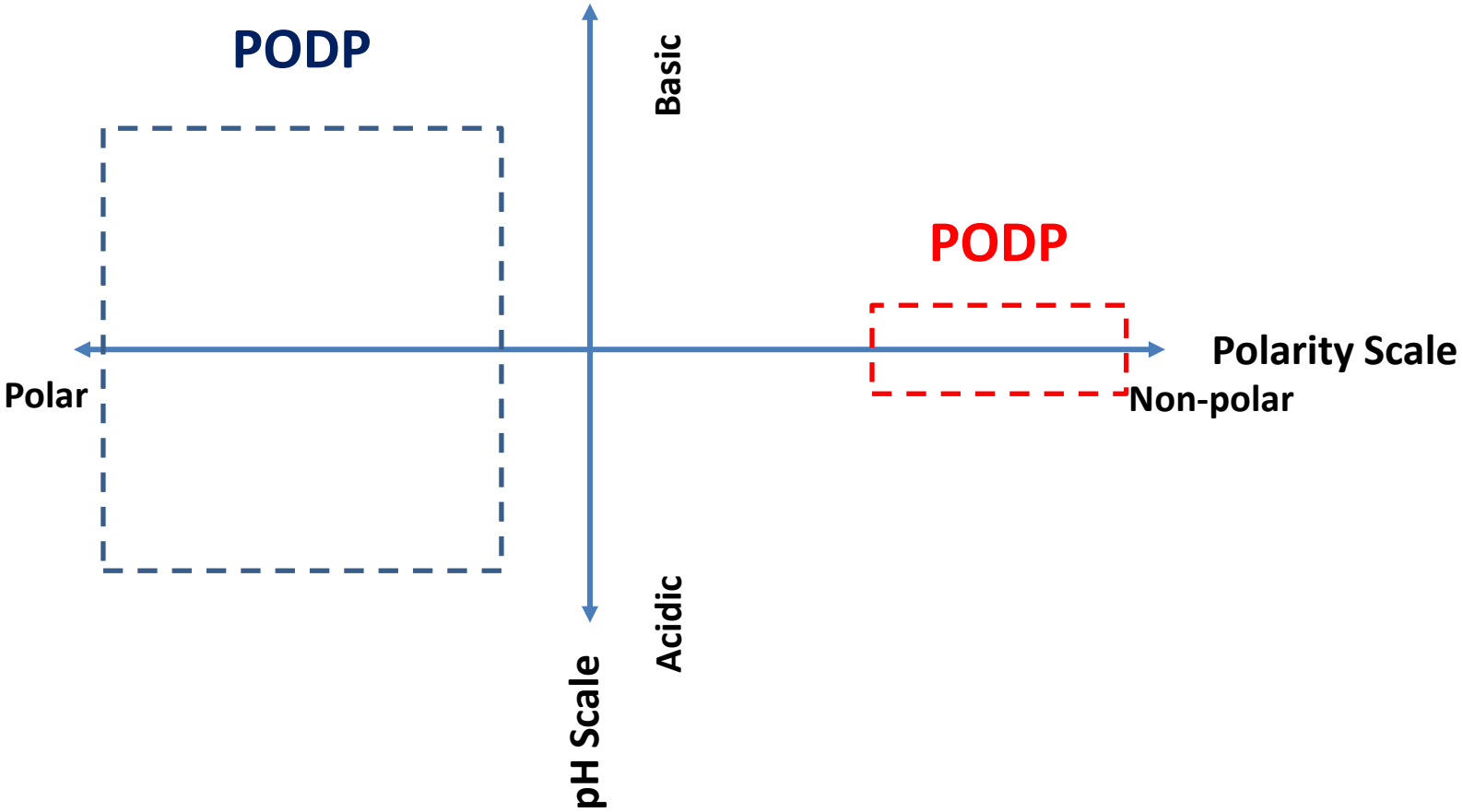
Vial Products

Ophthalmic Bottles

Tip Cap

Barrel

Attributes that OINDP and PODP Do Not Share: Chemical Formulation



Attributes that OINDP And PODP Do Not Share: Additional Attributes

1. **Dosing Regimen: Acute versus Chronic.**
2. **Patient Population and Disease State Treated.**
3. **Heat History.**
4. **Others???**

Bottom Line:

It is not a trivial exercise to extrapolate the OINDP Conclusions and Recommendations to PODPs.

PODP Best Demonstrated Practice Recommendations – Chemistry: Overall Conclusion

It is relevant and appropriate to note that

1. *The data generated and experiences gained in the PODP studies, which were performed on materials relevant for PODP products and with methods appropriate for PODP dosage forms, and*

2. *The accumulated experiences and technical knowledge of the individual members of the PODP Chemistry Working Group*

support the spirit, if not the exact letter, of all the (OINDP) recommendations as they are applied to the PODP situation.

PODP Best Demonstrated Practice Recommendations – Chemistry: Types of Changes from OINDP to PODP

1. **No change at all.**

2. **Change with Clarification.**

3. **Change with Modification.**

4. **Addition.**

Note that you do not see: **Remove** or **Replace**

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP - PODP Unchanged

Controlled Extraction Studies (CES) should:

- Include careful sample preparation based on a knowledge of the analytical techniques used,
- Include a defined and systematic process for the identification of individual extractables,
- Include a re-examination of supplier information describing component formulation.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP - PODP with Clarification

OINDP Recommendation:

A Controlled Extraction Study should include multiple analytical techniques.

PODP Recommendation:

A Controlled Extraction Study should utilize an analytical process with thoughtfully chosen **multiple** orthogonal **analytical techniques** for the purpose of discovering, identifying and quantifying relevant and appropriate extractables. Included in the analytical process is a consideration of the completeness of the analytical process.

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Discussion:

The language in the PODP Recommendation captures concepts that were included in the OINDP Recommendations document but not specifically captured in the abbreviated OINDP Recommendation statement.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP - PODP with Clarification

OINDP Recommendation:

Scientifically justifiable analytical thresholds for extractables and leachables in OINDP can be established.

PODP Recommendation:

Scientifically justifiable analytical thresholds for extractables and leachables in PODP can be established.

However:

The absolute values of the analytical thresholds will differ, OINDP versus PODP, consistent with the inherent differences in these dosage forms, including their dosing and conditions of use.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP – PODP with Clarification

- Material characterization (i.e., identify and quantify the additives and ingredients in a material, as ingredients and additives may be used to forecast extractables),
- Packaging assessment (i.e., identify extractables as a means of forecasting leachables in a specific dosage form, simulation study),
- Quality Control (i.e., exercise control over the quality of incoming materials of construction for a packaging system).
- Change Control (i.e., respond to changes in the materials and/or processes associated with a packaging system.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP – PODP with Modification

OINDP Definition:

Controlled Extraction Study (CES) - a laboratory investigation into the qualitative and quantitative nature of extractables profiles of critical components of an OINDP container/closure system.

PODP Definition:

Controlled Extraction Study – a laboratory investigation into the qualitative and quantitative nature of extractables profiles of a container/closure system and/or **its critical components** and **materials of construction**.

Discussion:

The language in the PODP Recommendation expands the scope of the CES to make it more generally applicable to all dosage forms and to include materials of construction to capture materials characterization studies.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP - PODP with Modification

OINDP Recommendation:

A Controlled Extraction Study should:

1. **Employ vigorous extraction with multiple solvents of varying polarity, and**
2. **Incorporate multiple extraction techniques.**

PODP Recommendation:

Controlled extractions studies should use a combination of **multiple extraction solvents** and **extraction techniques** as appropriate for, and consistent with, the intent and purpose of the controlled extraction study.

Discussion:

The language in the PODP Recommendation captures concepts that were included in the OINDP Recommendations document but not specifically captured in the abbreviated OINDP Recommendation statement.

PODP Best Demonstrated Practice Recommendations – Chemistry: The Simulation Study

In situations of analytically challenging Analytical Evaluation Thresholds (AETs) for certain PODPs (e.g., large volume parenterals), a special type of extraction study termed a "Simulation Study," should be applied in lieu of or to supplement drug product leachables studies. These studies can establish an extractables profile representing the worst-case leachables profile of the packaged drug product that the study simulates.

"since the extractables profile is the same as the leachables profile, then one can safety assess the extractables profile and not perform subsequent leachables testing." The appropriateness of such an answer rests on the rigor of the simulation and its associated **justification**.

PODP Best Demonstrated Practice Recommendations – Chemistry: The Simulation Study

Table 3.3. Comparison of Key Operational Parameters, Simulation Study Versus Leachables Study

Operational Parameter	Value for Simulation Study	Value for Leachables Study
Test Sample	Simulating solvent (s)	Drug product
Test System	Marketed Packaging System[1]	Marketed Packaging System
Test Conditions	Accelerated clinical use	Clinical Use[2]

Notes:

[1]In some situations, a simulation study may use an exaggerated packaging system. For example, if the packaging system has a single port tube and the purpose of the study is to assess leachables derived from the port tube, then the exaggerated system could be constructed with two ports.

[2]It is the case that leachables studies (for example leachables testing performed as part of a stability study) could also include accelerated clinical use conditions.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP - PODP by Addition

PODP Recommendation:

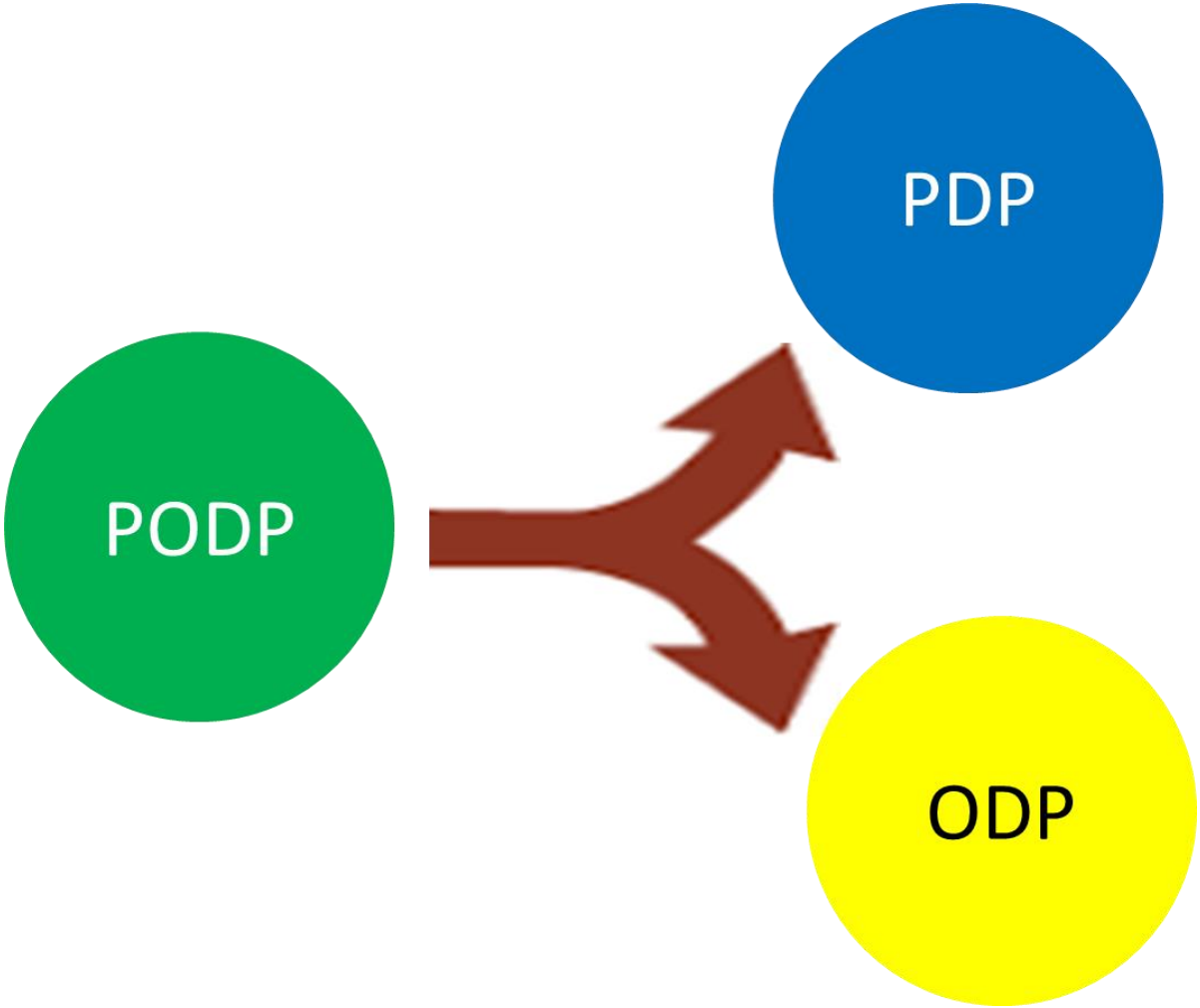
When assessing the potential product impact of leachables, the following factors must be considered:

- The ability of the leachable to directly affect patient safety due to the inherent toxicity of the of the leachable,
- The ability of the leachable to indirectly affect patient safety due to the leachable's interaction with the drug product and its ingredients,
- The ability of the leachable to impact the product's general chemical and physical characteristics (e.g., pH, appearance),
- The ability of the leachable to impact the drug product's efficacy and/or stability, and
- The ability of the leachable to impact drug product quality attributes which are not specified above.

Discussion:

The OINDP Recommendations were primarily focused on patient safety as affected by the inherent toxicity of leachables, although the more general effect of leachables on product quality was discussed in the OINDP Recommendation document. The PODP drug products may, in certain cases, be more generally susceptible to packaging-related quality issues (e.g., protein biologics).

PODP Best Demonstrated Practice Recommendations – Chemistry: At some point, PDPs and ODPs Diverge



PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP - PDP with Modification

OINDP Recommendation:

A Controlled Extraction Study should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted safety concern threshold.

PDP Recommendation:

A Controlled Extraction Study for a PDP should be guided by an Analytical Evaluation Threshold (AET) that is based on an accepted and relevant safety standard such as the **safety concern threshold.**

Discussion:

The OINDP Recommendation has been modestly expanded to include relevant and appropriate safety standards and thresholds other than the safety concern threshold, as the application of the SCT may not be appropriate for some dosage forms (e.g., ophthalmic). It is noted that use of the AET to guide the Controlled Extraction Study will affect the strategies and tactics used to design and complete the Study.

PODP Best Demonstrated Practice Recommendations – Chemistry: OINDP - ODP with Modification

OINDP Recommendation:

Controlled Extraction Studies should be accomplished on all critical components incorporated into the container/closure systems of every type of OINDP.

ODP Recommendation:

Extractables and leachables assessments of drug products in semipermeable container closure systems (e.g., ODP in LDPE) must include packaging components that do not make direct drug product contact (e.g., labels, product information inserts, unit cartons).

Discussion:

The semi-permeable container closure systems that are more typically used with ophthalmic drug products are poor barriers and thus it is more likely that ophthalmic drug products would contain foreign impurities that are associated with secondary, tertiary and/or auxiliary sources.

PODP Best Demonstrated Practice Recommendations – Chemistry; Cited References

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

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

[3]D. Jenke, J. Castner, T. Egert, T Feinberg, A. Hendricker, C. Houston, D.G. Hunt, M. Lynch, A. Shaw, K. Nicholas, D.L. Norwood, D. Paskiet, M. Ruberto, E.J. Smith, F. Holcomb. Extractables characterization of five materials of construction representative of packaging systems used for parenteral and ophthalmic drug products. PDA J Pharm Sci Technol. 76(5): 448-511 (2013).

[4]D. Jenke, T. Egert, A. Hendricker, J. Castner, T. Feinberg, C. Houston, D.G. Hunt, M. Lynch, L. Markovic, K. Nicholas, D.L. Norwood, D. Paskiet, M. Ruberto, E.J. Smith, and F. Holcomb. Simulated Leaching (Migration) Study for a Model Container-closure System Applicable to Parenteral and Ophthalmic Drug Products (PODPs). *PDA J Pharm Sci Technol.* **71(2)**: 68-87 (2017).

PDP and ODP Best Demonstrated Practice Recommendations – Toxicology

The issue of safety is not exactly the same for PDP and ODP. Oversimplifying greatly,

- Safety assessment of leachables in ophthalmics requires a greater focus on local topical effects and recognizes the importance of irritation and toxicity as key endpoints.
- Safety assessment of leachables in parenterals requires a greater focus on systemic effects and recognizes cancer risk as a key endpoint.
- As a result, the PDP recommendations around thresholds will differ from those for ODP.

PDP and ODP Best Demonstrated Practice Recommendations – Toxicology, PDP Thresholds

OINDP Thresholds	
Qualification Threshold (QT) = 5 µg/day	Safety Concern Threshold (SCT) = 0.15 µg/day

PDP Thresholds		
Class I, General Toxicity (QT) = 50 µg/day**	Class 2, Sensitizers/Irritants = 5 µg/day	Class 3, Mutagens (**SCT**) = 1.5 µg/day

**Still under review by the FDA

Reconciling PDP Thresholds with ICH M7 TTCs

Acceptable Daily Intake, µg/day				
Toxicological Endpoint	Duration of Therapy			
	≤ 1 month	1 – 12 months	1 – 10 years	> 10 years
Mutagenicity, TTC (SCT)	120	20	10	1.5
Sensitization – irritation[1]	5	5	5	5
General[1], QT	50	50	50	50

[1]These endpoints are not affected by Duration of Therapy as they do not exhibit a dose-response relationship.

PDP and ODP Best Demonstrated Practice Recommendations – Toxicology, ODP Practices

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.

Thresholds based on "available data and industry practices" are difficult to establish for ODP as ocular toxicity data is rarely available.

Generally Accepted Practice for 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

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

PDP Best Demonstrated Practice Recommendations – Addition - Compatibility with Biopharmaceuticals

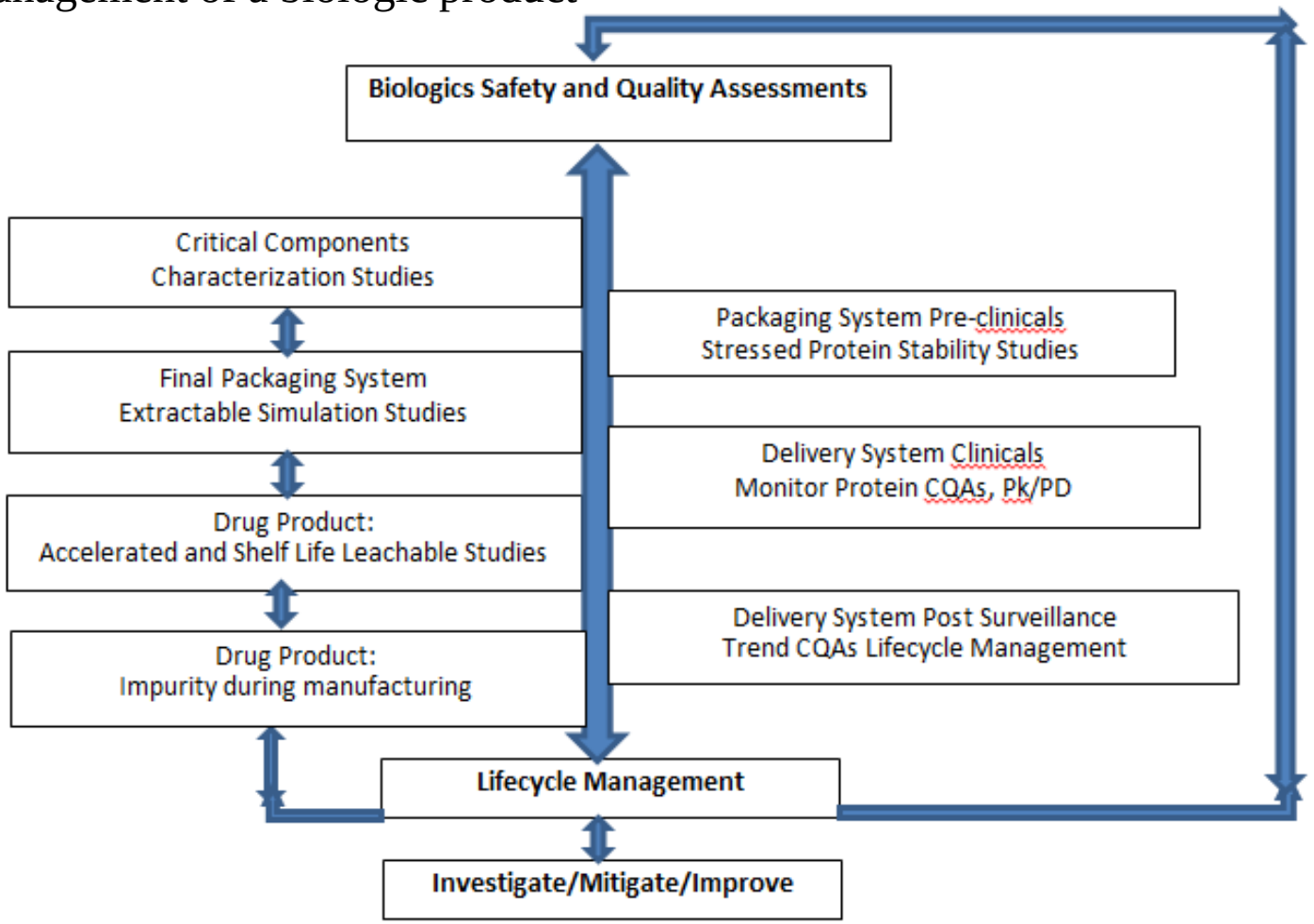
Beyond safety considerations, biotechnology products require additional considerations of the product quality attributes as biotechnology products are more susceptible to structural modifications than are chemically synthesized drug products, primarily due to their:

- large molecular weights,
- complex structures,
- abundance of binding sites on their surfaces

Structural modifications may alter product quality, safety, and/or efficacy.

PDP Best Demonstrated Practice Recommendations – Addition - Compatibility with Biopharmaceuticals

Figure 5.1. Evaluation of biologic safety and quality throughout the lifecycle management of a biologic product



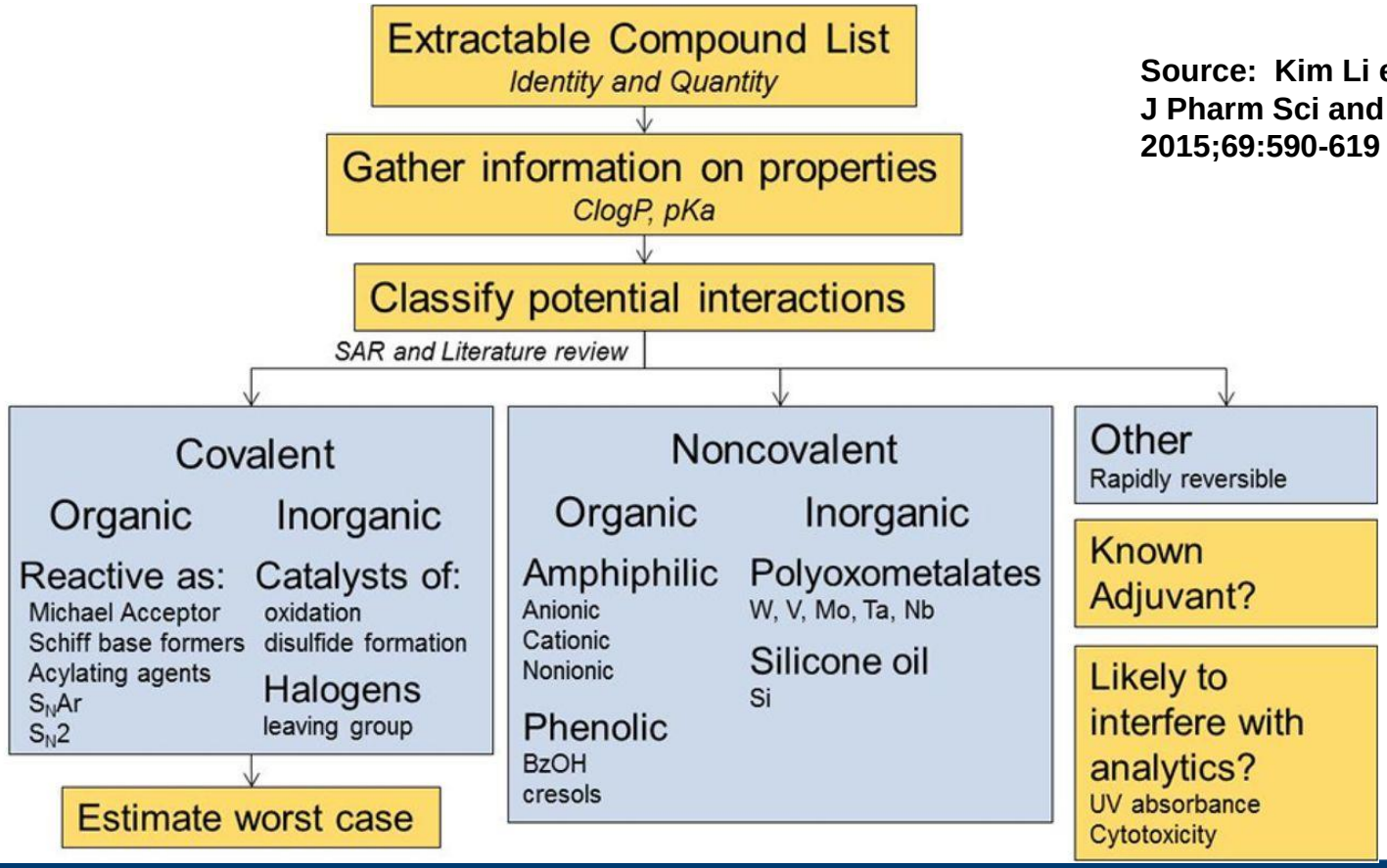
PDP Best Demonstrated Practice Recommendations – Addition - Compatibility with Biopharmaceuticals

Quality assessments for biotherapeutics would include identifying and mitigating risks related to the following:

- Changes in the dosage form purity, safety, stability
- Changes in the product appearance, physicochemical and molecular structure
- Loss of potency due to absorption or adsorption of the active drug substance
- Degradation of the active drug substance induced by a leachable
- Reduction in the concentration of API or excipient due to absorption or adsorption
- Leachable-induced changes in formulation pH, product degradation, precipitation, aggregation
- Changes in the packaging component or system (discoloration, surface, function, brittleness etc.)

PDP Best Demonstrated Practice Recommendations – Addition - Compatibility with Biopharmaceuticals

Schematic representation of a proposed strategy for assessing the potential impact of extractable compounds on product attributes



Source: Kim Li et al. PDA J Pharm Sci and Tech 2015;69:590-619

PDP Best Demonstrated Practice Recommendations – Addition - Compatibility with Biopharmaceuticals

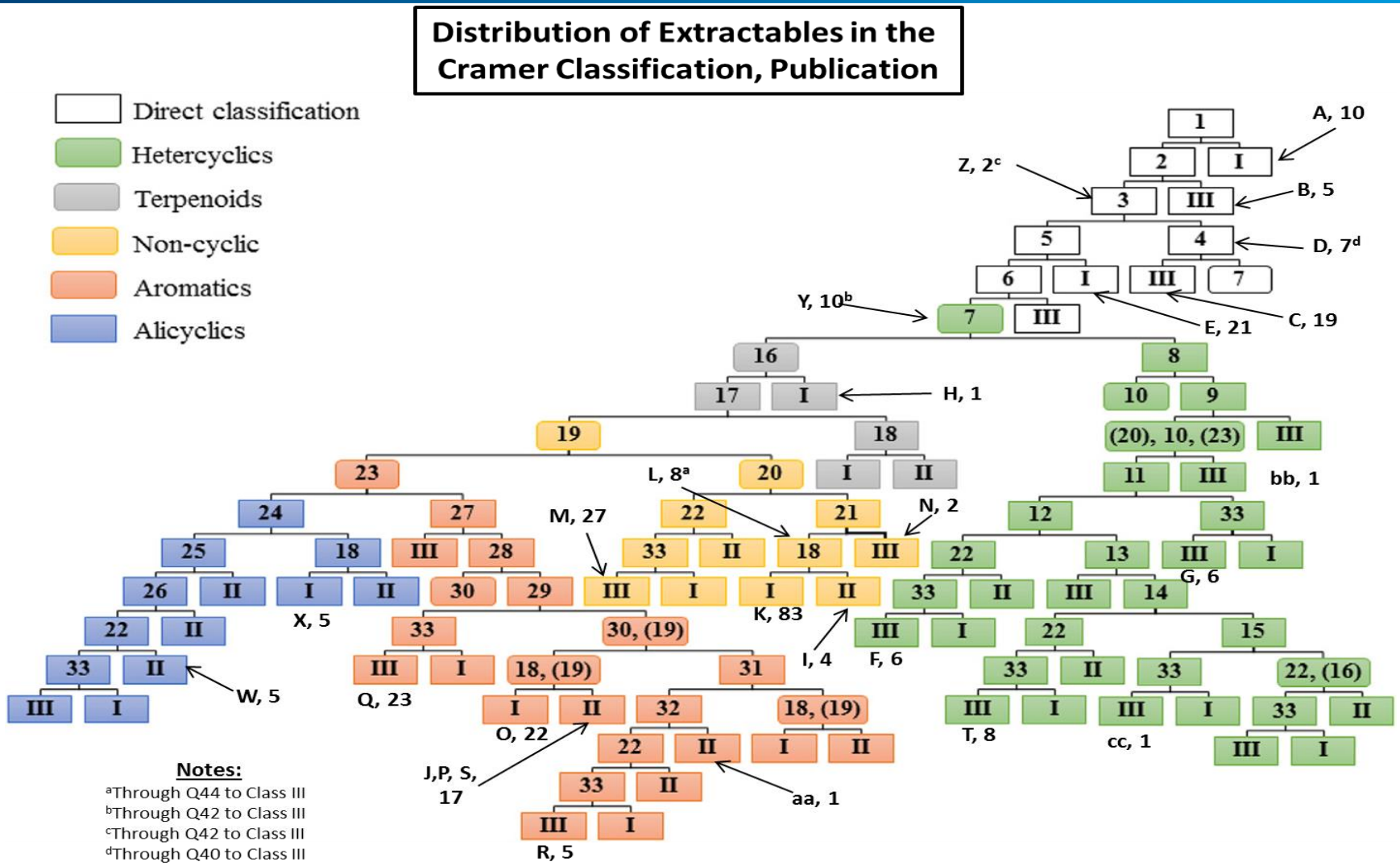
"Because of the irreversible nature of the protein modification, covalent binding presents a higher risk of affecting product quality attributes as compared to noncovalent binding"

A Partial List of Extractables that Could Induce Protein Modification via Covalent Binding

Agents or Mechanisms	Compounds
Michael acceptors	(2E,9Z)-Ethyl 12-oxoctadeca-2,9-dienoate 1-((2-Ethylheptyl)oxy)-**1**-oxopropan-2-yl (1-((2-ethylhexyl)oxy)-1-oxopropan-2-yl) maleate 1-((3-Butyl-4-methylcyclohexa-1,5-dien-1-yl)methoxy)-1-oxopropan-2-yl (1-((4-ethyl-3-methylbenzyl)oxy)-1-oxopropan-2-yl) maleate 1,6-Hexanedioldiacrylate 13-oxooctadeca-9,11-dienoic acid 1-Hydroxy-2-propyl methacrylate 1-oxo-1-(((2E,5E)-2-((Z)-prop-1-en-1-yl)octa-2,5-dien-1-yl)oxy)propan-2-yl (1-oxo-1-(((E)-2-((Z)-prop-1-en-1-yl)hept-2-en-1-yl)oxy)propan-2-yl) maleate 2,6 Di(tert-butyl)-4-hydroxy-4-methyl-2,5-cyclohexandien-1-one (BHT-OH) 2,6-di-tert-butyl-4-methylene-2,5-cyclohexandienone (BHT-quinone-methide) 2,6-Di-tert-butyl-p-benzoquinone (BHT-quinone) 2-Hydroxypropyl methacrylate 3-tert-Butyl-4-hydroxyanisole 4-ethyl 1-methyl 2-hexanoylsuccinate 7,9-bis(tert-butyl)-1-oxaspiro[4,5]deca-6,9-diene-2,8-dione (BODDD) Acrylic Acid Bis(1-((2-ethylhexyl)oxy)-1-oxopropan-2-yl) maleate Isomers Dibutylmaleate Dihexyl maleate (Methyl maleate) Isobornyl methacrylate Methacrylic acid (MAA) Tetraethylene glycol dimethacrylate Tetrahydrofurfuryl methacrylate

Source: Kim Li et al. PDA J Pharm Sci and Tech 2015;69:590-619

PDP Best Demonstrated Practice Recommendations – Biopharmaceutical Compatibility, the Ultimate Goal



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