



The PODP L&E Working Group: Status and Outlook

Thomas N. Feinberg, Ph.D.
Director, Structural Chemistry Services
Catalent Pharma Solutions
31 March 2011

1

IPAC-RS 2011 Conference

PQRI Mission Statement

The Product Quality Research Institute (PQRI) is a non-profit consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality and development.

By virtue of its diverse membership, PQRI provides a unique forum to focus critical thinking, conduct research, exchange information, and propose methodology or guidance to pharmaceutical companies, regulators, and standard setting organizations.



2

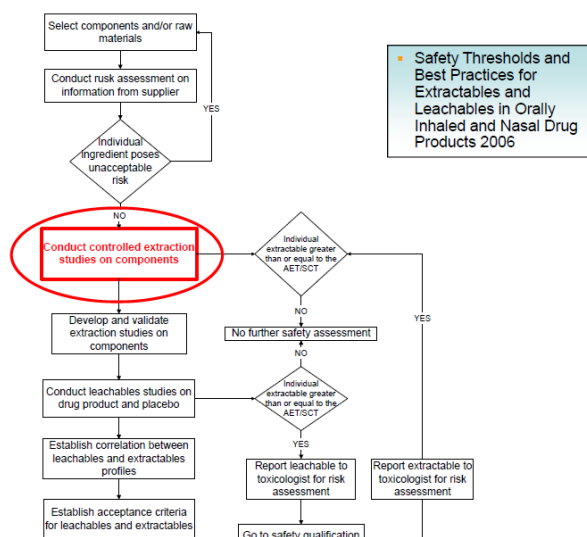
IPAC-RS 2011 Conference

Leachables Extractables 2001 PQRI OINDP L&E Hypotheses

- Scientifically **justifiable thresholds** can be developed for the reporting and safety qualification of leachables in OINDP and the reporting of extractables from critical components used in corresponding container/closure systems.
- Safety qualification of extractables would be scientifically justified on a **case-by- case basis**

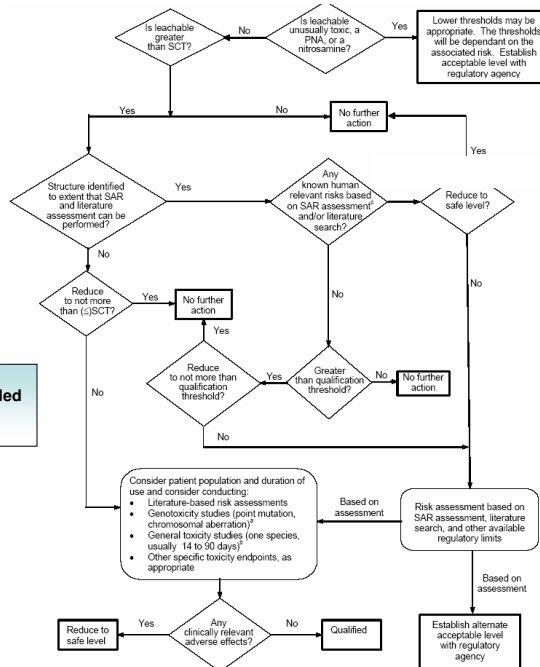


Central Activity of L&E: Controlled Extraction Study



Safety Qualification Decision Tree

Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products 2006



Controlled Extraction Studies PQRI OINDP Guiding Principles

- Employ vigorous extraction with multiple solvents
- Incorporate multiple extraction techniques.
- Include careful sample preparation based on knowledge of analytical techniques to be used.
- Employ multiple analytical techniques
- Include a defined and systematic process for identification of individual extractables
- “Definitive” extraction methods should be optimized.
- Revisit Supplier Information
- Guided by an Analytical Evaluation Threshold (AET) that is based on an accepted safety evaluation threshold
- Identify risk to leachables early in the pharmaceutical development process



PQRI OINDP Recommendations

- Best Practice Controlled Extraction studies are **not meant to be prescriptive** or to exclude other scientifically valid approaches to the analytical techniques, methods, or control strategies
- OINDP recommendations represent a consensus with-in the Working Group on current best practices with-in the pharmaceutical industry and are **designed to reduce the level of uncertainty** with-in the pharmaceutical development process for OINDP



Leachables and Extractables 2007

Hypothesis #1

Better safe than...

“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.”



Leachables and Extractables 2007

Hypothesis #2

If it's good for OINDP...

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



Leachables and Extractables 2007

Hypothesis #3

QbD QED

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



PQRI PODP Research Project Plan

Toxicology Task

- Form a toxicology subgroup that will extrapolate the OINDP SCT and QT concepts previously developed by PQRI and determine how they can be utilized to qualify the safety of leachables in PODP.



PQRI PODP Research Project Plan

Chemistry Task

- Form a chemistry subgroup that will extrapolate the AET concept for its utility in the evaluation of extractables and leachables in PODP. The subteam will investigate issues such as but not limited to:
 - * Addition of water and aqueous systems to the solvent systems considered in the OINDP document
 - * Addition of materials, components and/or packaging systems applicable to PODP
 - * Consideration of extraction and/or analysis methods which have unique applicability to PODP



Scope

- Dosage forms relevant to PODP Work Plan
 - Small-Volume Parenterals
 - Prefilled Syringes
 - Large-Volume Parenterals
 - Ophthalmics

Nice to Consider

- Disposable systems in the absence of defined and specific regulatory guidance for the safety assessment and qualification
 - Such as tank liners, storage containers, filters, tubing should be assessed

consistent with the principles of QbD and good science



L&E Workshop 2011

- Regulatory Focus
 - Supply Chain Control
 - Science Based Decisions and Justifications
- Challenges
 - Dosage Forms and Route of Administration
 - Case by Case
 - Comprehensive Knowledge Base
 - Managing Change
 - Improve
 - new discoveries/materials and/or patient needs
 - N+ Suppliers
 - global supply chain

The Starting Point

- 0.15 µg Total Daily Intake
 - Everyday life time



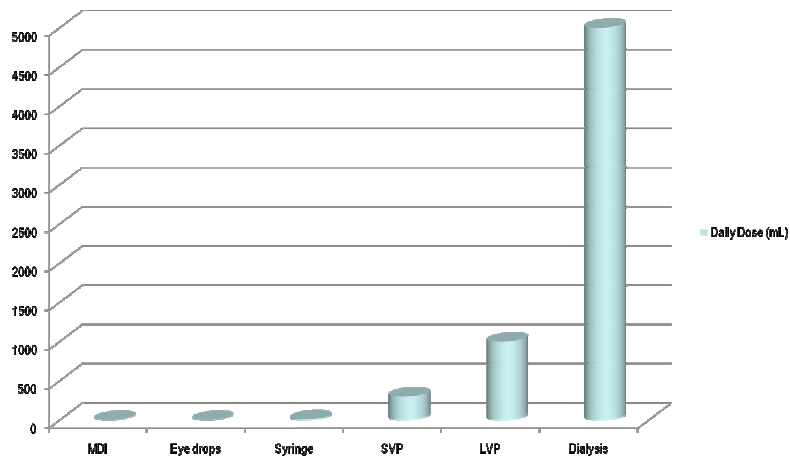
- How Low to Go
 - Dose
 - Duration
 - Patient Population
 - Other unique Attributes



IPAC-RS 2011 Conference

17

Daily Dose Volumes - General Classes



Impact to Leachable Detection

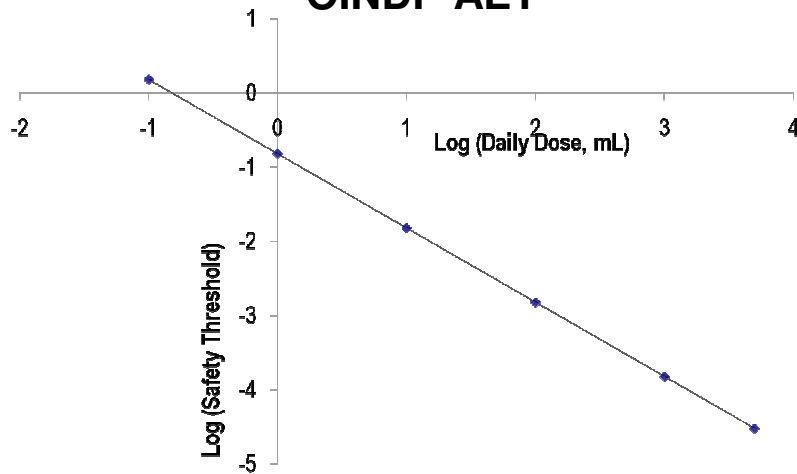
Jenke PQRI PODP Workshop February 22-23, 2011



IPAC-RS 2011 Conference

18

Effect of Daily Dose Volume on the OINDP AET



The value of the Analytical Threshold decreases in direct proportion to the increase in Daily Dose Volume.



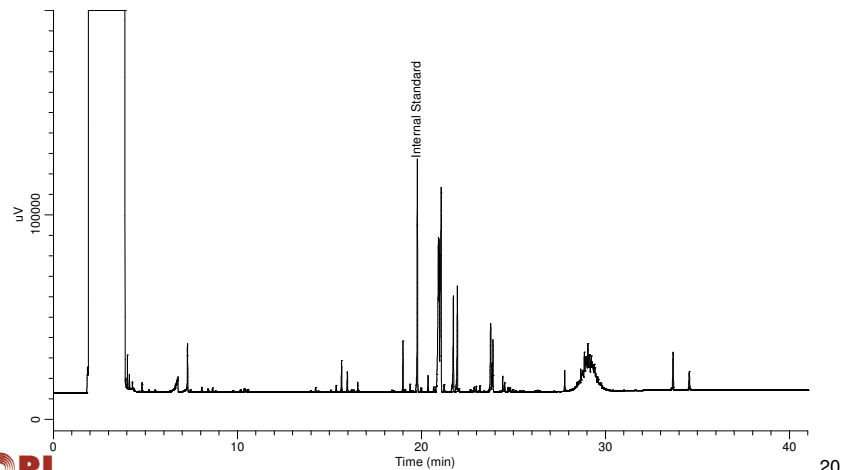
Jenke PQRI PODP Workshop February 22-23, 2011

19

IPAC-RS 2011 Conference

Lowering Extractables Threshold (#1)

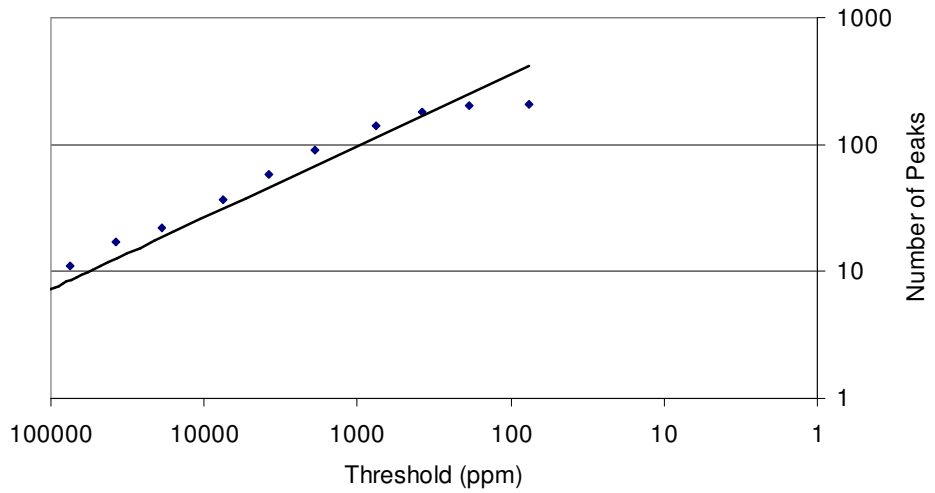
- Example
 - GC-FID Extractables Profile of ABS



IPAC-RS 2011 Conference

20

Is Asymptotic Behavior a Material Property?



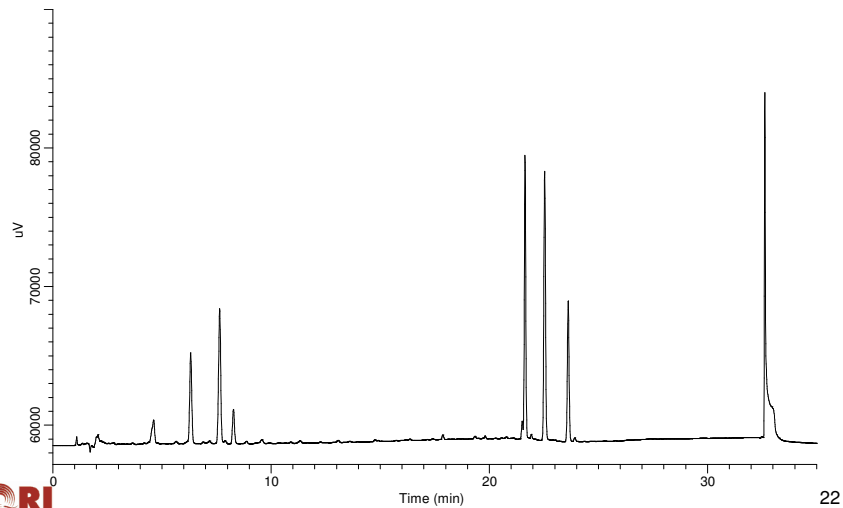
IPAC-RS 2011 Conference

21

Lowering Extractables Threshold #2

Example

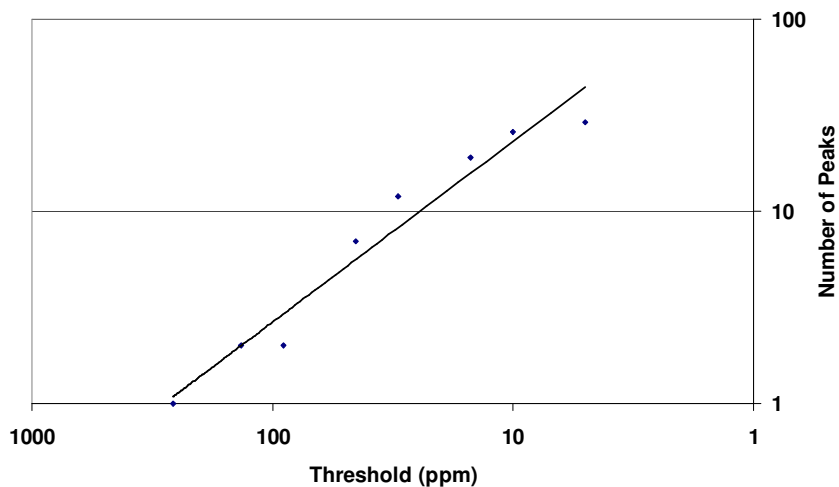
- HPLC-UV Extractables Profile of TPE



IPAC-RS 2011 Conference

22

Different Method/Material Different Asymptote



IPAC-RS 2011 Conference

23

“The Dilemma”

- For large volume/small number of doses aqueous based PODP (i.e., LVPs) Controlled Extraction Studies with organic solvents can be used for:
 - Materials selection, including initial safety evaluation of extractables.
 - Developing routine extractables control analytical methods.
 - Developing drug product leachables methods
- Controlled Extraction Studies with aqueous solvent systems can be used for detecting/identifying potential leachables at AET levels.
- Leachables analytical methods can then be developed (if necessary) as high sensitivity target compound assays, at AET levels.

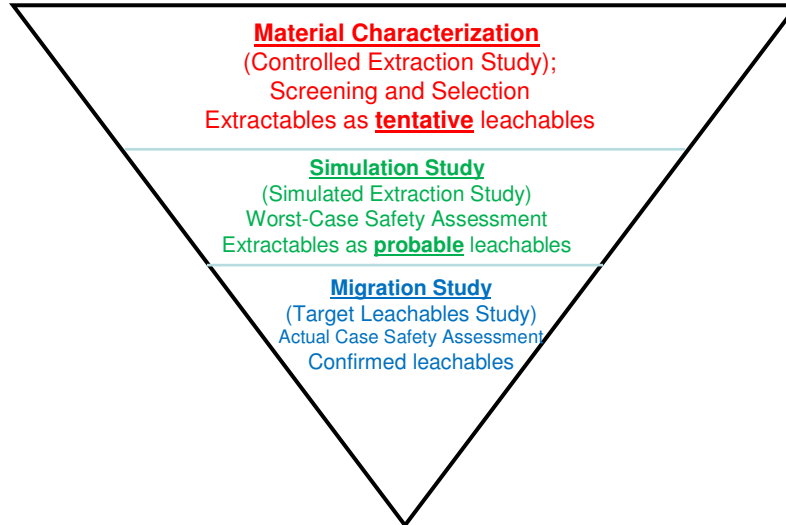
Norwood PQRI PODP Workshop February 22-23, 2011



IPAC-RS 2011 Conference

24

Safety Assessment Triad



Jenke PQRI PODP Workshop February 22-23, 2011

25

IPAC-RS 2011 Conference



Chem/Tox Investigations



IPAC-RS 2011 Conference

26

Toxicology Database

- Database of 606 Extractable and Leachable compounds
 - CAS, Chemical Structure, Common name
- Identified Cramer Class (ToxTree) and flagged genotoxicants (DEREK)
- Each compound classified:
 - Class I – Cramer Low risk
 - Class II – Cramer Medium risk
 - Class III – Cramer High risk
 - Class IV – Evidence for genotoxicity
 - *Supported* Derek alert for carcinogenicity/mutagenicity
 - *Conservative: Unsupported* Derek alert for carcinogenicity/mutagenicity
 - No alert but known carcinogen/mutagen
 - No alert but close neighbor of a known carcinogen/mutagen

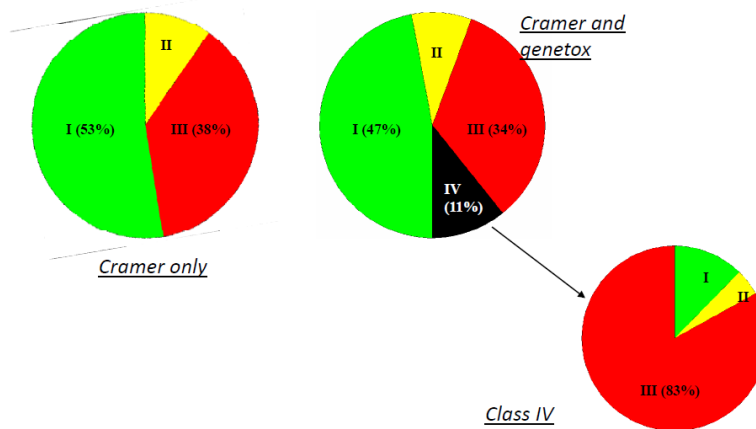


Ball PQRI PODP Workshop February 22-23, 2011

27

IPAC-RS 2011 Conference

First-Pass In Silico Screening



Ball PQRI PODP Workshop February 22-23, 2011

28

IPAC-RS 2011 Conference

Safety Class Categorization



- The team envisions the final recommendations, based on the described approach, to be categorized and captured in a table such as the following:

	Class I	Class II	Class III	Class IV Sensitizer	Class IV Irritant	Class V Genotoxicant
Threshold Level (ug/day)	150	45	7.5	5	5	0.15

- The PQRI toxicology sub-team recognizes that the subject of thresholds for potentially genotoxic substances continues to be a matter for international discussion and debate.
- As such, while our proposals are consistent with the most current thinking related to that subject, any changes in perspective will be closely monitored by the PQRI team and the proposals cited may require revision, accordingly.



Materials, Materials, Materials

Test Articles (Material Type)	Format	Composition (Supplier Information)	Application	Category
Polycarbonate (PC)	Injection moulded plaques	<ul style="list-style-type: none"> 0.05 PHR Irganox 1076 0.1 PHR Irgafos 168 	Ports, Tubes	LVP
Rubber Elastomer (Bromobutyl)	Sheet	<ul style="list-style-type: none"> Brominated isobutylene isoprene copolymer (57.3%) calcined aluminum silicate, 38.2% titanium dioxide, 1.2%; paraffinic oil, 1.2%; zinc oxide, 0.6% polyethylene 0.6% SRF Carbon block mixture, 0.4% calcined magnesium oxide, 0.3% 4,4'-dithiodi-morpholine/polyisobutylene, 0.3% 	Closures, Plungers, Gaskets	SVP
Cyclic Olefin Copolymer (COC)	Plaques	<ul style="list-style-type: none"> Irganox 1010 Ultramarine Blue 	 Syringes, Vials	PFS, SVP
Polyvinylchloride (PVC)	Pellets	<ul style="list-style-type: none"> PVC resin DEHP 30% Epoxidized oil 7% Zn stearate 0.5% Ca stearate 0.5% Stearamide 1% 	 Bags, Tubing	LVP
Low density polyethylene (LDPE)	Blown Film	<ul style="list-style-type: none"> Irganox B 215 (2:1 blend of Irgafos 168 and Irganox 1010) 1000 ppm BHT 200 ppm Calcium Stearate 500 ppm Erucamide 500 ppm Chimassorb 944 2000 ppm 	Overpouch, BFS, Containers	BFS, SVP, LVP



Solvents

- The majority of PODP are represented by aqueous based formulations !
- Cosolvents can be subdivided into two groups:

A: Polarity Neutral

Primary function of excipient is not drug solubilization
Generally compounds with high aqueous solubility:

- Diluents (dextrose, saline)
- Buffers (acetate, lactate, bicarbonate, phosphate)
- Amino acids
- Vitamins

B: Polarity Impacting

Components primary function is to increase the solubility of the drug

- Tween 80
- Cyclodextrins
- SDS
- Lipids up to 20% wt/wt
- Surfactants, Emollients



Aqueous pH 2.5 / 9.5



Isopropanol / Water

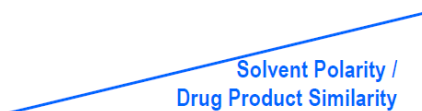


Egert PQRI PODP Workshop February 22-23, 2011

31

IPAC-RS 2011 Conference

Extraction Conditions



	Thermal	n-Hexane	Iso-propanol	Isopropanol/Water	Aqueous pH 2.5	Aqueous pH 9.5
Headspace	X	---	---	---	---	---
Reflux	---	X	X	PC/PVC only	---	---
Soxhlet	---	X	X	---	---	---
Sealed Vessel	---	---	---	55°C/3d	(121°C/1hr) ¹	(121°C/1hr) ¹
Sonication	---	---	---	---	x	x

¹: autoclave conditions: (121°C/1hr)



Egert PQRI PODP Workshop February 22-23, 2011

32

IPAC-RS 2011 Conference

Identification to “the Extent Practical” ...

Category	Supporting Identification Data
A	Mass spectrometric fragmentation behaviour
B	Confirmation of molecular weight
C	Confirmation of elemental composition
D	Mass spectrum matches automated library or literature spectrum
E	Mass spectrum and chromatographic retention index match authentic specimen
Confirmed	Categories A, B(or)C and D(or)E fulfilled
Confident	Sufficient Data to preclude all but the most closely related structures have been obtained
Tentative	Data have obtained that are consistent with a class only

Confirmed ID
SAR End-points



Egert PQRI PODP Workshop February 22-23, 2011

IPAC-RS 2011 Conference

33

Ophthalmic Products- Strategy

- Ophthalmic products have unique characteristics which may impact the approach/rationale applied to qualify leachables
 - small dose volume/dose
 - impact of primary and secondary packaging
 - importance of local effects vs. systemic effects
 - lack of ocular irritation data at relevant concentrations
- However, similar to other endpoints, a qualification threshold approach may be considered relevant for ocular irritation
- Further evaluation will verify this assumption and help establish the appropriate level



Richardson PQRI PODP Workshop February 22-23, 2011

IPAC-RS 2011 Conference

34

Ophthalmic Products- Current Practice (US)

- One-time study until next change
- One batch leachables stability test, appropriate technique to pick up leachables, report in parts-per-million (ppm)
- Report above 1 ppm
- Identify at 10 ppm
- Qualify at 20 ppm
- Not included in specification if detected at 1000-fold lower than toxicological risk



Ng PQRI PODP Workshop February 22-23, 2011

35

IPAC-RS 2011 Conference

Biologics are Different

- Safety
 - Animal models are much less sensitive than humans (1000-fold less for LPS)
 - Routine analytical methods will not detect finite changes in potency but may affect immunogenicity
 - Leachables as adjuvant and/or immunomodulatory factors (literature), e.g. silicone oil, DEHP, MEHP, PAHs, soluble Fe, Cd, Ni and alkyl phenols
- Efficacy
 - EPREX, Fe catalyzed oxidation of preservative triggering formation of protein-preservative adducts, divalent cation inactivation, W causes unfolding and protein aggregation, alkali oxide delamination, aluminum phosphate particulates, barium sulfate particulates, silicone oil
- Quality
 - Stability studies are not geared to detect leachables



Markovic PQRI PODP Workshop February 22-23, 2011

36

IPAC-RS 2011 Conference

PODP Accomplishments

Toxicology Team

- Developed Classification Strategy
- Proposed Tiered Approach- Toxtree/Cramer systems
 - Five toxicity classes
 - Determine Appropriate Toxicity Classifications based on data
- Submitted a Briefing Document for FDA and Health Canada
- Presented Strategies to Health Canada

Chemistry Team

- Defined Subject Matter and Developed Project Plan
- Compiled Extractable/Leachable List Compiled for Toxicology Team
- Obtained Materials from Suppliers
- Created the Experimental Protocol
- Acquired and Evaluated Test Data
- Conceived a Tiered Approach for Extractable Evaluation



IPAC-RS 2011 Conference

37

PODP Next Steps

Toxicology Team

- Develop a strategy to adequately support science-based safety assessments
 - combination of analytical, toxicological, risk-benefit or other approaches and could vary on a case-by-case basis.
- Verify Classifications
 - Apply in silico methods to classify ~500 known L/E in ug/day

Chemistry Team

- Demonstration of AET Best Practice
- Secondary Packaging Considerations



Build Consensus

IPAC-RS 2011 Conference

38

Work Product End-Game

- Drafting Recommendation Document
 - Data Acquired
 - Industry Comments/Learnings
 - Workshops
 - Peer Review Process
- Submit to PQRI Steering Committee
 - Regulatory Agencies
- Workshops
- Publications



39

IPAC-RS 2011 Conference

PODP Working Group Members

- Chair
 - Diane Paskiet, Associate Director of Scientific Affairs, West
- Toxicology and Chemistry Chairs
 - Douglas J. Ball, Research Fellow, Pfizer, Toxicology
 - Dennis Jenke; Senior Baxter Research Scientist, Baxter HealthCare, Chemistry
- Drug Technical Committee Liaison
 - Frank Holcomb, Jr., Ph.D.
US Food and Drug Administration



40

IPAC-RS 2011 Conference

Toxicology Team

- Stephen A. Barat, Ph.D., Director, Toxicology and Operations, Forest Research Institute
- William P. Beierschmitt Ph.D., D.A.B.T, Associate Research Fellow, Pfizer, Inc.
- Steve Beck, CEMDD Liaison, GlaxoSmithKline
- Jacqueline A. Kunzler, Director of Drug and Device Safety and Efficacy, Life Sciences Division, Baxter Healthcare
- Mary Richardson, Ph.D., DABT, Director of Nonclinical Safety, Bausch & Lomb
- Alisa Vespa, Ph.D., Assessment Officer, Metabolic and Musculoskeletal Drugs Division, Bureau of Metabolism, Oncology and Reproductive Sciences Therapeutic Products Directorate, HC



41

IPAC-RS 2011 Conference

Chemistry Team

- James Castner, Senior Principal Research Scientist, Lantheus Medical Imaging
- Thomas Egert, Research Scientist, Boehringer Ingelheim Pharma. GmbH & Co. KG
- Thomas Feinberg, Director, Structural Chemistry, Catalent Pharma Solutions, LLC
- Christopher Houston, Principal Scientist, Bausch & Lomb
- Desmond G. Hunt, M.S., Ph.D. Scientist, Department of Standards Development, USP
- Kumudini Nicholas, Generic Drugs Quality Division, Bureau of Pharmaceutical Sciences, Therapeutic Products Directorate, HC
- Mike Ruberto, Ph.D., President, Material Needs Consulting, LLC
- Daniel Norwood, M.S.P.H., Ph.D., Distinguished Research Fellow, Boehringer Ingelheim Pharmaceuticals, Inc.
- Edward Smith, Ph.D., Principal Consultant, Packaging Science Resources
- Michael Lynch, Ph.D., Associate Research Fellow, Pfizer



42

IPAC-RS 2011 Conference

Acknowledgements

Parenteral and Ophthalmic Drug Products (PODP)
Leachables and Extractables Working Group

PQRI Member Organizations



All research work supported under the direction of PQRI



IPAC-RS 2011 Conference