About OMICS Group

OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 700+ online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 1000+ International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

OMICS International Conferences

OMICS International is a pioneer and leading science event organizer, which publishes around 700+ open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 1000+ conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Parenteral and Ophthalmic Leachables and Extractables Working Group

Diane Paskiet
Director Scientific Affairs

Parenterals & Injectables 2015
August 17-19
Chicago, USA

Objectives

- Background on PQRI Leachables and Extractables Working Group
- Parenteral and Ophthalmic Drug Products (PODP)
  - Project Scope
  - Key Challenges
  - Output

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Container Closure Guidance

Degree of Concern Associated with Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	• Inhalation Aerosals and Solutions • Injections and Injectables Suspensions	• Sterile Powders and Powders for Injection • Inhalation Powders	
High	• Ophthalmic Solutions and Suspensions • Transdermal Ointments and Patches • Nasal Aerosals and Sprays		
Low	• Topical Solutions and Suspensions • Topical and Lingual Aerosols • Oral Solutions and Suspensions	• Topical Powders; Oral Powders	• Oral Tablets • Oral Capsules

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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.

PQRI provides a unique forum to:

focus critical thinking

conduct research

exchange information

propose methodology/guidance

Academia-Industry-FDA Working Cooperatively

PQRI L&E Background

- FDA, Industry and Academia Collaboration
  - Data to demonstrate science-based approaches for identifying and qualifying leachables in drug products
- Orally Inhaled and Nasal Drug Products (OINDP) Leachables and Extractables Working Group
  - Develop thresholds and examine best practices for Leachables and extractables OINDP
  - PODP Working Group
    - Plan to extrapolate OINDP thresholds and best practices

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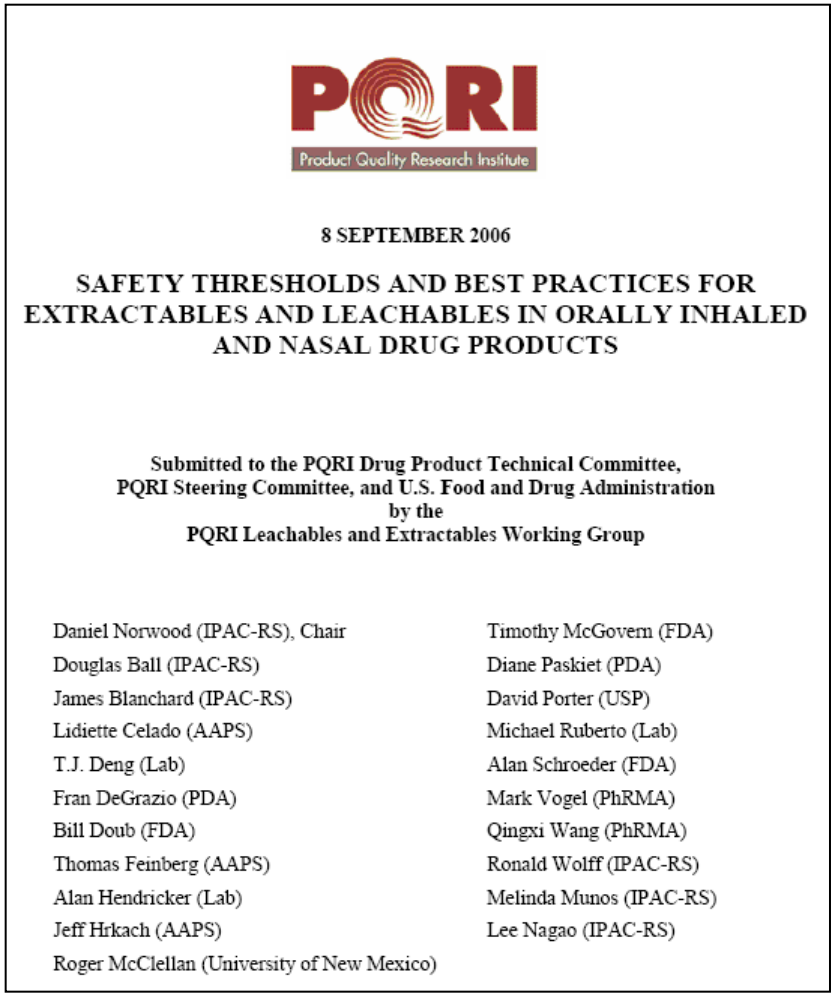
OINDP Outcome



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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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- Safety Concern Threshold (SCT)
  - Low Risk Leachables Not Identified
    - <0.15 ug/day
- Qualification Threshold (QT)
  - Assessment of Identified Leachable
    - non-carcinogenic >5 µg/day
- Best Practices for E&L studies
  - Analytical Evaluation Threshold (AET)
    - Identification threshold derived from SCT

Note:

- *Designed to reduce level of uncertainty within the pharmaceutical development*
- *Not meant to be proscriptive*

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Linking Chemistry SCT derived AET

"The AET is defined as the threshold at or above which a pharmaceutical development team should identify and quantify a particular extractable and/or leachable and report it for potential toxicological assessment."

"How low to go to Identify Potential Leachables"

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Controlled Extraction Studies

PQRI OINDP Guiding Principles

1. Employ vigorous extraction with multiple solvents
2. Incorporate multiple extraction techniques.
3. Include sample preparation based on knowledge of analytical techniques
4. Employ multiple analytical techniques
5. Include a systematic process for identification of individual extractables
6. Definitive" extraction methods should be optimized
7. Sponsors Should Revisit Supplier Information
8. Guided by an Analytical Evaluation Threshold (AET)
9. Evaluate special case compounds by specific analytical techniques
10. Identify risk to leachables early in the pharmaceutical development

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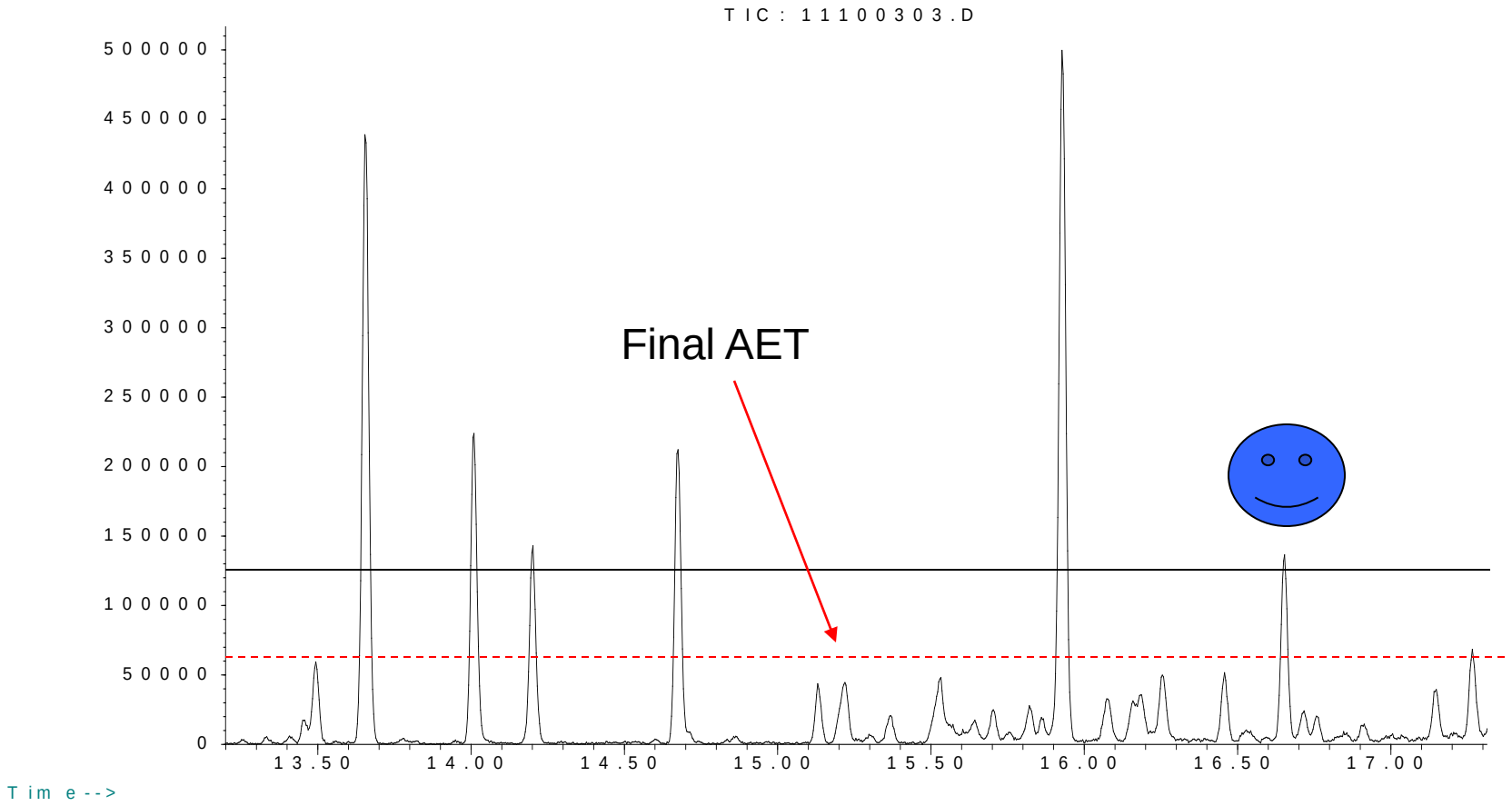
Application of AET
Identification of Peaks



Uncertainty Based on RRF Data Base

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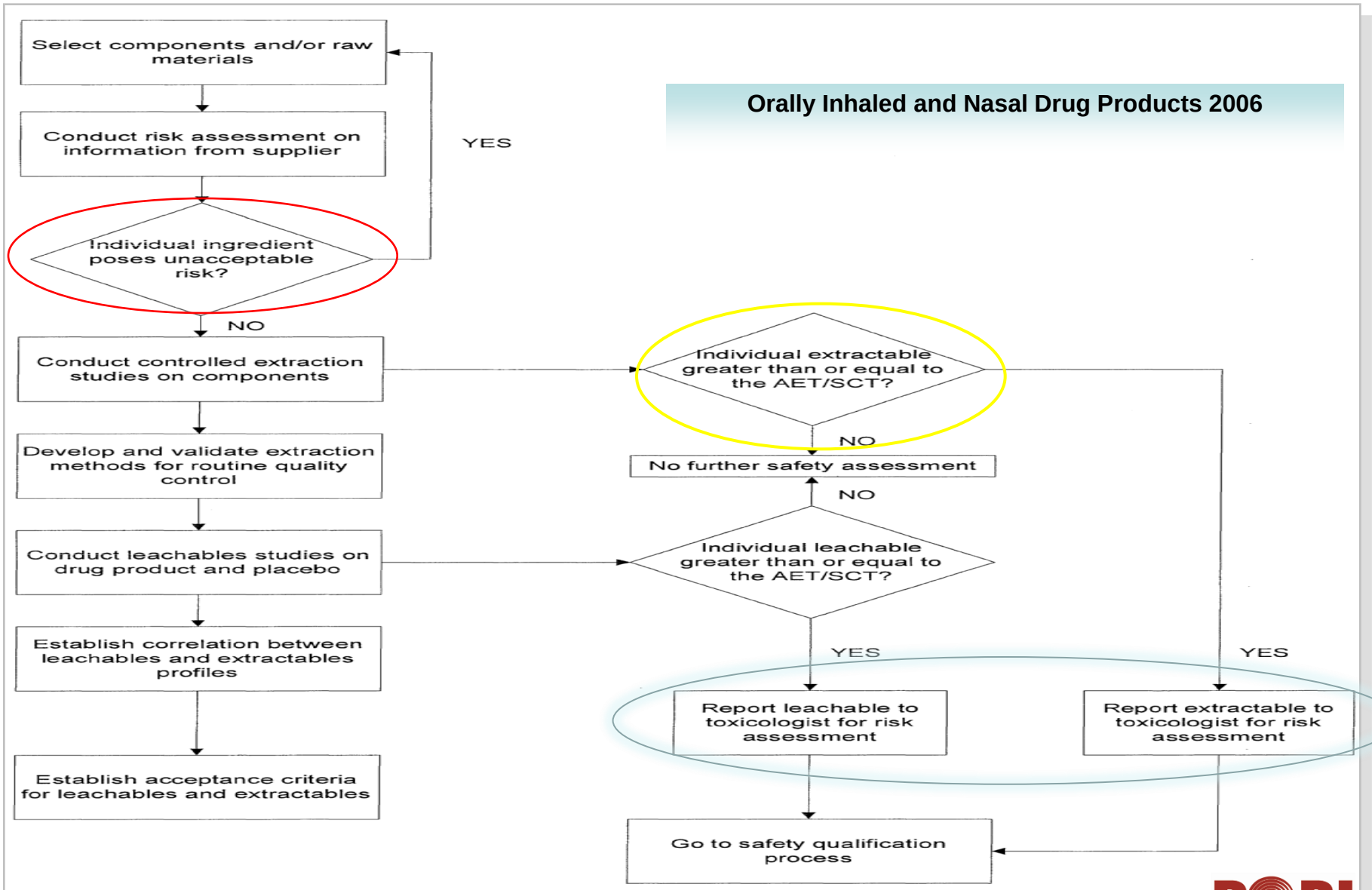
Process Flow



PQRI Threshold Summary
Linking Chemistry and Toxicology

- Leachables above the SCT are subject to chemical and risk assessments
- Identification threshold (AET)
  - SCT-Dose-Container Closure System
- Risk at the Controlled Extraction Phase
  - Facilitates component selection and safety qualification
  - Targeted leachable identification
- Risk to Patient will be Case-by-Case
  - Component Material-Drug/Biologic-Intended use

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Sound Science Based on Risk

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

Approved WORK PLAN, 2009

Development of Scientifically Justifiable Thresholds and Best Demonstrated Characterization Practices for Leachables and Extractables in Parenterals and Ophthalmic Drug Products (PODP)

- Threshold concepts and best demonstrated practices developed for leachables in OINDP can be extrapolated to PODP with considerations of factors i.e. dose, duration, patient population, materials and product characteristics of PODP.
- Considered for: Prefilled Syringe (PFS), Small and Large Volume Parenterals (SVP)/(LVP), and Ophthalmic/Blow Fill Seal (BFS)
- Disposable systems should also be considered in the absence of defined and specific regulatory guidance
- Consistent with the principles of QbD and good science

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PODP Example Materials

Test Articles (Material Type)	Format	Composition (Supplier Information)	Application	Category
Polycarbonate (PC)	Injection moulded plaques	• 0.05 PHR Irganox 1076 • 0.1 PHR Irgafos 168	Ports, Tubes	LVP
Rubber Elastomer (Bromobutyl)	Sheet	• Brominated isobutylene isoprene copolymer (57.3%) • calcined aluminum silicate, 38.2% • titanium dioxide, 1.2%; • paraffinic oil, 1.2%; • zinc oxide, 0.6% • polyethylene0.6% • SRF Carbon block mixture, 0.4% • calcined magnesium oxide, 0.3% • 4,4'-dithiodi-morpholine/polyisobutylene, 0.3%	Closures, Plungers, Gaskets	
Cyclic Olefin Copolymer (COC)	Plaques	• Irganox 1010 • Ultramarine Blue	Syringes, Vials	PFS, SVP
Polyvinylchloride (PVC)	Pellets	• 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	• 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

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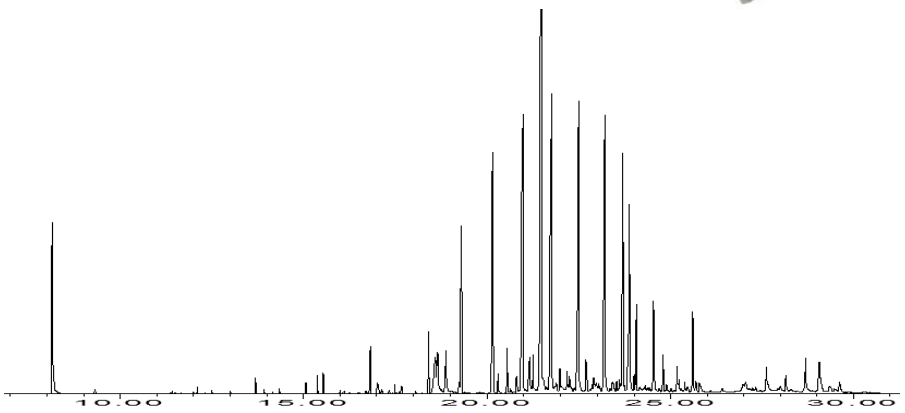
Not Marketed Components

Leachable Safety Based on Intended Use

- Dosage Form
- Route of Administration
- Material(s) of Construction
- Patient Population
- Dosing
- Duration



0.15µg/day ← **ID Thresholds** → **1.5µg/day**

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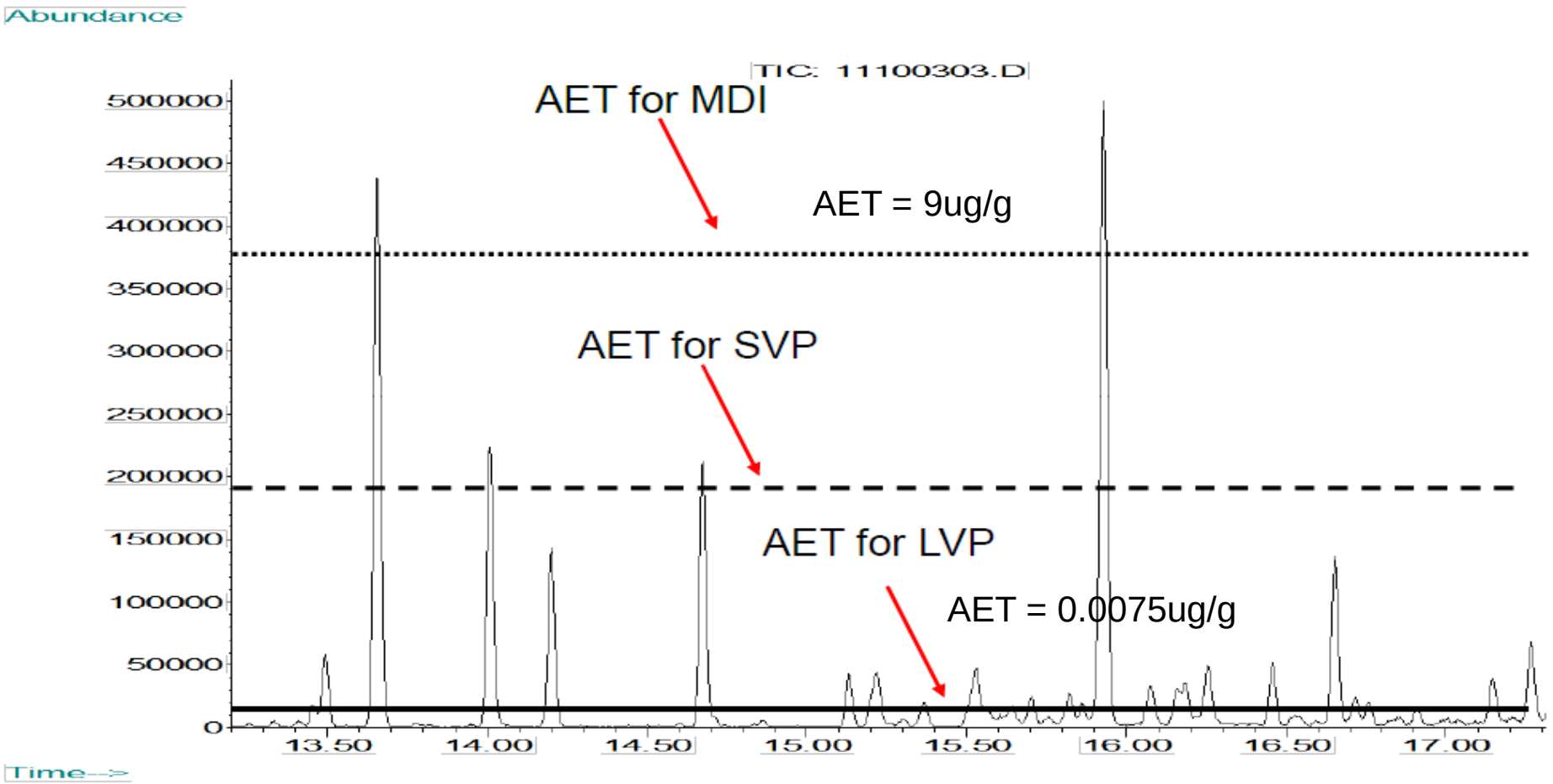
PODP Identification Challenges
Daily Dose and the AET



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PODP Chemistry Key Outcomes

- Robust methods to characterize Extractables
  - Multiple solvents/multiple and orthogonal techniques
  - Extractions/Techniques focus on aqueous and strong solvents
- The Analytical Evaluation Threshold (AET) limited for LVP
  - Extremely dilute based on a single dose in large volume container and with a single dose
  - Characterizations Studies followed by Simulation Studies can guide the AET
- Simulations studies can be used to represent extractables
  - model systems
  - migration of secondary packaging /label migration
- Should the potential for special case compounds exist for a material, they will be appropriately considered
  - PNAs, Nitrosamines and 2-MBT are not universal to all materials

The AET (derived from SCT) Identifies Potential Leachables for Safety Qualification

Biologics may Deserve a Special Consideration

- Manufacturing and stability issues:
  - Protein conformation (e.g., secondary, tertiary) is sensitive to external environment
  - Aggregation and/or degradation
  - Deamidation and/or oxidation
  - Changes in glycosylation
- Routine analytical testing often doesn't detect finite changes in the protein (e.g., release testing is unlikely to detect areas of protein unfolding unless it impacts the function)
- Large size (e.g., MAb 150 KD) and extensive surface area ensures →high frequency of potential sites of interaction
- Proteins may be more efficient in solubilizing leachables due to abundance of both hydrophilic and hydrophobic sites (the latter are usually buried in the interior of the protein)
- Drug dose, mode and frequency of administration (e.g., many biologics are sterile injectables administered frequently at relatively high volumes and doses of mg/ml)

Critical Information

- Product Quality
  - Is the product altered and therefore less stable due to leachable interacting with active pharmaceutical ingredients and/or excipients in the formulation
- Safety
  - What is (a) the chemical entity and (b) amount e.g., ug/dose; and how often will the patient be exposed to leachables present in the product

Ingrid Markovic: Regulatory Perspective on E&L
USP/PQRI Workshop: Systems, Dec 9-10, 2013

Safety Qualification, Information and Perspective

Proper Context.

- With respect to safety qualification, the following must be clearly determined and communicated:
  - Which extractables are indeed leachables?
  - Is compound-specific toxicology data available for any leachables?
  - What are the use conditions of the drug product?
  - What are the inadvertent daily “doses” of leachables under such use conditions?
  - Does the leachable profile present any specific concerns related to safety, both local and systemic?

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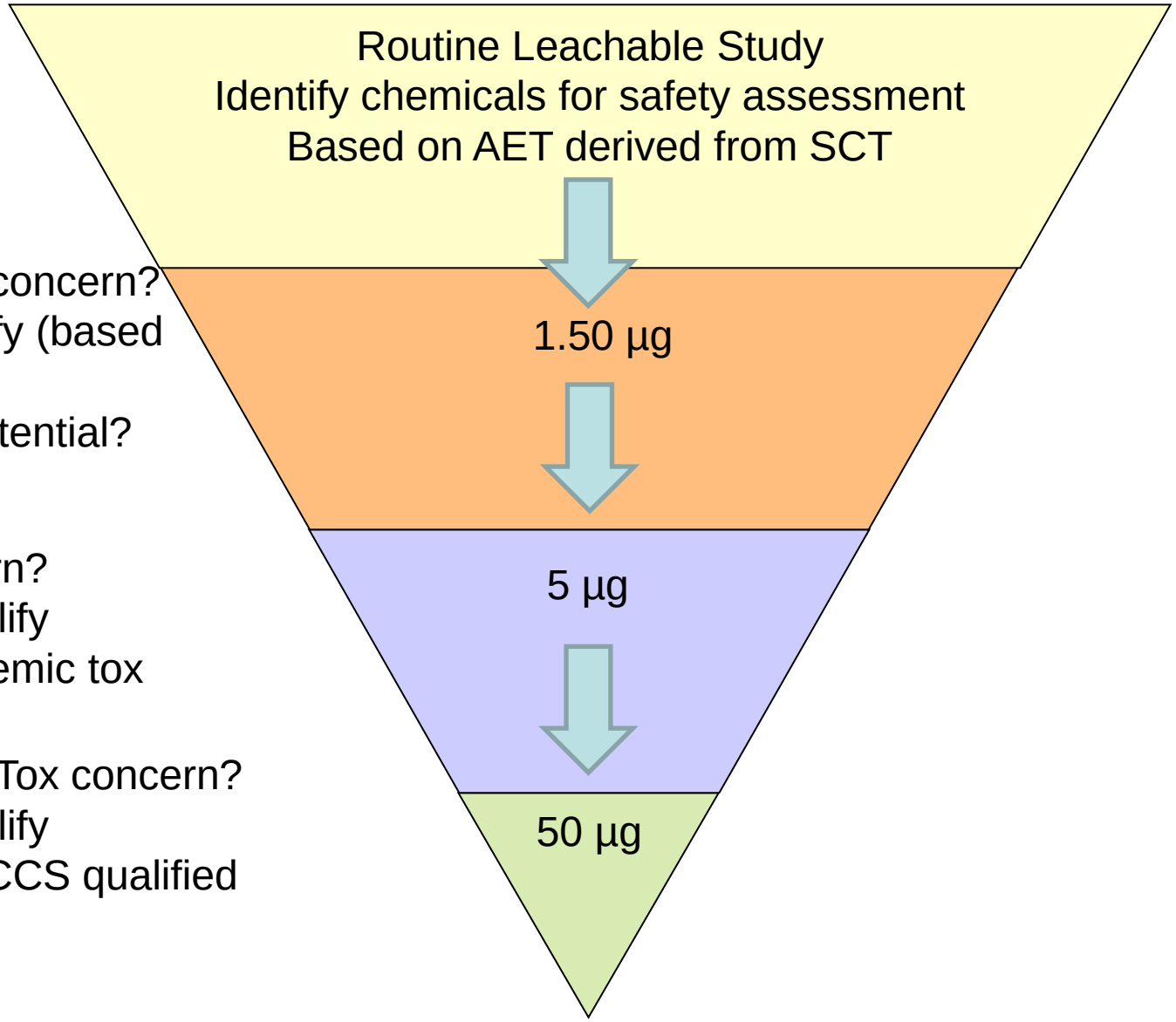
PQRI Proposed Qualification Process



Genotoxic concern?
Yes – qualify (based on ICH M7)
No – S/I potential?

S/I concern?
Yes – qualify
No – systemic tox

Systemic Tox concern?
Yes – qualify
No – DP CCS qualified

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PODP Resources

www.PQRI.org

Current

PODP Proposal

Work Plan

Study Protocols

PODP 2011 Workshop Presentations and Posters

Access to 2013 Manuscripts

Meeting Minutes

Future 2015-1216

Recommendation Document

(hypothesis - results - data)

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PQRI Global Out Reach

Regulators:

HC

MHRA

MHLW

CFDA

EMA/SWP

Organizations:

IQ

EFPIA

Conferences:

US, Europe, China, India

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Let us meet again..

We welcome you all to our future conferences of OMICS International

2nd International Conference and Expo on

Parenterals and Injectables

On

October 24-26, 2016 at **Istanbul, Turkey**

http://parenterals-injectables.pharmaceuticalconferences.com/