



Brief Overview of the PQRI Recommendations: Challenges and Successes

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Available FDA Guidances

- *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.
"Packaging Guidance"
- *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products*; Draft Guidance for Industry; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Rockville, MD, October 1998.
"MDI/DPI Guidance"
- *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*; Guidance for Industry; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Rockville, MD, July 2002.
"Nasal Spray Guidance"



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Gradient of Leachables “Risk”

Table 1. Examples of Packaging Concerns for Common Classes of Drug Products. (1)

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*	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

Notes: (1) From Guidance for Industry. Container Closure Systems for Packaging Human Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Rockville, MD, May, 1999.²
 * For the purpose of this table, the term suspension is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.



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What are OINDP?



- Metered Dose Inhalers
- Dry Powder Inhalers
- Inhalation Solutions
- Inhalation Sprays
- Nasal Sprays

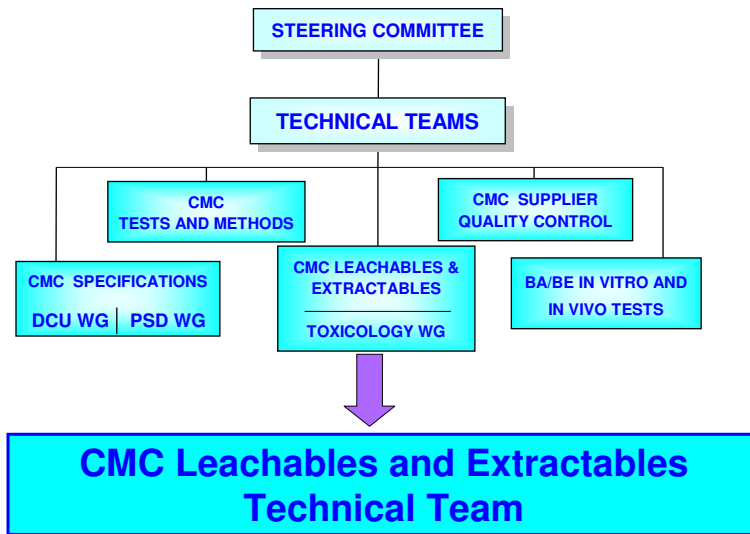


MDI Schematic Provided by Bepak Europe



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IPAC/ITFG Collaboration (1999-2001)



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Team Overview of Draft CMC Guidances

- Team supported efforts of Agency in drafting guidance documents which address requirements for leachables and extractables for orally inhaled and nasal drug products
- Team believed that current draft Guidances could be enhanced by clarification in specific areas
- Team identified key areas of draft Guidances which would benefit from further investigation and dialogue with Agency



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Key Issues and Process

What are appropriate reporting/identification/qualification thresholds for leachables & extractables?

How is a correlation between leachables and extractables established?

What are appropriate practices for establishing safety of leachables?

Is extractables profiling appropriate for control of component composition?

Which critical components should be subject to routine extractables testing?

- Collected drug product specific leachables and extractables data in order to investigate the concept of correlation
- Formed toxicology WG to address toxicology issues for leachables
- Investigated current supplier practices for control of component composition and extractables profiles



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Points to Consider Technical Paper

Submitted *Points to Consider* (March 2001) technical paper which proposed:

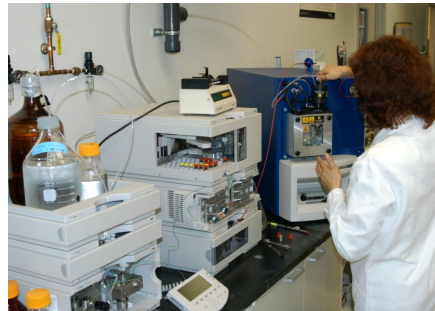
- Alternate language for the draft Guidances, which clarifies the requirements for leachables and extractables studies
- Reporting and qualification thresholds for leachables
- A leachables qualification process



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What is PQRI?

- *Product Quality Research Institute*
- Not-for-profit, non-stock, tax-exempt entity incorporated in Virginia
- Serves as a forum for academia, industry and FDA to work cooperatively
- PODP Leachables and Extractables Working Group currently in operation



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Highlights of PQRI Process

- Opportunity to collect raw data through independent experiments/studies, or through data-mining
- Scrutiny of data by scientists from diverse backgrounds
- Discussion of data outside of NDA process



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History of PQRI OINDP Leachables and Extractables Working Group

- Proposal to develop thresholds and examine best practices for L&E in OINDP drafted by IPAC-RS and submitted to PQRI
- Working Group formed in 2001, consisting of chemists and toxicologists from FDA, industry and academia
- Working Group developed a hypothesis and step-wise plan to investigate per established PQRI process
- Workplan approved by PQRI DPTC and Steering Committee in 2002
- Toxicologists and chemists formed sub-groups



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History of PQRI OINDP Leachables and Extractables Working Group

- Toxicologists: acquired data through extensive literature and database searches and analyses
- Chemists: acquired data by conducting extractions studies and placebo leachables study
- Developed recommendations, “Safety Thresholds and Best Practices for Leachables and Extractables Testing in Orally Inhaled and Nasal Drug Products”
- Submitted final to PQRI and FDA in summer 2006
 - Science and data-based recommendations to PQRI and FDA. Not a policy/regulatory document



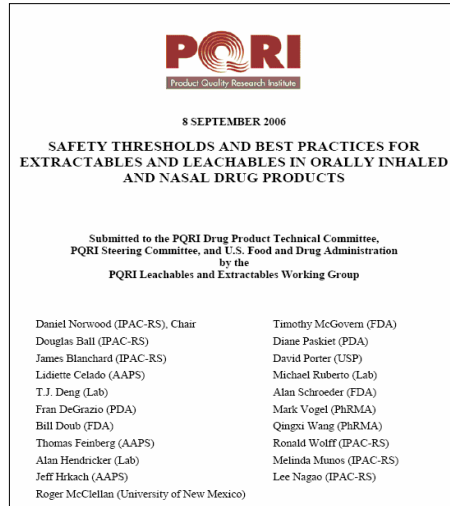
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Why Produce L&E Recommendations?

- To reduce uncertainty in the pharmaceutical development process for OINDP
- To reduce or eliminate “Horror Stories”
- To support regulatory initiatives, such as Quality by Design and Risk Management



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Recommendations - Best Practices Overview

- Application of safety thresholds
 - Safety Concern Threshold (SCT)
 - Qualification Threshold (QT)
- Integration of safety expertise into component selection, controlled extraction studies, leachables studies and routine extractables testing
- Analytical/chemistry
 - Selection of components
 - Controlled Extraction Studies
 - Leachables Studies and Routine Extractables Testing
 - The Analytical Evaluation Threshold (AET)



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Definition of SCT and QT

- Safety Concern Threshold (0.15 µg/day):
 - Dose below which concern for carcinogenicity and noncarcinogenic toxicity is negligible
 - Identification of leachables below this threshold generally would not be necessary
- Qualification Threshold (5 µg/day)
 - Dose below which concern for noncarcinogenic toxicity is negligible
 - Leachables below this threshold without structural alerts for carcinogenicity or irritation would not require compound-specific risk assessment



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Definition Analytical Evaluation Threshold (AET)

- The AET is the threshold at or above which an OINDP pharmaceutical development team should identify and quantify a particular extractable and/or leachable and report it for potential toxicological assessment
- The AET is based directly on the SCT, but is a relative value, not an absolute value



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Example AET Calculation for a Metered Dose Inhaler

Consider an MDI with 120 labeled actuations per canister, a recommended dose of 8 actuations per day, and a critical component elastomer mass per valve of 250 mg. For an individual organic leachable derived from this elastomer, the estimated AET would be:

$$\text{Estimated AET} = \left(\frac{0.15 \mu\text{g/day}}{8 \text{ actuations/day}} \times 120 \text{ labeled actuations/canister} \right)$$

$$\text{Estimated AET} \approx 2.25 \mu\text{g/canister}$$



Example AET Calculation for a Metered Dose Inhaler

Consider an MDI with 120 labeled actuations per canister, a recommended dose of 8 actuations per day, and a critical component elastomer mass per valve of 250 mg. For an individual organic leachable derived from this elastomer, the estimated AET would be:

$$\text{Estimated AET} = \left(\frac{2.25 \mu\text{g/canister} \times 1 \text{ canister/ valve}}{0.25 \text{ g of elastomer/valve}} \right)$$

$$\text{Estimated AET} \approx 9.00 \mu\text{g/g of elastomer}$$



Response Factor Database

Analyte	RRF (vs. 2-Fluorobiphenyl)	RRF (vs. p-Terphenyl-d ₁₄)
Palmitic acid	0.377	0.274
1,3-diacetylbenzene	0.383	0.231
Stearic acid	0.385	0.274
2,2'-methylene bis(6-tert-butyl-4-methyl phenol)	0.519	0.666
Docosane	0.568	0.402
4-tert-butylphenol	0.574	0.372
2,2'-methylene bis(6-tert-butyl-4 ethyl-phenol)	0.574	0.639
Tetracosane	0.584	0.424
2,4-diphenyl-4-methyl-1-pentene	0.824	0.527
Bis-2-ethylhexyl phthalate	0.870	0.654
BHT	1.062	0.694
Mean	0.611	0.469
Standard Deviation	0.221	0.175
% Relative Standard Deviation	36.1	37.2



Example AET Calculation for a Metered Dose Inhaler Component

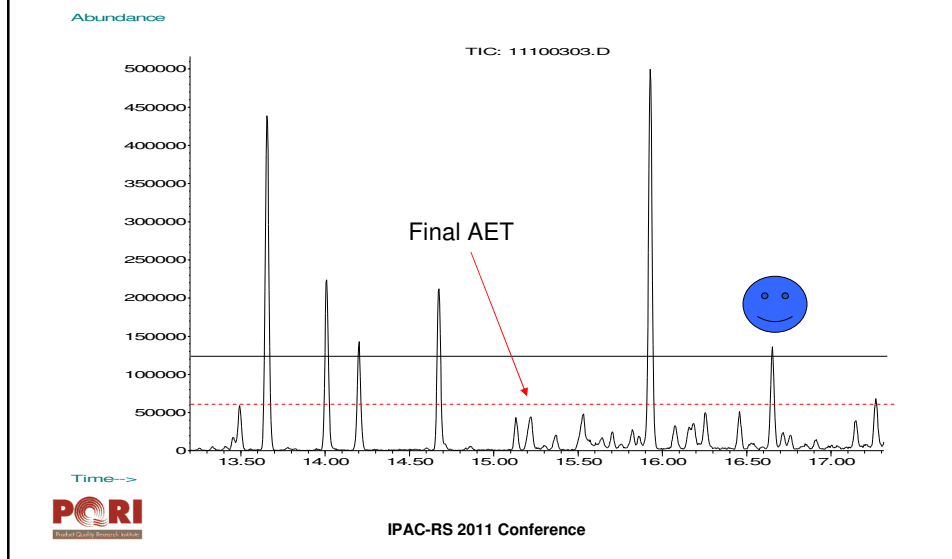
Using the uncertainty as determined from the previous database the following is defined as how low one may go for this analysis:

$$\text{Final AET} = 2.25 \mu\text{g/canister of elastomer} \cdot 0.361 (2.25 \mu\text{g/canister})$$

$$\text{Final AET} = 1.44 \mu\text{g/canister}$$



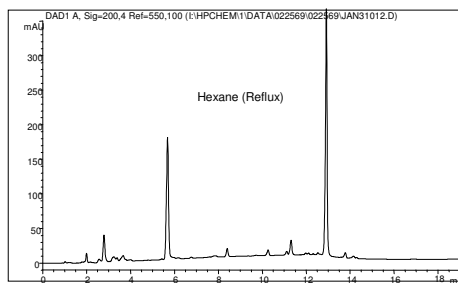
Final AET Profile



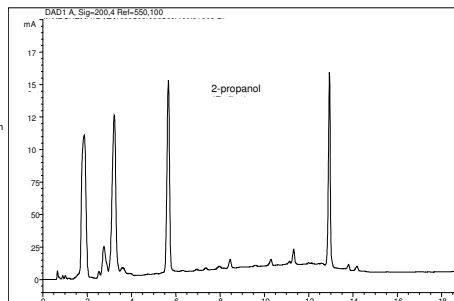
Controlled Extraction Studies Recommendations

- Controlled Extraction Studies should employ **vigorous extraction** with **multiple solvents** of **varying polarity**.
- Controlled Extraction Studies should incorporate **multiple extraction techniques**.
- Controlled Extraction Studies should include **careful sample preparation** based on knowledge of analytical techniques to be used.
- Controlled Extraction Studies should employ **multiple analytical techniques**.
- Controlled Extraction Studies should include a **defined and systematic process for identification** of individual extractables.
- Controlled Extraction Study “**definitive**” **extraction techniques/methods** should be **optimized**.
- During the Controlled Extraction Study process, sponsors should **revisit supplier information** describing component formulation.

Multiple Solvents – Polypropylene (example data)



Hexane Reflux



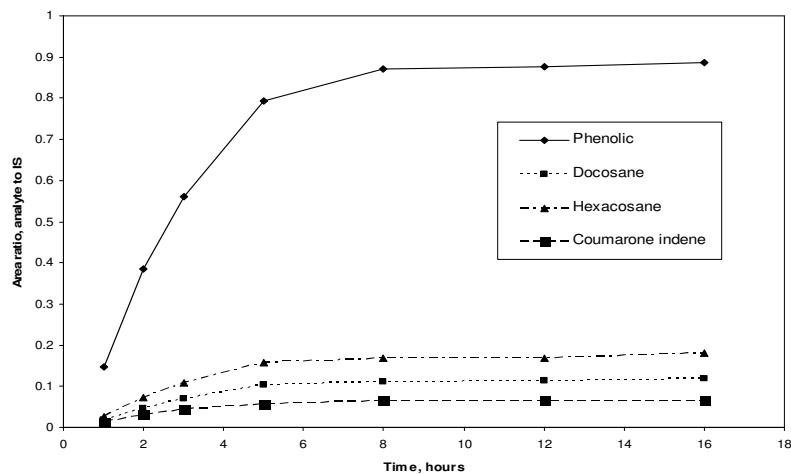
2-Propanol Reflux



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Sulfur-cured Elastomer Asymptotic Extraction (example data)

PQRI Extractives Phase II Exp. 2



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Additional Content of the Best Practices Recommendations

- Definition of “leachables/extractables correlation”
- Data driven definition of “asymptotic levels”
- An overall pharmaceutical development process for OINDP relative to extractables/leachables



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Other Accomplishments of the PQRI OINDP Leachables and Extractables Working Group

- Training courses in the United States, Europe and Canada.
- Peer reviewed publications:
 - *Pharmaceutical Research*
 - *Toxicological Sciences*
- A comprehensive book on leachables and extractables (in progress).
- Numerous public scientific presentations and short courses (e.g., EAS).



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Challenges and Questions



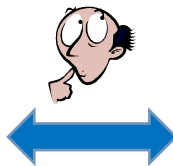
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“The AET Dilemma”

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



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



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“The Dilemma” (continued)



This dilemma was recognized by the OINDP Leachables and Extractables Working Group:

Consider an Inhalation Solution with 3 mL of drug product contained in a low density polyethylene (LDPE) container (1 g total weight LDPE), with a recommended dose of 3 containers per day. For an individual organic leachable the estimated AET would be:



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“The Dilemma” (continued)

$$\text{Estimated AET} = \left(\frac{0.15 \mu\text{g/day}}{3 \text{ doses/day}} \times 1 \text{ dose/container} \right)$$

$$\text{Estimated AET} \approx 0.05 \mu\text{g/container}$$

$$\text{Estimated AET} = \left(\frac{0.05 \mu\text{g/container}}{3 \text{ mL/container}} \right)$$

$$\text{Estimated AET} \approx 0.017 \mu\text{g/mL} \quad \longrightarrow \quad \text{This is 17 ug/L which is at environmental trace analysis levels.}$$



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OINDP Recommendations – Inhalation Solutions

The Working Group recommends that if it can be scientifically demonstrated that:

- 1. Aqueous and/or drug product formulation extracts of Inhalation Solution direct formulation contact container closure system material yield no extractables at Final AET levels, or no extractables above final AET levels with safety concern; AND***
- 2. There is no evidence for migration of organic chemical entites through the unit dose container into the drug product formulation; THEN***

Drug product leachables studies are not required.



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Additional Challenges and Questions

- Analytical techniques and response factors, i.e., how to set an AET for an analytical technique/method with widely varying RFs/RRFs, such as LC/UV and LC/MS?
- Why is the Safety concern threshold for OINDP set at 0.15µg/day when the genotoxic impurities guidelines specify 1.5µg/day?
- If the Safety concern threshold is “protective” of all leachables at levels less than 0.15µg/day why are there “special cases”? That is, what defines a special case?
- Have the PQRI recommendations resulted in a more efficient evaluation of leachables & extractables for industry and regulators?
- Are US regulators accepting of the PQRI recommendations for OINDP? Other regions?



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