



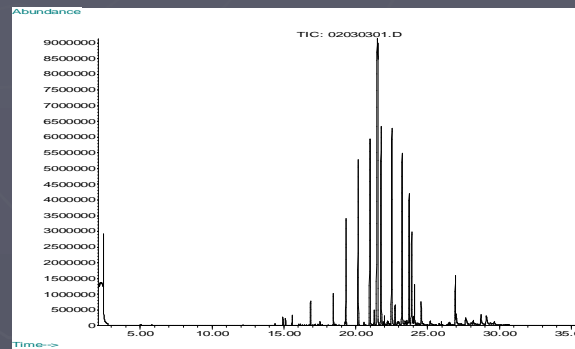
**Best Practices for OINDP Pharmaceutical  
Development Programs  
Leachables and Extractables**

*PQRI Leachables & Extractables Working Group*

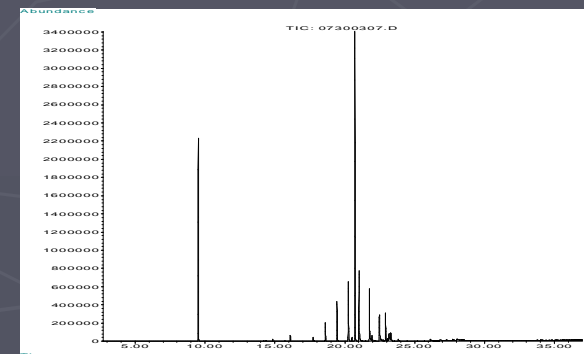
PQRI Training Course  
12-13 April 2007  
Chicago, IL

# What are leachables and extractables?

- *Extractables – Compounds that can be extracted from elastomeric, plastic components or coatings of the container and closure system when in the presence of an appropriate solvent(s).*



- *Leachables – Compounds that leach from elastomeric, plastic components or coatings of the container and closure system as a result of direct contact with the formulation.*



# What are OINDP?

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

MDI Schematic Provided by Bepak Europe



# Why are we interested leachables and extractables?

- FDA Guidances:

- Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation;
- Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation

- Approvals:

- We want them!!!!!!!

- Ethical and professional obligations.

# We want approvals!!!!!!!!!!!!!!!!!!!!



I've heard it all!!!!!!!!!!!!!!

"A person is exposed to more PNAs standing behind a city bus than from an MDI."

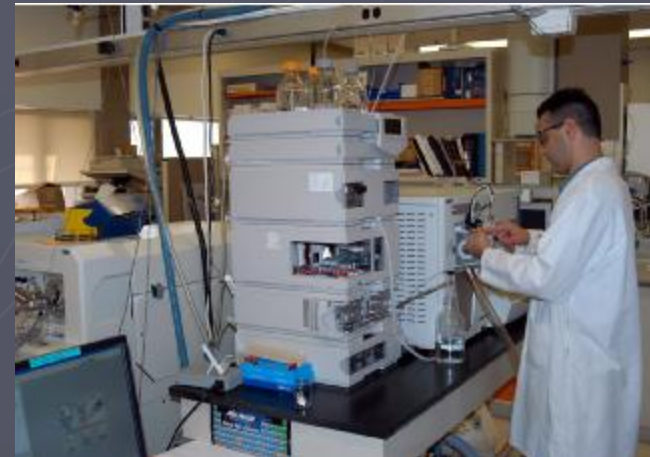
"One charbroiled steak is equal to 1,000,000 MDIs!"

"Bloody Americans – over the top as usual!!!!!!!!!"

"We have horror-stories."

# 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
- Working Group on Leachables and Extractables currently in operation

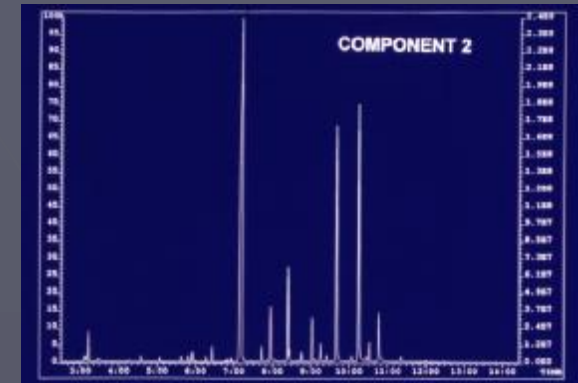


# PQRI Member Organizations

- AAPS
- Consumer Healthcare Products Association
- PDA
- PhRMA
- U.S. FDA, Center for Drug Evaluation and Research
- BIO
- International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)
- International Pharmaceutical Excipients Council of the Americas (IPEC)
- USP



- The International Pharmaceutical Aerosol Consortium (IPAC) formed in 1989 to address regulatory consequences for MDIs of Montreal and Kyoto Protocols
- In 2001, the International Pharmaceutical Aerosol Consortium for Regulation and Science (IPAC-RS) was officially formed as a separate Consortium
  - IPAC-RS Mission: To advance consensus-based and scientifically driven standards and regulations for inhaled and nasal drug products (OINDP).
  - IPAC-RS Overall Goal: Development of scientifically justified regulatory approaches for orally inhaled and nasal drug products



# History of PQRI 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

# History of PQRI 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

# Leachables and Extractables Working Group Members

Dan Norwood, Chair (IPAC-RS)

Doug Ball (IPAC-RS)

Jim Blanchard (IPAC-RS)

Lidiette Celado (AAPS)

Fran DeGrazio (PDA)

T.J. Deng (Lab - PPD)

Bill Doub (Lab - FDA)

Tom Feinberg (AAPS)

Alan Hendricker (Lab - Cardinal)

Jeff Hrkach (AAPS)

Roger McClellan (UNM)

Tim McGovern (FDA)

Diane Paskiet (PDA)

Paul Curry (USP)

Michael Ruberto (Lab - CIBA)

Alan Schroeder (FDA)

Mark Vogel (PhRMA)

Charles Wang (PhRMA)

Ron Wolff (IPAC-RS)

Michael Golden (DPTC, IPAC-RS)

Guirag Poochikian (DPTC, FDA)

Gordon Hansen (SC, IPAC-RS)

# Recommendation Document Overview

---

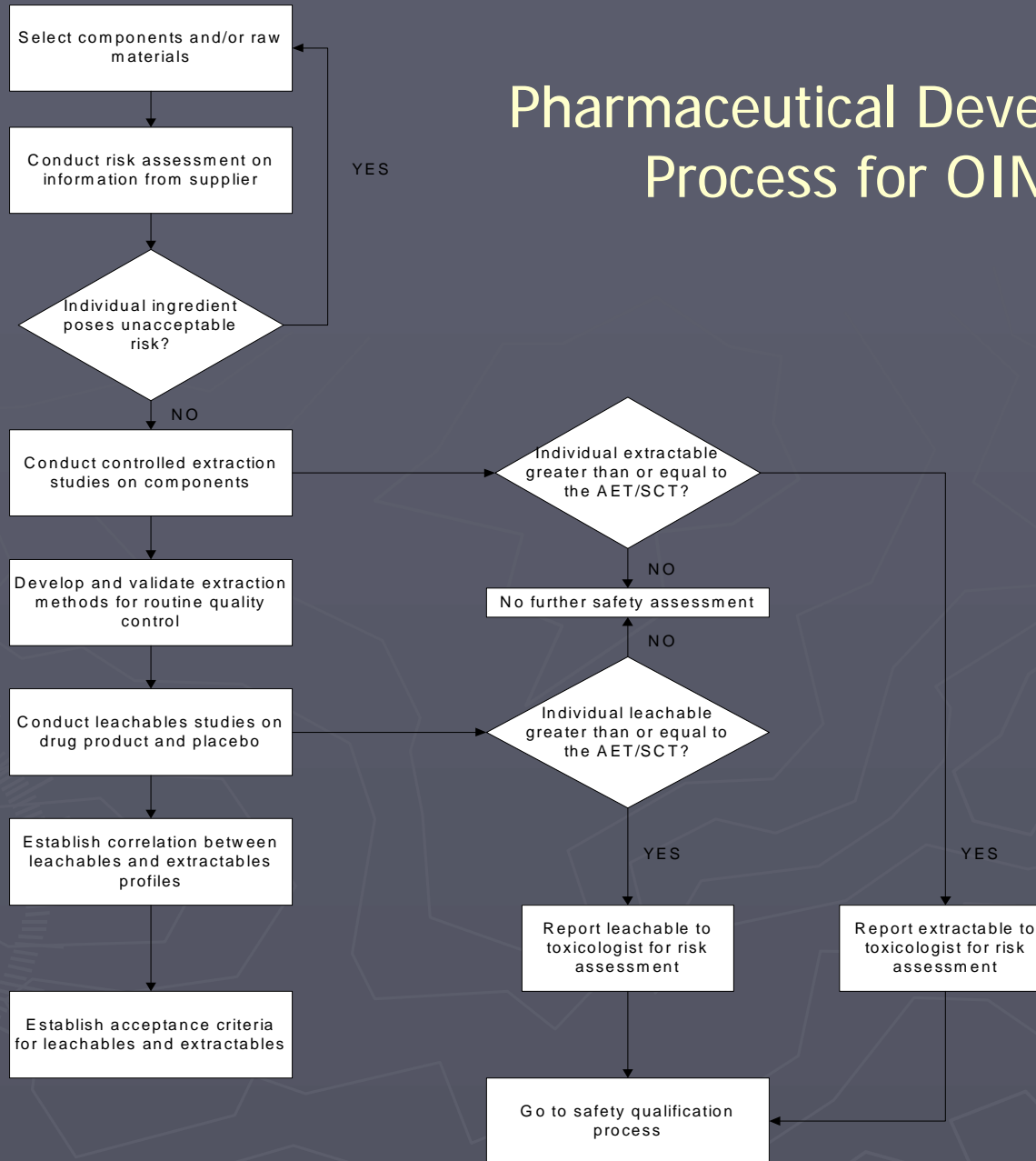
- Introduction and Summary of Recommendations
- Derivation and justification of safety thresholds, and application of safety thresholds
- Chemistry Best Practices
- Appendices

# Best Practices Overview

---

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

# Pharmaceutical Development Process for OINDP



# Training Course Overview

---

- OINDP Container Closure Systems
- Safety Evaluation of Extractables and Leachables
- Analysis of Extractables and Leachables
- Characterization of Extractables
- Special Case Compounds
- Characterization of Leachables
- Quality Control and Specification Setting
- Panel Discussion

# Faculty

---

- Dan Norwood – *Director Physical and Chemical Analysis, Boehringer Ingelheim Pharmaceuticals, Inc. (Working Group Chair)*
- Michael Ruberto – *Head Regulatory Services, Ciba Expert Services*
- Doug Ball – *Research Fellow, Drug Safety, Pfizer, Inc. (Toxicology Subgroup Chair)*
- Diane Paskiet – *Associate Director of Analytical Laboratories, West Monarch Analytical Labs*
- James Mullis – *Senior Scientist, Physical and Chemical Analysis, Boehringer Ingelheim Pharmaceuticals, Inc.*
- Tom Feinberg – *Director Structural Chemistry, Pharmaceutical Development, Cardinal Health*
- Terry Tougas – *Highly Distinguished Scientist, Boehringer Ingelheim Pharmaceuticals, Inc. (DPTC Chair)*

# Feedback

