

# IPAC-RS Symposium on Extractables in Materials for OINDP

## ☪ Welcome!

## ☪ Objectives

- Provide Information and Resources
- Share Perspectives
- Open Dialogue

## ☪ Ask Questions

## ☪ Provide Feedback

## ☪ Share Experiences

Thank You

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## IPAC-RS Member Companies



3M  
Abbott  
Aradigm  
AstraZeneca  
Boehringer Ingelheim  
GlaxoSmithKline

Nektar Therapeutics  
Novartis  
Novo Nordisk  
Pfizer  
sanofi-aventis  
Schering-Plough  
Teva

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## IPAC-RS OINDP Materials Working Group

Previously known as IPAC-RS Elastomers Working Group

**NEKTAR**<sup>™</sup> u Cheryl Stults, Co-Chair  
Bringing Therapy to Life

**KOS** u Barbara Falco, Co-Chair  
**Abbott**  
A Promise for Life

**gsk** Jason Creasey  
GlaxoSmithKline

**sanoFi** Nigél Miller  
aventis

**Boehringer**  
Ingelheim

**AstraZeneca** Andrew Feilden

**Pfizer** Andy Rignall  
Arthur Shaw

Daniel Norwood  
Gaby Reckzuegel  
Jamie Mullis

Suppliers Participating in Symposium Planning:

**Valois** François Billard

**WEST** Pharmaceutical SERVICES Jennifer Riter

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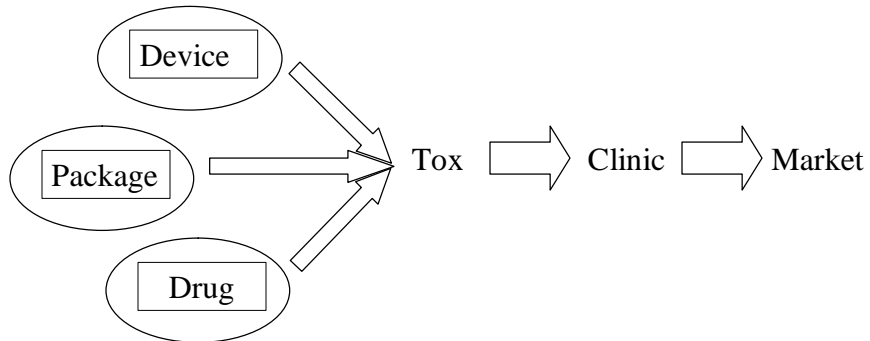
## Overview of OINDP—Importance of Extractables and Challenges

Cheryl L.M. Stults, Ph.D.  
Staff Scientist

IPAC-RS Symposium:

Extractables in Materials for Inhalation & Nasal Drug Products  
February 13, 2007

## OINDP Overview



### ┌ Modes of Administration

- Oral Inhalation
- Nasal

OINDP = Orally Inhaled and Nasal Drug Products

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## Inhalation Device Overview

### Compressed Air Based Nebulizers Dry Powder Inhalers (DPIs)

- Breath synchronized nebulizers
- Compressed gas generation
- Numerous patient driven DPIs

### Liquified Propellant Based Pressurized Metered Dose Inhalers (pMDIs)

- Breath synchronized
- Spacer designs
- Novel formulation technology



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## Inhalation Device Overview

### Vibrating mesh Omron, Pari eFlow, Nektar

- Portable nebulizers
- Shorter nebulization times
- “pMDI” substitute



### Ultrasound Oriol, Microdose



- Patient independent DPIs

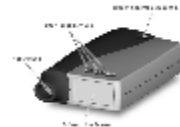
### Electronic Atomization Kurve



- Nasal controlled particle dispersion

### Extrusion Aradigm, RespiMat

- “pMDI” substitute
- Unit dose / efficiency

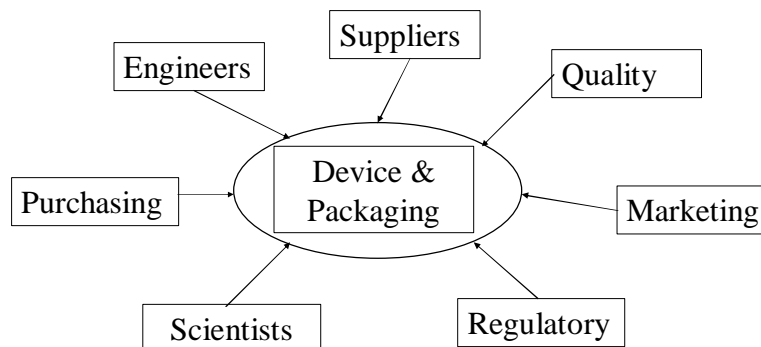


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## Inhalation Product Development

Design → Development → Commercialization



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## Inhalation Device Materials

### ▮ Pharmaceutical Inhalation Device Components

- Drug Container
- Dosing mechanism (for multi-dose products)
- Dispersing mechanism
- Mouthpiece

### ▮ Use of Plastics in Inhalation Devices

- Housing/Container
- Functional/mechanical components
- Aesthetic components

### ▮ Other Materials Commonly Used

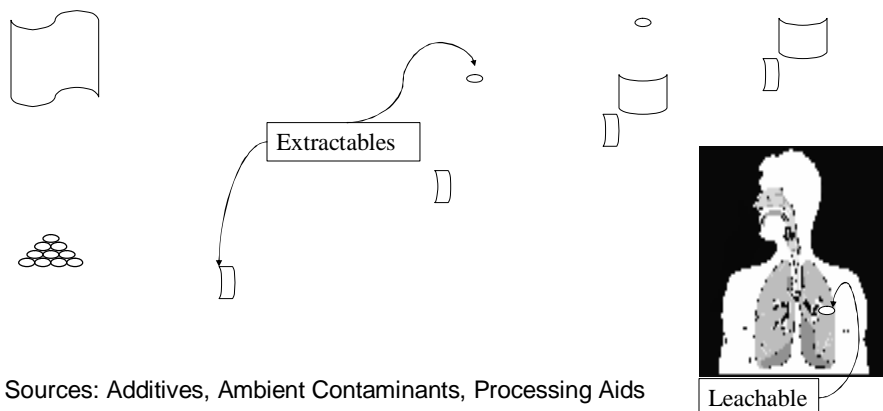
- Elastomers—valves and seals
- Metal—containers; functional/mechanical components

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## Life of An Extractable

Material Supplier → Component Mfr → Filler/Assembler → Pharm Mfr → Patient



Sources: Additives, Ambient Contaminants, Processing Aids

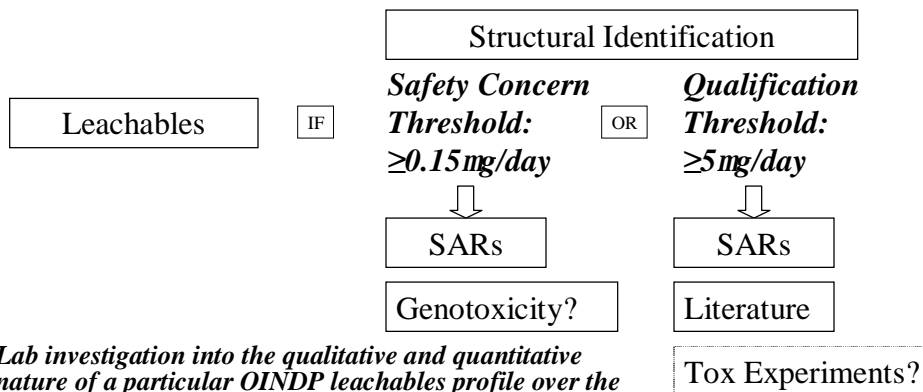
Leachable

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## Leachables—Safety Assessment

Product = Drug + Pkg + Device



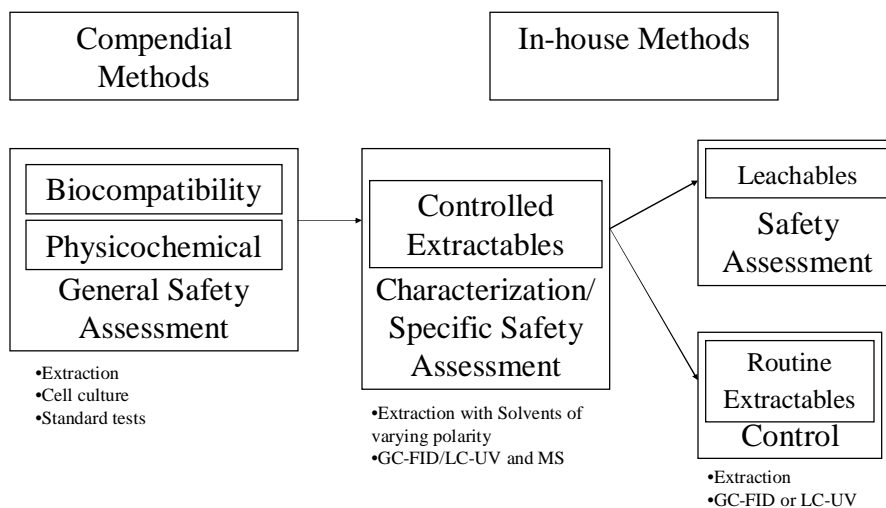
*Lab investigation into the qualitative and quantitative nature of a particular OINDP leachables profile over the proposed shelf life of the product.*

(Ref: Recommendations from PQRI Leachables & Extractables Workshop, Dec 2005)

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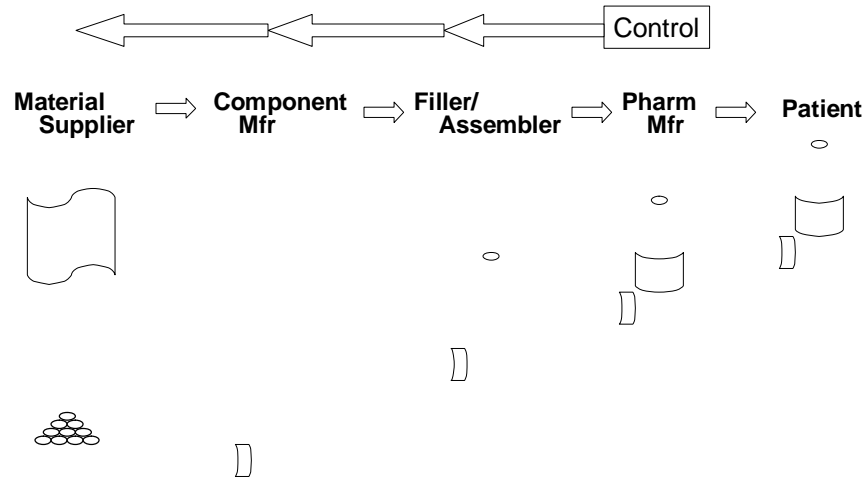
## Drug or Mucosal Contacting Components— Extractables for Characterization/Control



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## Control of Extractables



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## Component Extractables Controls— MDI/DPI Draft Guidance 1998

### Section III.G.2.a

“Critical components of the DPI are defined as those that contact either the patient (i.e., the mouthpiece) or the formulation, components that affect the mechanics of the overall performance of the device, or any necessary protective packaging.”

### Section III.G.2.c

“...the applicant should establish discriminatory test methods and set appropriate acceptance criteria of the extractable profile(s) for routine testing of incoming individual critical device components”

### Section III.G.2.e

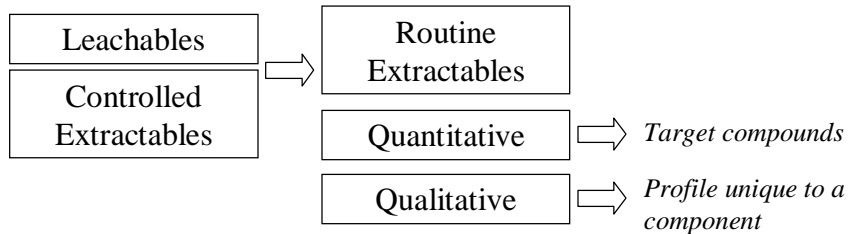
“Specifications should include...qualitative and quantitative extraction profile(s) of each individual component for indirect control of composition...”

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## Routine Extractables Method Development

*Molecules ID'd*



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## Routine Extractables Methodology

- Sample preparation
- Extraction
- Analysis



Stainless Beaker



Cryogenic Grinder



ASE (Accelerated Solvent Extractor)



GC-FID or  
HPLC-UV

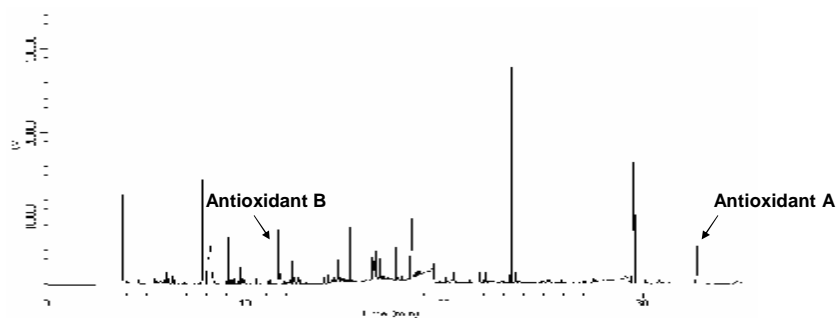


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## Routine Extractables Example

- Sample preparation: ground polypropylene
- Extraction: ASE
- Analysis: GC-FID

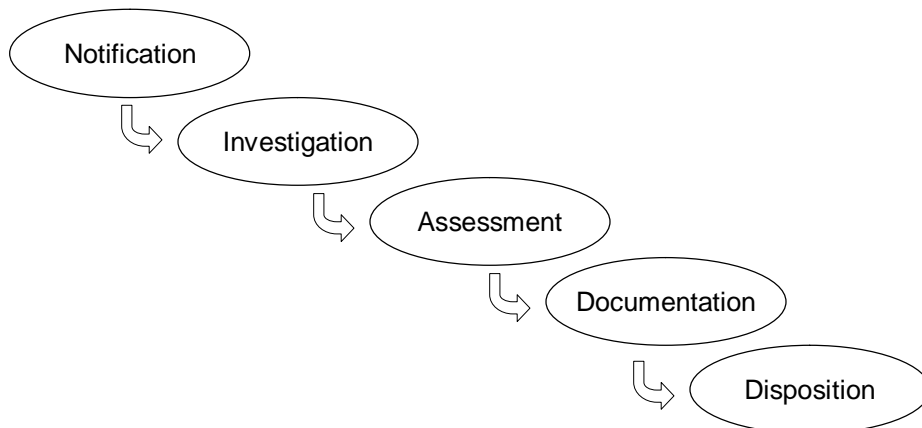


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## Component Extractables Controls— Managing the Unexpected

- What happens when an extractable result is out of specification?



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## Component Extractables Controls— Managing the Unexpected

u What happens when an extractable result is out of specification?

u **Case Study #1**

- Device component – elastomer
- Target compound level above upper limit
- Lab investigation shows result is accurate
- Batch rejected

u **Case Study #2**

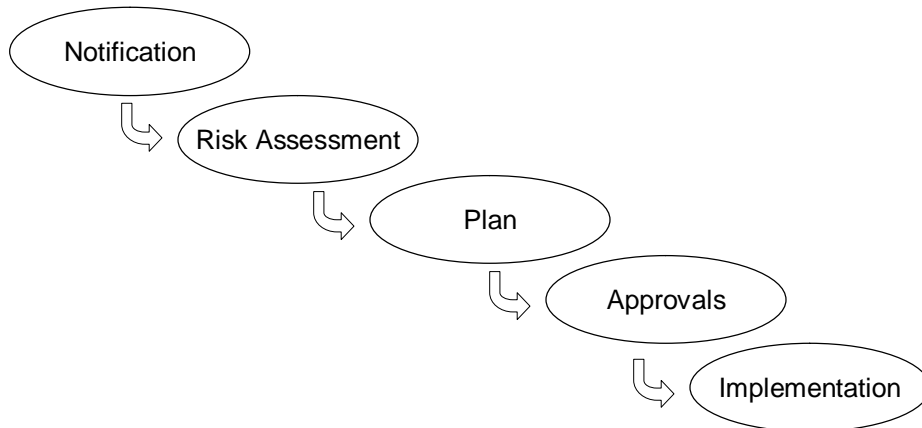
- Device component – elastomer
- Peak previously below threshold appears above threshold in chromatogram
- Lab investigation reveals identity of peak
- No concern based on safety evaluation of compound
- Batch released

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## Component Extractables Controls— Managing the Unexpected

u What happens when a critical component material goes obsolete?

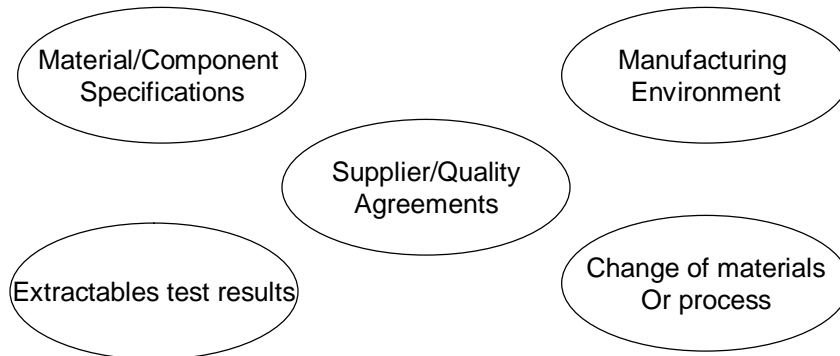


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## Component Extractables Controls— Managing the Challenges Together

- **Opportunities for interactions between OINDP Manufacturers and Suppliers**



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## Summary

- **A steady pipeline of Inhalation Products means a continuous need for high quality materials**
- **Extractables testing is expected as an indirect control of material consistency**
- **Recent recommendations call for very low levels of any detectable compounds, which in turn demand high levels of control over material and process throughout the supply chain**
- **Several opportunities exist for open communication between OINDP manufacturers and suppliers throughout the development and commercialization of OINDP**

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