



## IPAC-RS Related Activities Overview

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## Background on IPAC-RS



- **1989:** International Pharmaceutical Aerosol Consortium (IPAC) formed to address regulatory consequences for MDIs of Montreal and Kyoto Protocols
- **1999:** IPAC formed a Working Group to prepare comments on the FDA draft CMC Guidances for MDIs, DPIs, Nasal Sprays, and Inhalation Solutions/Suspensions
- **2001:** International Pharmaceutical Aerosol Consortium for Regulation and Science (IPAC-RS) formed as a separate Consortium

**Mission:** To advance scientifically driven approaches to enhancing product quality of inhaled and intranasal drug products



## IPAC-RS Member Companies



<b>3M</b>	<b>MannKind Corp</b>
<b>Abbott</b>	<b>Novartis</b>
<b>AstraZeneca</b>	<b>Pfizer</b>
<b>Boehringer Ingelheim</b>	<b>sanofi-aventis</b>
<b>Chiesi</b>	<b>Schering-Plough</b>
<b>GlaxoSmithKline</b>	<b>Teva</b>
	<b>Vectura</b>



## Overview of Working Groups

- **Supplier Quality**
- **Extractables & Leachables**
- **Materials**
- **L&E Development Paradigm**





## Supplier QC Working Group: A Unique Collaboration

- One of first IPAC-RS Working Groups
  - Initially addressed all topics related to component quality. Now focuses on GMP at component suppliers
  - OINDP suppliers were invited to join the Supplier QC Working Group as Associate IPAC-RS members. Current supplier members:

Valois 

bespak   
A division of Consort Medical plc

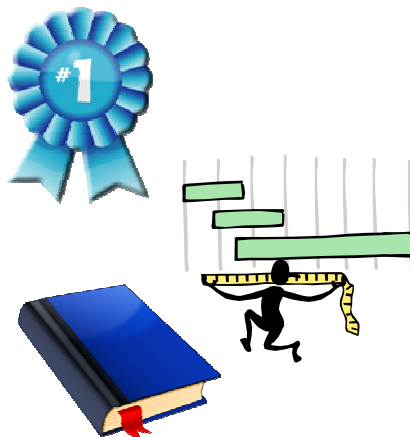
 SHL GROUP

REXAM

WEST   
Pharmaceutical  
SERVICES



## Working Group Mission: Product Quality and Patient Safety



Working Group seeks to:

- Encourage quality through design rather than through testing
- Enable the provision of consistently high quality OINDP components by promoting the implementation of robust quality systems at OINDP component manufacturers
- Simplify the quality control process by promoting harmonized quality standards for OINDP components



## Impetus for Guideline Development: Quality

- Ensuring high and consistent quality OINDP components is critical to QbD for OINDP
  - Quality of OINDP components significantly impacts the quality of finished OINDP and CMC tests
- Some aspects of quality are particularly important to OINDP
  - **change control**
  - **control of extractables**



## Working Group's Initial Focus: Gap Analysis



- Survey OINDP Suppliers and Manufacturers to determine:
  - Whether a quality guideline for OINDP suppliers is needed
  - If so, what topics this guideline should address
- Develop guideline for OINDP component suppliers
- Conduct education/training for OINDP manufacturers and their suppliers on use of the GMP Guideline



## Impetus for Guideline Development: Need for Further Guidelines

- **Lack of detailed quality guidelines specific to development and manufacture of OINDP components**
- **Hypothesis:**
  - **Quality practices vary widely between component suppliers**
  - **OINDP manufacturers (e.g., IPAC-RS members) each have slightly different expectations for component suppliers, and audit them using different standards**



## IPAC-RS GMP Guideline: Filling a Void

- **3-in-1 Guideline:**
  - ISO 9001:2000
  - **PS 9000:2001**
  - **IPAC-RS GMP Guideline**
- **Global Applicability**
  - The Guideline takes into account regulations and expectations for OINDP in all regions
  - The Guideline is intended to be used by suppliers in all regions
- **Provides tools to achieve and maintain compliance with GMPs (In alignment with 21 CFR 210-211 and 820)**
- **Does not address stand-alone devices or device manufacturers**





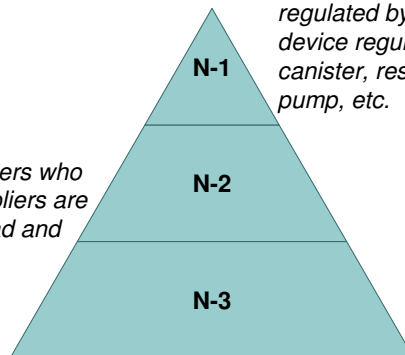
## Key Sections of IPAC-RS Guideline

- OINDP Components/Sub-components
- Quality Unit
- Change Control
- Supply/Quality Agreements & Specifications
- Control of Suppliers and Sub-contractors
- Design and Development Planning
- Monitoring & Measurement of Product
- Contamination Control & Cleaning



## Applicability of the IPAC-RS GMP Guideline

*n-2 and n-3 suppliers who supply to n-1 suppliers are encouraged to read and follow guideline*



*Applies to n-1 suppliers of components for OINDP not regulated by FDA or other device regulations, e.g., canister, reservoir, actuator, pump, etc.*

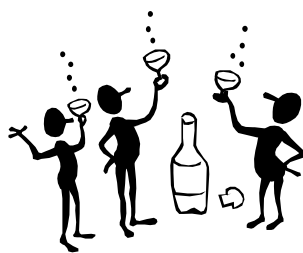


## Implementation of the Guideline

- OINDP manufacturers are encouraged to audit their suppliers against the guideline
- Responsibility for final drug product quality still rests with the OINDP manufacturer
- Over last 3 years, IPAC-RS has hosted workshops and training sessions in US and EU on OINDP Supplier GMP to introduce the guideline to suppliers, manufacturers and regulators
  - Held at cost to encourage supplier attendance



## Benefits of the Guideline



- Regulators:
  - More confidence in OINDP container closure system and device components
- Pharma:
  - Consistent, high quality components
  - Better relationship with suppliers
  - Fewer supply chain events
- Suppliers:
  - Clear understanding of customers' expectations
  - More consistent expectations and audits
  - Better relationship with customers
  - Improved quality systems

## Opportunities: Broader Applicability of Guideline

- Guideline can be applied to supply chain for other pharmaceutical dosage forms (e.g., parenterals, ophthalmics)
- “Toolkits” based on concepts in Guideline can be broadly applied



## Leachables & Extractables Working Group: A spin-off of Supplier QC

- The Leachables and Extractables Tech Team was spun off as a separate topic from the Supplier Quality WG
- The members of the L&E Tech Team were representatives from the IPAC-RS member companies
- In 2001, IPAC-RS in collaboration with ITFG (AAPS) developed *Leachables and Extractables Testing: Points to Consider*, which provided comments to Draft FDA guidances and also proposed safety thresholds
- In 2001, IPAC-RS submitted a proposal to PQRI to develop safety thresholds and best practices for L&E in OINDP
- PQRI L&E Working Group formed and lead by IPAC-RS

## PQRI Working Group Mission: Thresholds & Best Practices



- The development of safety thresholds and analytical best practices for extractables and leachables in OINDP.

## Key Deliverables from PQRI

- In 2001 the L&E WG was moved into the Product Quality Research Institute (PQRI)
- PQRI L&E Working Group has issued specific recommendations regarding extractables and leachables management and thresholds
  - Completed training courses based on PQRI L&E Recommendations
  - Publishing books and papers based on Recommendations



## L&E/PQRI WG Publications

- **Recently published:**

- *Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products: An Overview of the PQRI Recommendations*. D. L. Norwood, D. Paskiet, M. Ruberto, T. Feinberg, A. Schroeder, G. Poochikian, Q. Wang, T. J. Deng, F. DeGrazio, M. K. Munos, and L. M. Nagao, *Pharmaceutical Research*, 25(4), 727-739 (2008).

- **Books in progress:**

- Drafting *Development of Safety Qualification Thresholds and Their use in the Evaluation of Orally Inhaled and Nasal Drug Products*
- Contributing information to *IPAC-RS Handbook for Extractables and Leachables Evaluation in Pharmaceutical Products* (“L&E Handbook”)



## Materials Working Group: A spin-off of L&E

- Originally formed as IPAC-RS Elastomers Working Group as a spin-off of the L&E Work Group
- The members of the Materials WG are representatives from the IPAC-RS member companies
  - Focus was on making recommendations regarding end-product testing of PNAs and nitrosamines in elastomeric components.
- Consideration of the PNA/nitrosamine question highlighted broader issues important not only to PNAs and nitrosamines in elastomers, but to all extractables and component materials.

## Working Group Mission: Component Quality throughout the Supply Chain



- **Working Group seeks to:**
  - Improve materials quality and integrity
  - Reduce supply chain problems
  - Promote reduction or elimination of unnecessary testing through:
    - scientific, peer-reviewed publication(s) on the improvements in OINDP quality, and
    - education and training of all parties involved with the supply chain for OINDP components.

## Impetus for WG direction: Need for Further Communication/Education



- Varied perceptions of the extractables/leachables requirements for OINDP among Pharmaceutical Manufacturers and their Suppliers
- Movement toward management of extractables and leachables using an information-rich, risk-based approach
- Establishment of component quality beginning with material selection and support of robust quality systems throughout the supply chain



## Working Group's Initial Focus: Gap Analysis and Education

- Communication/understanding gaps were driver to establish workshops to bring together Pharma, Regulators and Suppliers
- Workshop topics included:
  - Regulatory perspectives
  - Material Selection, Characterization and Evaluation
  - Establishment of Routine Controls
  - Managing Change
- Workshop participants shared perspectives on:
  - Ways to improve communication from product design through development and commercialization
  - Selection of appropriate acceptance criteria through information-rich data sets and appropriate risk assessment
  - Importance of mutual understanding of suppliers' and OINDP manufacturers' expectations.



## Key Activities of Materials WG

- Helped develop and participated in IPAC-RS workshops and training course on supplier quality and extractables
- Advised on program for PIRA 2008 conference
- Contributing chapters to IPAC-RS L&E Handbook
- **Holding workshop on materials and extractables for Spring 2009**
- Drafting paper for publication in journals for suppliers of plastics and elastomers
- Developed half-day symposium on *Elastomeric Materials: Challenges in Pharmaceutical/Biomedical Applications*, for the American Chemical Society Rubber Division 174<sup>th</sup> Technical Meeting, 14-16 Oct 2008.

## Opportunities: Education & Global Outreach



- **Outcome of work to date:**
  - **Suggestions for additional tools to aid in closing the communication/understanding gaps (e.g. publications on technical requirements)**
  - **Additional workshops to include more global focus**

## L&E Development Paradigm Working Group: A spin-off of Materials/L&E

- **The L&E DP WG was developed to address how “QbD” concepts could be applied practically to L&E management for OINDP**
- **The members of the L&E DP WG are representatives from the IPAC-RS member companies**
  - Package engineering
  - Product Design
  - Quality





## Working Group Mission: Investigate QbD for OINDP L&E



- Working Group seeks to:
- Investigate how new and traditional approaches can be used to create a development paradigm for OINDP extractables and leachables



## Working Group's Initial Focus: Creating a Roadmap

- Activities:
  - Created decision trees and maps to illustrate and identify key component manufacturing processes that could affect extractables/leachables (using MDI as example)
  - Linked these processes back to product profile
  - Identified component manufacturing unit operations for which to develop quantitative models (e.g., injection molding, vulcanization)
  - Will develop statistically based quantitative models to demonstrate effect of manufacturing parameters on extractables profiles

