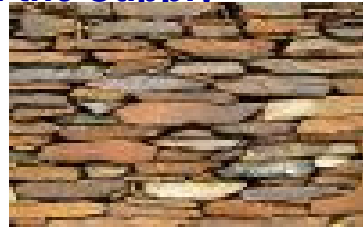




## **Strong Foundations: Building Quality through the Supply Chain**

**Barbara Falco  
IPAC-RS**





## Overview

- What is the IPAC-RS Supplier Quality WG?
- What is the Supply Chain?
- Why is quality in the supply chain important to patients?
- What are OINDP manufacturers doing to ensure supply chain quality?
- IPAC-RS Supplier GMP Guideline



## IPAC-RS Supplier Quality Working Group: A Unique Collaboration

- One of first IPAC-RS Working Groups, formed in 2000
  - Initially addressed all topics related to component quality. Now focuses on GMP for container closure system and device component suppliers
  - OINDP suppliers can join the Working Group as Associate IPAC-RS members. Current supplier members:

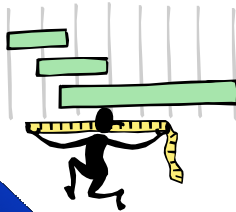
Aptargroup

REXAM

SHL GROUP

WEST Pharmaceutical SERVICES

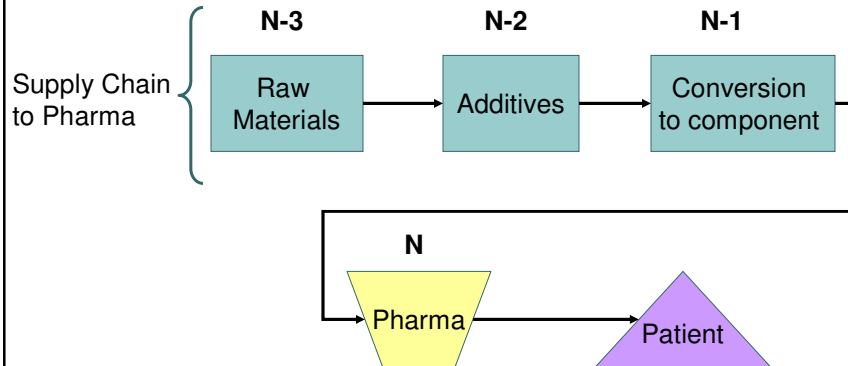
## Working Group Mission: Product Quality and Patient Safety



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

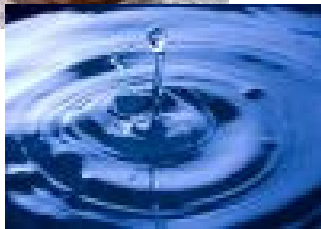
## Example Supply Chain



Most Supply Chains are much more complex!



## IPAC-RS interested in supply chain for OINDP container closure systems and devices



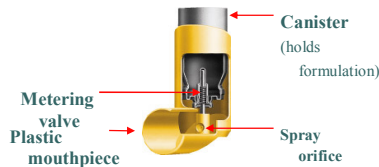
- **Quality of OINDP CCS/device components may significantly impact the safety and efficacy of finished OINDP**
- **Directly affects patients**



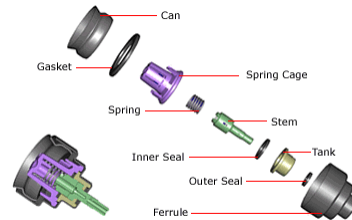
## Component Materials: Pressurized MDI (Plastic & Metal)



**Metered Dose Inhaler (MDI)**



**Metering valve**



Sources of Images: public industry presentations/ web sites



Multidose DPI



Single Dose DPI



Re-fillable DPI

Disposable or semi-disposable plastic devices (metal parts)



## Nebulizers & Nasal Sprays

Nebulizer

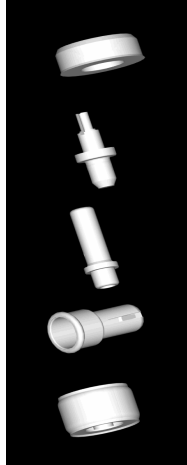


Nasal Sprays



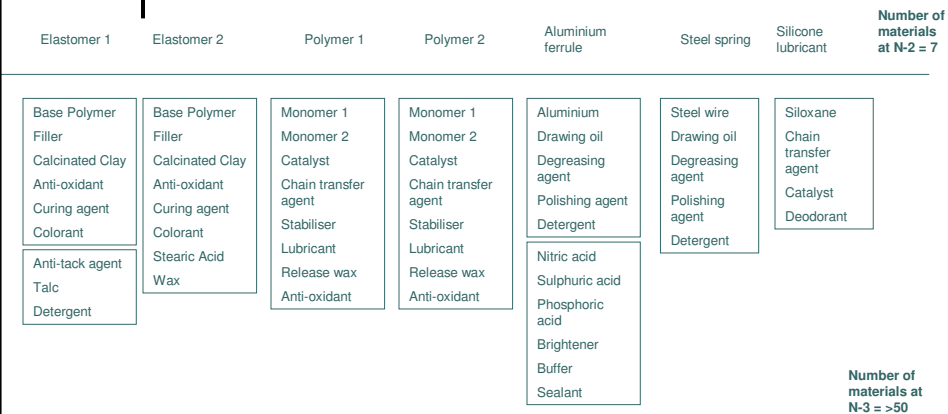
# Component Materials

## Plastics



- POM (acetal resin)
  - Most commonly used
- PBT (Polyester)
  - no formaldehyde release
- Nylon
  - Act as moisture sink

# MDI Valve Supply Chain



## CMC Tests for OINDP in FDA Guideline

### Component quality plays a critical role in many OINDP CMC tests

1. *Assessment of Packaging Materials*
2. Appearance / Description of Product
3. Color
4. Identification (2 specific tests)
5. Chiral Specificity, if applicable
6. *Microbial Limits*
7. *Microbial Challenge*
8. *Water Content*
9. Alcohol Assay if applicable
10. Content Assay
11. Assay for other excipients
12. Net Content Weight
13. *Leak Rate*
14. *Pressure Testing*
15. *Spray Pattern*
16. *Plume Geometry*
17. *Valve Delivery (Shot Weight)*
18. *Dose Content Uniformity (uniformity of API delivered from mouthpiece)*
19. *Dose Content Uniformity Through Canister Life (API delivered from mouthpiece at beginning, middle, end of canister)*
20. Particle Size Distribution of API – Mass Balance and Groupings (Cascade Impactor)
21. *Effect of Storage on Particle Size Distribution*
22. Microscopic Evaluation (particle size, morphology, crystallinity, amorphous forms, agglomerates, etc.)
23. *Foreign particles (enumeration, characterization)*
24. *Leachables*
25. *Extractables*
26. *Dissolved metals*
27. Impurities and Degradation Products
28. *Number of Doses Delivered*
29. Effect of Resting Time
30. *Priming and Re-priming*
31. *Drug Deposition on Mouthpiece and/or Other Accessories*
32. *Profiling of Actuators Near Canister Exhaustion*
33. In vitro Dose Proportionality (multi-strength doses)
34. *Effect of Flow Rates*

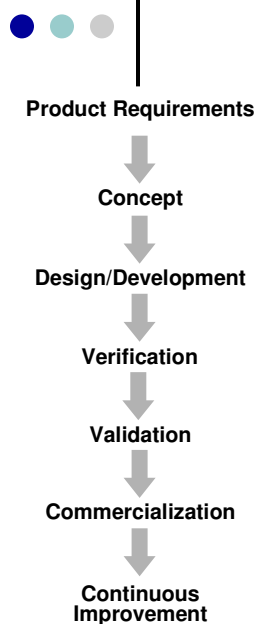
## Health Canada Pharmaceutical Quality of Inhalation and Nasal Products (2006): Pharmaceutical Development Tests

- Shaking requirements
- Initial & re-priming requirements
- Cleaning requirements
- *Actuator / mouthpiece deposition*
- *Low temperature performance*
- *Performance after temperature cycling*
- *Effect of environmental moisture*
- *Robustness*
- *Physical characterisation*
- *Minimum fill justification*
- *Extractables / Leachables*
- *Delivered dose uniformity & fine particle mass through container life*
- *Delivered dose uniformity & fine particle mass over patient flow rate range*
- *Fine particle mass with spacer use*
- *Single dose fine particle mass*
- *Particle / droplet size distribution*
- *Drug delivery rate and total drug delivered*
- *Delivery device development*
- *Preservative effectiveness / efficacy*
- *Compatibility*

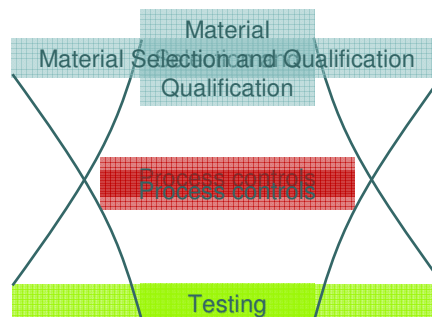
## Supplier Quality Landscape ~2000

- Quality practices varied widely between component suppliers
- OINDP manufacturers (e.g., IPAC-RS members) had slightly different expectations for component suppliers, and audited them using different standards
- Lack of detailed quality guidelines specific to development and manufacture of OINDP components

## Risk-based Approach



- Phase appropriate
- Information/data based
- Emphasis on upstream mitigations

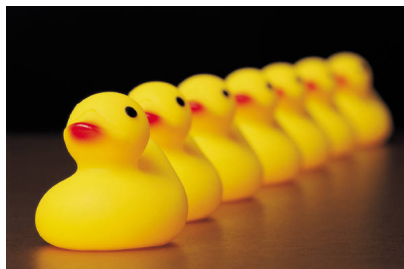


## Working Group Developed the IPAC-RS Supplier GMP Guideline



- Conducted a survey of suppliers to determine if gaps in GMP understanding and uniformity of customer expectations
- Determined that guideline was needed
- Guideline published in 2006

## 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

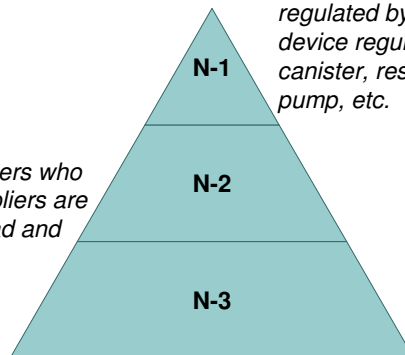
## IPAC-RS GMP Guideline: Filling a Void



- **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)**
- **Is intended to compliment stand-alone devices or device manufacturers current practices**

## Applicability of the IPAC-RS GMP Guideline

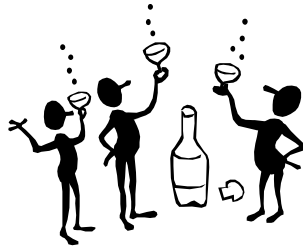
*n-2 and n-3 suppliers who supply to n-1 suppliers are encouraged to read and follow guideline*



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



## Benefits of the Guideline



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



## Primary Benefit

- **Serving the Patient**





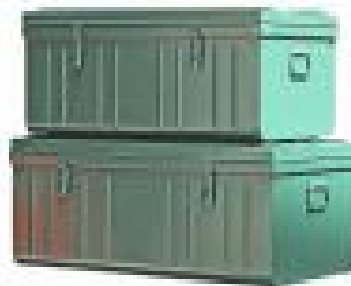
## Implementation of the Guideline

- **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 4 years, IPAC-RS has hosted workshops, training sessions, and web-seminars on OINDP Supplier GMP to introduce the guideline to suppliers, manufacturers and regulators**
  - **US, EU, Asia**
  - **FDA, Health Canada**



## On-going Work -- Toolkits

- Toolkits for pharma and suppliers publicly available at [www.ipacrs.com](http://www.ipacrs.com)
  - Quality Agreement Template
  - Regulatory Requirements
  - OINDP Performance Requirements





## On-going Work – PS 9000:2011

The Pharmaceutical Quality Group



- IPAC-RS collaborating with PQG to develop the PS 9000:2011 for pharmaceutical packaging and CCS. Includes:
  - Language from PS 9000:2000
  - Language from IPAC-RS guideline for OINDP component suppliers
  - Concepts from ISO 9001:2008 and ISO 15378
- PQG drafting group comprised of Pharmaceutical manufacturers, packaging component suppliers and service providers



## On-going Work – PS 9000:2011

- Drafting group met face-to-face 6 times in 2010/2011 to generate document
- First draft circulated widely to suppliers and pharmaceutical manufacturers for comments in 2010
- All comments addressed in face-to-face meetings – Nov 2010/Jan 2011
- Final Draft document completed February 2011





## On-going Work – PS 9000:2011

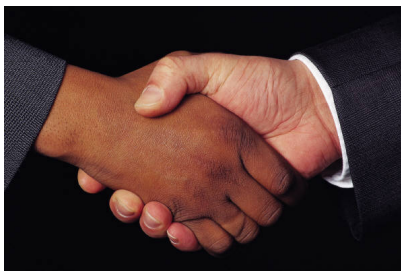


- Launch of PS 9000:2011 scheduled for September 2011
  - Launch to include extensive training on how to use and comply with the document
- Plan to have document accessible via web
- Interactive: user can choose to only review text for primary packaging or secondary packaging, etc



## On-going Work: Outreach and Collaborations

- Continue to collaborate with IPAC-RS Materials WG on international workshops and training sessions – EU, US, Asia
- Look for opportunities to collaborate where necessary with other supply chain organizations (e.g., Rx-360)





## Summary

- The supply chain for OINDP has significant impact on the quality, safety and efficacy of product for patients
- IPAC-RS continues to partner with the OINDP supply chain to help ensure quality of CCS/device components
  - Communication
  - Relationship building
  - Trust!



THANKS!