



24 Sept 2007

Guidance on GMP for OINDP Components IPAC-RS GMP Guideline

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*Workshop on Extractables and GMP for Components of
Inhalation and Nasal Drug Products*
September 24, 2007



Guidance on GMP for OINDP Components: IPAC-RS GMP Guideline

24 Sept 2007

Slide no 2

Agenda

- 1 History & Mission
- 2 Regulatory Framework
- 3 Layout & Application of IPAC-RS GMP Guideline
- 4 Using the IPAC-RS GMP Guideline
 - Suppliers
 - OINDP Manufacturers
 - General Principles



GOALS

- Understand
 - The application and use of the IPAC-RS Guideline
 - How to apply the guideline to your processes and products --- to foster improvements
 - How to use the Guideline as a tool for
 - Communication
 - Auditing



IPAC-RS Supplier QC Working Group

- Includes representatives from Pharma (IPAC-RS members) and Suppliers
- Strives to be open and transparent
- Mission:
 - Product Quality & Patient Safety
 - Encourage quality through design -- rather than through testing
 - Enable consistently high quality OINDP components by:
 - promoting the implementation of robust quality systems at OINDP component manufacturers
 - To simplify the quality control process by:
 - promoting harmonized quality standards for OINDP components



IPAC-RS Guideline Working Group

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Teva	John Goulding
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West	Fran DeGrazio Tom Gaspar

Why Develop a Guideline ???

- Ensuring high and consistent quality components is critical to QbD for OINDP
 - Component Quality significantly impacts quality of finished OINDP & CMC tests
 - Some aspects are particularly important
 - change control
 - control of extractables
- No existing quality guideline provides guidance for OINDP components
- Hypothesis
 - Quality practices vary widely between component suppliers
 - OINDP Pharma Mfg's each have different expectations and audit component suppliers using different standards

Benefits of the Guideline

Regulators:

- Ø More confidence in OINDP container closure system and device components

Pharma:

- Ø Consistent, high quality components
- Ø Better relationship with suppliers
- Ø Fewer supply chain events

Suppliers:

- Ø Clear understanding of expectations
- Ø More consistent expectations & audits
- Ø Improved quality systems



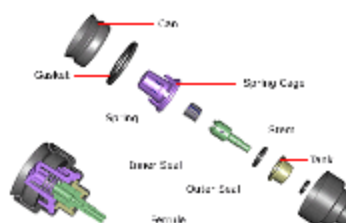
Component Materials: Pressurized MDI (Plastic & Metal)



Metered Dose Inhaler (MDI)



Metering valve



© 3M



Sources of Images: public industry presentations/ web sites





Multidose DPI



Single Dose DPI



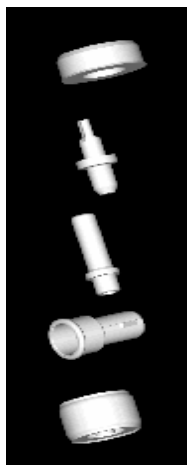
Re-fillable DPI

Disposable or semi-disposable plastic devices (metal parts)



Component Materials

Plastics



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

Aerogen Technology

- AeroNeb™ based on Aerogens OnQ™ aerosol generator technology - a micro pump for nebulizers.
- The aerosol generator consists of a domed shaped plate that contains up to 1000 precision-formed tapered holes surrounded by a vibrational element.

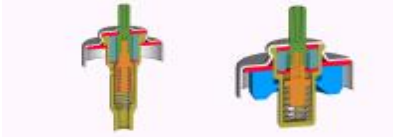


<http://www.aerogen.com>



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Component Materials




Metering Valves

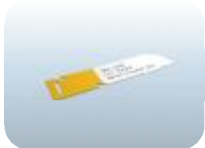
- Valve, Internal Gaskets, Sealing Gaskets, Rings (Polyester, Nitrile, Chlorprene, etc.)
- Mfg under class 10,000 and GMP.
- Materials comply with EP, USP, FDA.

**AERx® iDMS
Single Use Insulin Strip**




- Multi-laminate container system holding liquid insulin formulation
- Materials comply with EP, USP, FDA.






Gaskets



Valois


- All 'white' gaskets avoiding the extracts issues associated with carbon black fillers.
- No Latex (only synthetic rubber)
- All materials comply with EP, USP, FDA
 - Elastomer or base rubber:
 - Nitrile, Chloroprene, E.P.D.M., TPE (thermoplastic elastomer), Novel Alloys
- Curing Agent, Accelerators, Activators, Fillers, Antioxidants, Processing Aids, Coloring or Pigments



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Laws, Regulations, Guidances

- U.S. Law, Guidance:
 - The Federal Food, Drug, and Cosmetic Act requires that adequate information be submitted in support of drug packaging materials
 - "a drug or device shall be deemed to be adulterated if its container is composed in whole or in part of any poisonous or deleterious substance which may render the contents injurious to health" (Section 510(a)(3))
 - 21CFR § 210 and 211
 - 21CFR § 820
 - Guidance documents for:
 - MDI, DPI Drug Products
 - Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products
 - USP
- European and Canadian Guidance:
 - MHRA Rules and Guidance for Pharmaceutical Manufacturers and Distributors - "Orange Book"
 - Joint EMEA/Health Canada Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products
 - EMEA Guideline on Plastic Immediate Packaging Materials
 - European Pharmacopoeia
- International Guidelines
 - ICH
 - ISO 15378
 - ISO 9001
 - PS: 9000: 2001



European Directorate for the Quality of Medicines



Regulation of OINDP

- Regulatory Agencies - control the drug product (device/components/formulation) produced by pharma, not suppliers of drug product components
 - Guidances for OINDP set forth expectations for the quality of OINDP components
 - Joint EMEA/Health Canada Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products, 2006
 - EMEA Guideline on Plastic Immediate Packaging Materials, EMEA 2005
 - Nasal Spray & Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing & Controls Documentation, FDA, CDER, 2002
 - Draft Guidance for MDI and DPI Drug Products, CDER, 1998
- HOWEVER:
 - Many CMC requirements are impacted by component quality



Expectations from Guidance Documents

"...potential **leaching of compounds** from the elastomeric and plastic components...is a serious concern that should be addressed. Therefore, the **composition and quality of the materials** used in the manufacture of the container and closure system components should be carefully selected."

"the **compatibility** of the pump, container and closure with **formulation** components should be thoroughly investigated and established before initiating critical clinical, bioequivalence, primary stability studies"

"The identity and concentration of recurring **leachables** in the drug product or placebo formulation.....should be correlated with the **extractables** profiles of the container closure components....."

Source: Container Closure System & Component Quality from MDI/DPI Draft Guidance and 2002 Inhalation Guidance,

" **Metering valves** for aerosols are more **complex pieces of engineering** than most items used in pharmaceutical production. Their **specifications, sampling and testing should recognize this...**

"Valves should be **cleaned** using a validated procedure.....to ensure the absence of any contaminants such as fabrication aids (e.g. lubricants)...."

Source: MHRA Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007



CMC Tests for OINDP in FDA Guidances

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, and 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 Actuations Near Canister Exhaustion**
33. In vitro Dose Proportionality (multi-strength doses)
34. **Effect of Flow Rates**

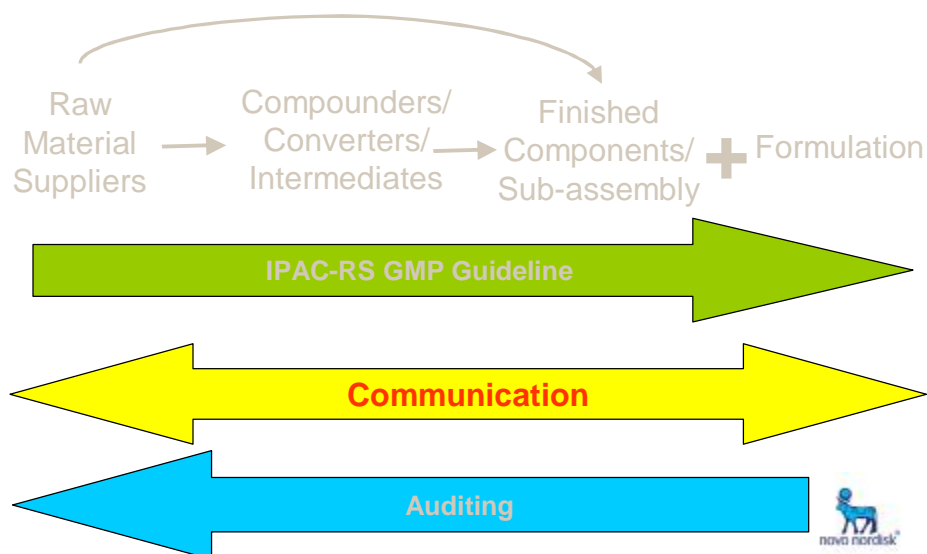


Initiatives: Quality by Design & Supplier Quality Control

- **ICH Q8: Pharmaceutical Development:**
 - *"It is important to recognize the quality cannot be tested into products; i.e., quality should be built in by design."*
 - Build quality into the product from the beginning
 - Start with the design phase
- **ICH Q9: Quality Risk Management**
 - *"To assess the critical attributes of raw materials, solvents, API, excipients, packaging materials"*
 - *"To decrease variability of quality attributes:*
 - reduce product and material defects
 - reduce manufacturing defects
 - Make the use of the "design space" concept (ICH Q8)"
- **ICH Q10: Pharmaceutical Quality System**
- **Quality begins with the components**
 - Ensuring high and consistent quality OINDP components is critical to QbD for OINDP.
 - Foundation for this is:
 - Robust quality systems at suppliers (& manufacturers)
 - Constructive communication between suppliers and customers



Quality by Design for OINDP (with focus on supply chain)



Why the IPAC-RS GMP Guideline?

- Typical OINDP includes many different components interacting with each other and the formulation

- Components are critical to delivery of the drug product

- End product testing alone is not sufficient to ensure product quality

- Specifications look for what you expect

- An overall system that builds in quality

- "Chain of Implicit Trust"

No
regulation of
/ or guidance
to suppliers

IPAC-RS GMP
Guideline for
Suppliers of
OINDP
Components



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What is the IPAC-RS Guideline?

- 3-in-1 Guideline: >200 pages
 - ISO 9001:2000
 - PS 9000:2001
 - IPAC-RS GMP Guideline
- A “toolbox” to achieve and maintain compliance with GMPs
 - In alignment with 21 CFR 210-211 and 820
 - Based on ANSI/ISO/ASQ
 - Serve as a framework to address component quality, control of suppliers, consistency within the industry



Layout

- Guideline includes requirements from 3 standards:
 - ISO 9001 (Boxed black text)
 - PS 9000 (Boxed blue text)
 - IPAC-RS (Boxed green text)
- Guideline also includes ISO 9004 as guidance (non-boxed black text)
- Layout follows layout of PS 9000, e.g.,
 - ISO 9004 1
 - ISO 9001 1, 1.1, 1.2
 - PS 9000 1, 1.1, 1.2
 - IPAC-RS 1, 1.1, 1.2
 - ISO 9004 2
 - ISO 9001 2, 2.1, 2.2 etc.



Application

- Applies to suppliers of components for OINDP not regulated by international or device regulations, e.g.,
 - Canister / reservoir / primary package
 - Actuator
 - Pump
 - etc
- Does not address stand-alone devices or device manufacturers
- Applies to n-1 suppliers
 - n-2 and n-3 suppliers who supply to n-1 suppliers are encouraged to read and follow Guideline
 - Toolbox to achieve and maintain compliance with GMPs



Global Applicability of the IPAC-RS GMP Guideline

- Takes into account regulations and expectations for OINDP worldwide
- For use by suppliers in all regions



Relationship to ISO 15378

- ISO 15378:2006: Primary Packaging Materials for Medicinal Products –
 - Particular requirements for the application of ISO 9001:2000
 - Incorporates many aspects of PS 9000
 - IPAC-RS became aware of 15378 in late 2005
 - Does not conflict with IPAC-RS Guideline
- Next Steps
 - IPAC-RS to work with ISO to incorporate IPAC-RS Guideline text into next version of ISO 15378
 - Investigating working with ASTM to develop IPAC-RS Guideline text into a standard



Relationship to ISO 15378

- ISO 15378 will get you ~80% of the way to compliance with the IPAC-RS Guideline; good starting point
- IPAC-RS Guideline is slightly more detailed with respect to:
 - Quality Unit Responsibility and Authority
 - Change Control
 - Design Inputs
 - Specifications
 - Batch Documentation
 - Material Changeover/Line Clearance
 - Component Cleaning
- IPAC-RS Guideline also addresses a few topics not covered in ISO 15378
 - Extractables
 - Supply & Quality Agreements



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Key Sections of IPAC-RS GMP 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



OINDP Components/Sub-components



- **Defines system of supply chain**
 - n OINDP pharmaceutical company
 - n-1 supplier of component to pharmaceutical company
 - n-2 supplier to n-1
- **Defines Component/Sub-component**
 - direct contact with formulation or patient mucosa (primary packing, mouthpiece)
 - integral part of inhaler, nebulizer critical to performance (metering valve, airway, pump)
- **Terms and Definitions**
 - provide GMP background
 - inhalation focus



Quality Unit



- **Quality Unit**
 - key foundation for quality management system
 - authorities
 - approve/reject components
 - review and approve changes
 - responsibilities
 - approve/reject procedures, non-conformances
 - review complaints, determine need for investigation
 - assess suppliers
 - approve validation, verification, qualification



Change Control



- Ensures changes to process, materials, specifications.....affecting functionality, quality, safety
 - have a valid approach
 - are documented
 - agreed upon
- OINDP manufacturers and component suppliers should discuss, understand, and agree on:
 - What constitutes a significant change
 - What type of changes require notification and/or approval
 - How changes will be implemented
 - evaluate for impact on quality
 - validation required?
 - Suppliers should ensure that their suppliers have adequate change control programs



Change Control



- Why is it important?
 - OINDP considered "high risk"
 - Drug delivery via inhalation can be as quick as an injection
 - Lung/respiratory system less robust than e.g. digestive system
- Each OINDP device is composed of **multiple components from multiple materials –which can impact device performance and drug delivery**
 - rubber valve with improper additives may swell
 - change in antioxidant may impact component functionality
 - change in cleaning process may result in new foreign particulates or leachables
 - change to resin or component of the resin may change the extractables/leachable profile



Change Control



- **Consequences of Unapproved/Unanticipated Component or Material Change**
 - **Best Case:** Unapproved change is detected at receipt /incoming testing by customer
 - Results in supplier investigation (time/resources); material scrap; customer production delays
 - **Worst Case:** unapproved changes to component/material causes final product failure in the field
 - Customer (OINDP Mfg) must recall product
 - Ø Notification to Regulatory Body
 - Ø Cost
 - Ø Customer market perception
 - Time must be spent on investigations to determine cause and fix



Supply Agreements & Quality Agreements



- **Supply Agreements**
 - pricing, legal terms
 - GOAL= sustained supply
- **Quality Agreements**
 - batch records & manufacturing environment
 - responsibility matrix
 - release & approval
 - audits
 - recall
 - process validation
 - change control and notification
 - reference to ISO, IPAC-RS Guideline, etc.



Control of Suppliers and Sub Contractors

- **Subcontracting**

- Ensure control of your supply chain –
Functionality, Quality, Safety



- Supplier qualification
 - questionnaire
 - site visit
 - periodic verification of data
 - Contractual agreement
 - change control
 - what requires notification
 - documentation (CoA, CoC)
 - level of control for n-1, n-2, n-∞



Design and Development Planning

- **Component Design and Development**

- Understand intended use of product & component
 - Performance requirements.....affecting
 - functionality
 - quality
 - safety
 - compatibility
 - stability over time
 - "Use-By" or "Requalification" Date
 - stability to the design features post....sterilization, gamma irradiation
 - Have a valid approach
 - document – User Requirements Specification (URS)
 - utilize FMEA / FMECA
 - agreed upon



" Metering valves for aerosols are more complex pieces of engineering than most items used in pharmaceutical production. Their specifications, sampling and testing should recognize this..." MHRA Rules and Guidance

"It is important to recognize quality cannot be tested into products; i.e. quality should be built in by design..ICH Q8



Monitoring & Measurement of Product



- Characterization and Functionality testing
 - Specifications & testing requirements
 - sampling, attributes validation, acceptance criteria
- Control of ancillary materials (mould release agents, lubricants, etc.)
 - Establish acceptability
 - Compliance to
 - Ph.Eur. Sections 3.1 & 3.2 (Containers)
 - EMEA Guideline on Plastic Immediate Packaging Materials, 2005
 - GRAS, FDA/21CFR



Monitoring & Measurement of Product



- Extractables
 - Design and Development Planning
 - Partnership
 - Compatibility to formulation
 - Patient contact



Contamination Control/Cleaning



- **Cleaning and Foreign Particulates**
 - What is the level required for the component?
- **Residues from manufacturing process**
 - Mould release agents
 - Lubricants
 - Etc
- **Environmental contamination and particulates**
- **Microbial contamination**
- **Cross-contamination from other materials**
 - Particularly with use of non-dedicated equipment



Cleaning

Why Clean?



- **Patient safety**
 - Minute quantities of residue can leach into the drug product, exposing patients to compounds with potential safety issues
 - Small particulates can irritate airways, particularly individuals with compromised respiratory systems
- **Product quality**
- **Impact on OINDP manufacturers' regulatory compliance**
 - Potential impact on drug product registration
 - Leachables & extractables testing and specifications
 - Characterization of foreign particulates
 - Microbiological testing and specifications



“Cleaning” Scope



- Environment -Facility Design
 - ISO Clean Room conditions
 - Enhanced conditions
- Dedicated and Non-Dedicated Equipment
 - Risk Assessment (process, material, component)
 - Purge Cycle
- Component and Equipment Cleaning
 - “what” are you removing
 - requirements
- Validation & monitoring
- Packaging and Storage
- Ensure that cleaning processes/products do not introduce additional contaminants!
- Customer and Supplier
 - Discuss
 - Agree
 - Document



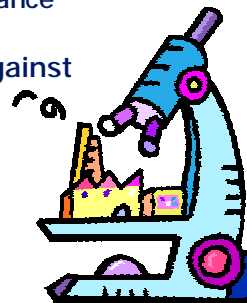
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Expectations: n-1 Component Suppliers

- Expected to read and follow the contents of the IPAC-RS, PS 9000, and ISO 9001 sections of the Guideline (boxed text)
 - ISO 9004 text provides additional guidance but is not required
- May be audited by OINDP customers against sections:
 - IPAC-RS
 - PS 9000: 2001
 - ISO 9001: 2000
- US Regulatory Agency embraces the guideline



Use: n-1 Component Suppliers

- Guideline allows room for variation based on needs of customer and supplier:
 - Many requirements are
 - Ø "as defined by the customer"
 - Ø "as agreed between the supplier and the customer,"
 - Ø "where applicable"
- **Communication** between the supplier and customer is emphasized in the Guideline and is a key element of the Guideline
- **Communicate** with your sub-suppliers



Use: n-2/n-3 Component Suppliers

- Are **critical to the final quality** of OINDP components
 - Additives ...pigments, antioxidants in bulk materials (e.g., rubber, elastomer) can produce extractables
 - Raw material attributes are linked to performance of the final product
- Are encouraged to read and follow the Guideline where applicable/ appropriate



Ventaira Mystic™



Use: n-2/n-3 Component Suppliers

- Topics of particular importance at the n-2/n-3 level include:
 - Change control
 - Cleaning and material changeover procedures
- n-2/n-3 suppliers should **communicate** with their customers regarding which sections of the Guideline may apply
- n-2/n-3 suppliers should **communicate** with customers to understand the use of their materials and the impact of potential changes



Use: Five Steps for Component Suppliers



- Review the Guideline
- Assess
 - Do changes need to be made to procedures, processes, or other documentation?
 - Are new procedures needed?
- Ensure that employees are trained on any changes to affected processes/procedures
- **Consult** with your customers
- **Inform** your suppliers/sub-suppliers and subcontractors of expectations



Use: Five Steps for OINDP Manufacturers



- Review it!
- Make your suppliers aware of the Guideline
- Encourage suppliers to **use** it
- Make your auditors aware of the Guideline
 - train them in its purpose and use
- **Consult** with your suppliers
- **Ensure** that they have the necessary information from you regarding:
 - how their component will be used
 - your requirements for their component
- **Consult** with your suppliers to determine whether they need assistance in meeting the Guideline's requirements



Use: General Principles

- Review
- Assess
- Train
- **Communicate**
- **Ask Questions**
- Remember- Goals are
 - Consistently high quality OINDP components,
 - Clear, uniform quality standards for OINDP suppliers



Benefits of the Guideline

↳ Regulators:

- Ø More confidence in OINDP container closure system and device components

↳ Pharma:

- Ø Consistent, high quality components
- Ø Better relationship with suppliers
- Ø Fewer supply chain events

↳ Suppliers:

- Ø Clear understanding of expectations
- Ø More consistent expectations & audits
- Ø Better relationship with customers
- Ø Improved quality systems

↳ Patients:

- Ø Confidence and Trust in their medication
 - Ø Consistent delivery & performance
 - Ø Product safety and quality



Overarching Goals

- Patient Safety
- Regulatory Compliance
- Building a Quality Foundation
 - Quality by Design



Questions?

