



IPAC-RS GMP Guideline for OINDP Component Suppliers: Application and Use

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Outline

- Regulatory Framework
- Layout & Application of IPAC-RS GMP Guideline
- Use of IPAC-RS GMP Guideline
 - Suppliers
 - OINDP Manufacturers
 - General Principles

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Regulatory Framework



OINDP Regulation in the US

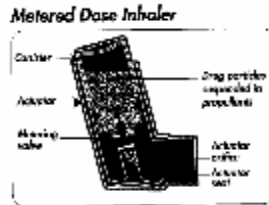
- The Federal Food, Drug, and Cosmetic Act requires that adequate information be submitted in support of drug packaging materials
- The Act states that

“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 501(a)(3))





OINDP Components



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Sources of Images:
IPAC-RS SQC WG and suppliers' public catalogues
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FDA Regulation of OINDP

- *Guidances* set forth FDA's current thinking on a particular topic.
- FDA Guidances apply only to companies that develop, manufacture, and/or market drug products
- FDA does not regulate suppliers of drug product components
- HOWEVER:
 - FDA Guidances for OINDP set forth expectations for the quality of OINDP components
 - Many CMC tests are impacted by component quality



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FDA Regulation of OINDP

- FDA regulates the drug product (device/components/formulation) produced by pharma, not suppliers of drug product components
 - Nasal Spray & Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing & Controls Documentation - July 2002
 - Draft Guidance, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing & Controls Documentation - 1998
 - Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation- 2001



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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.....”

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CMC Tests for OINDP in FDA Guidances

Component quality plays a critical role in many OINDP CMC tests

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

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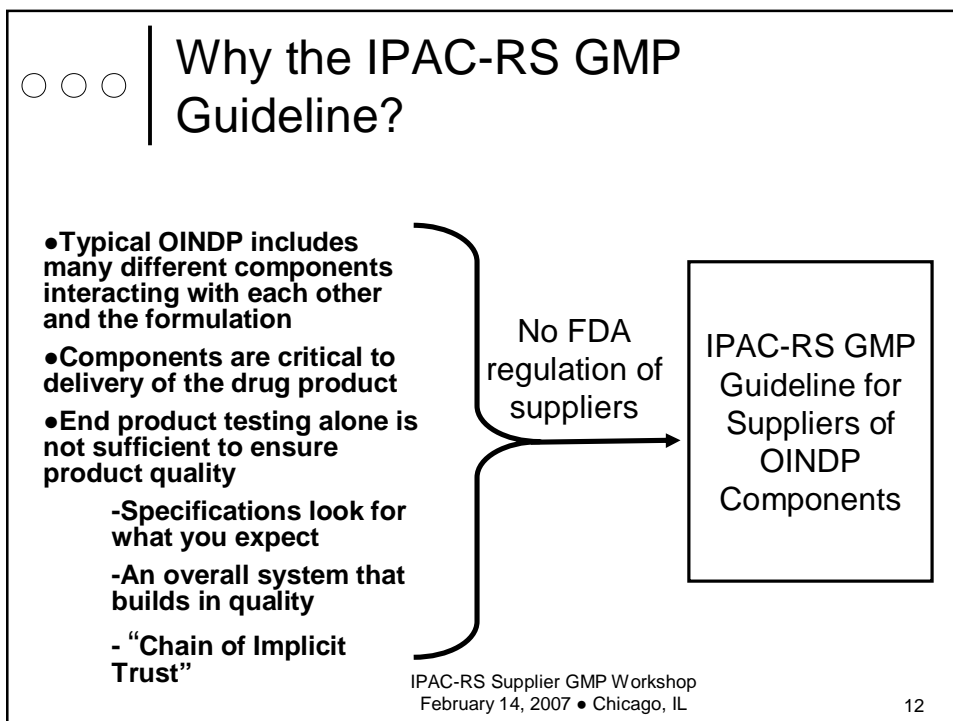
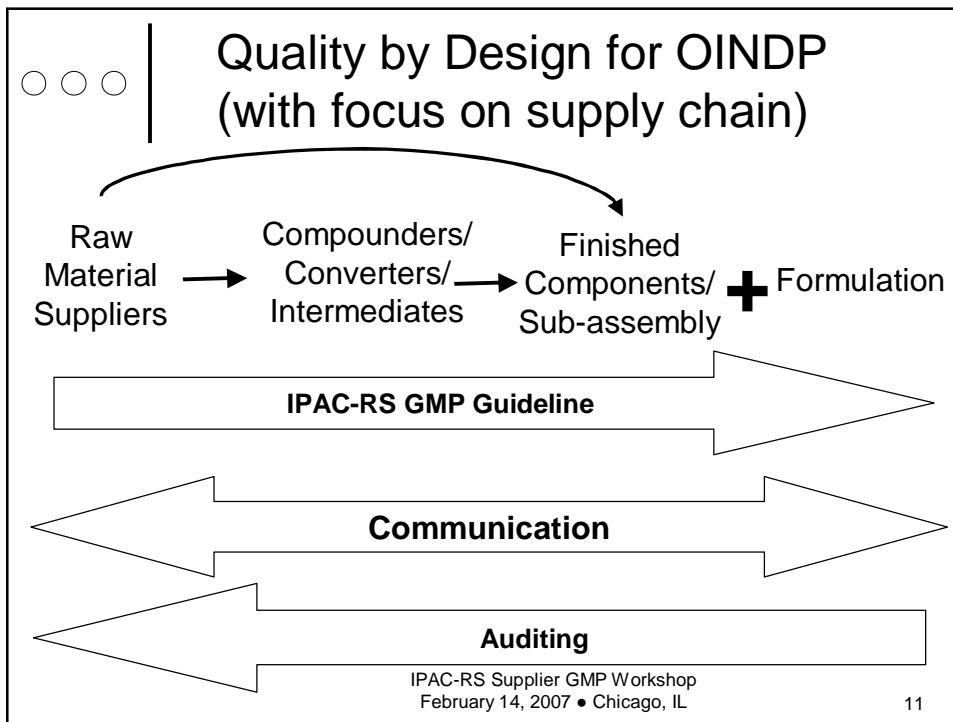


New FDA Initiatives and SQC

- **QBD** : Quality by Design
 - Build quality into the product from the beginning
 - Start with the design phase
- **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

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Application and Layout of the IPAC-RS GMP Guideline

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What is the IPAC-RS GMP Guideline?

- 3-in-1 Guideline:
 - ISO 9001:2000
 - PS 9000:2001
 - IPAC-RS GMP Guideline
- Provides tools 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.



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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.

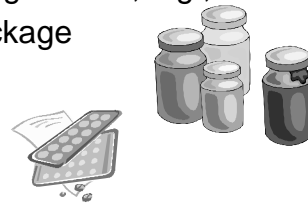
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Application

- Applies to suppliers of components for OINDP not regulated by FDA or other 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
 - provides tools to achieve and maintain compliance with GMPs



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Global Applicability of the IPAC-RS GMP Guideline

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



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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
 - IPAC-RS hopes to work with ISO to incorporate IPAC-RS Guideline text into next version of ISO 15378

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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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Using the IPAC-RS GMP Guideline

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Key Sections of IPAC-RS GMP Guideline



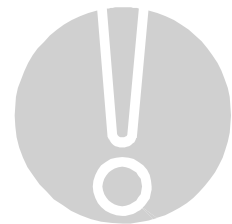
- OINDP Components/Sub-components
- Quality Unit
- Change Control (Tom Gaspar)
- Supply & Quality Agreements (Tina Arounsack)
- Control of suppliers and sub-contractors
- Extractables (Dan Norwood & Suzette Roan)
- Cleaning (Lisa Erdos)

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Key Sections of IPAC-RS GMP Guideline



- OINDP Components/Sub-components
 - direct contact with formulation or patient mucosa
 - integral part of inhaler, nebulizer critical to performance (metering valve, airway, mouthpiece)
- Terms and Definitions
 - provide GMP background
 - inhalation focus

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Key Sections of IPAC-RS GMP Guideline



- Quality Unit
 - key foundation for quality management system
 - authorities and responsibilities
- Change Control
 - ensures changes to process, materials, specifications.....affecting functionality, quality, safety
 - have a valid approach
 - are documented
 - agreed upon



Key Sections of IPAC-RS GMP Guideline



- Supply Agreements
 - pricing, legal terms
 - GOAL= sustained supply
- Quality Agreements
 - batch records
 - release & approval
 - audits
 - recall
 - process validation
 - change control



Key Sections of IPAC-RS GMP Guideline



- Extractables
 - Design and Development Planning
 - Partnership
 - Compatibility to formulation
 - Patient contact
- Cleaning and Foreign Particulates
 - What is the level required for the component?



Use: Informational Sections

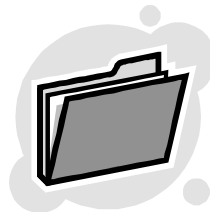


- IPAC-RS sections of the Guideline includes several informational sections
 - Drug Master Files (DMF)
 - Process Analytical Technology (PAT)
- These sections are included for information only and are not required
- ISO 9004 Guidelines (non-boxed black text) are also informational and not required



Drug Master Files (DMFs)

- A way to share necessary information about a component or raw material with FDA and to ensure that the information is kept current
- In a DMF, the supplier should identify information needed to support their customer's filing, e.g.,
 - physical description,
 - intended use,
 - chemical composition,
 - manufacturing processes and locations,
 - raw material types and grades, etc.
- DMFs must be updated on a yearly basis



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Drug Master Files (DMFs)

- DMFs are confidential to the supplier and to FDA
- **HOWEVER**, it is often important to share some of the information in a DMF with the customer.
 - Composition and processing information, e.g., can help predict interactions with the drug product and potential impurities or leachables.

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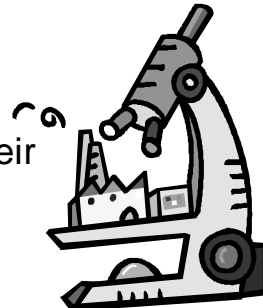
Drug Master File Developments

- FDA representatives have proposed changing the DMF system:
 - To promote more direct information sharing between suppliers and customers
 - Nature and timeline of changes are uncertain



Use: n-1 Suppliers

- n-1 suppliers are 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
- n-1 suppliers may be audited by their customers against IPAC-RS, PS 9000, and ISO 9001 sections





Use: n-1 Suppliers

- Guideline allows room for variation based on needs of customer and supplier:
 - Many requirements are "as defined by the customer," "as agreed between the supplier and the customer," or "where applicable"
- Communication between the supplier and customer is emphasized in the Guideline and is a key element of the Guideline
- n-1 Supplier should communicate with sub-suppliers



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Use: n-2/n-3 Suppliers

- n-2/n-3 suppliers are critical to the final quality of OINDP components
 - Pigments and additives in bulk materials (e.g., rubber) can produce extractables
 - Raw material attributes are linked to performance of the final product
- Therefore, n-2/n-3 suppliers are encouraged to read and follow the Guideline where applicable/ appropriate

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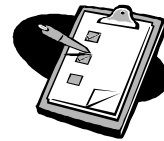


Use: n-2/n-3 Suppliers

- 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 Suppliers



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



Use: Five Steps for OINDP Manufacturers



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

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Use: General Principles

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



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Benefits of Using 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



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Overarching Goals

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

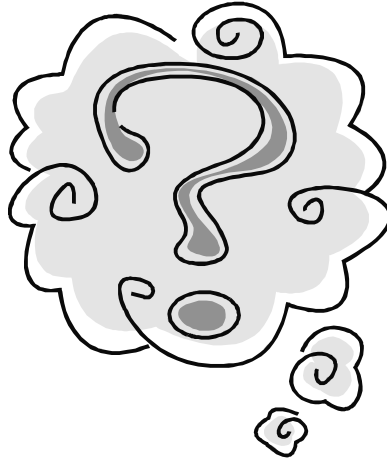


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Questions?



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