



## **Tools for Suppliers**

# **Regulation for Extractables in Materials/Components used in OINDP**

**IPAC-RS Symposium on Extractables in  
Materials for OINDP, Supplier GMP  
Workshop**

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## **Objective**

**To review the world-wide regulatory  
environment with respect to  
extractables in OINDP components  
and its relevance to suppliers.**



## Overview

- n Federal Food Drug and Cosmetic Act
  - Section 501, 502, 505
- n Current Good Manufacturing Practice (cGMP 1978/1996)
  - 21 CFR Parts 210 and 211 and QSR Guideline,
- n Guidance Documents
  - USFDA, EMEA, Health Canada
  - Industry Comments
- n IPAC-RS Suppliers Guideline
- n PQRI Recommendations
- n References
  - Standards/Compendia/CFSAN



## Federal Food Drug and Cosmetic Act

- n "a drug is deemed adulterated if its container is composed in whole or part of a poisonous or deleterious substance that may render the contents injurious to health..."
- n "an application shall include a full description of the methods used in the manufacturing, process and packaging of such a drug. This includes facilities and controls used in the packaging and drug product."



## **Good Manufacturing Practice cGMP**

### **n 21CFR 211.94 Drug Product Containers and Closures**

- Device containers should not be reactive, additive or absorptive as to alter the safety, identify, strength, quality or purity of the drug beyond the official or established requirements drug product.
- Standards or specifications, methods of testing and where indicated methods of cleaning, sterilizing and processing to remove pyrogenic properties shall be written and followed for drug product container and closures.



## **cGMP**

### **n 211.160 General Requirements**

- Laboratory Controls shall include the establishment of scientifically sound and applicable written specifications, standards, sampling plans, and test procedures including re-sampling, retesting, and data interpretation procedures designed to ensure that components, drug product containers, closures, in process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity.



## **USFDA Guidance for Industry**

### **n Non-Binding**

- Does not suggest specific test methods and acceptance criteria
- Does not suggest comprehensive list of tests
- Test methods and acceptance criteria based on good scientific principles for each specific system and product
- Acceptance criteria based on actual data for a particular system
- Ensure batch to batch uniformity of packaging components



## **cGMP Guidance Document**

### **n 2006 Quality Systems Approach to Pharmaceutical cGMP Regulation**

- n Risk Assessment
- n Preventative Action
- n Continuous Improvement
- **L&E Model**
  - n Defining expectations early in the development process
  - n Evaluating appropriate container closure materials and components
  - n Communication and collaboration in early stages of drug development
  - n Understanding and applying the science involved
  - n Control and ensure a quality product



## **Guidance Documents Extractables Recommendations**

- n FDA CDER Guidance for Industry
  - 2002 Draft Drug Products Packaged in Semipermeable Container Closure Systems
  - 2002 Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products
  - 1998 Draft Metered Dose Inhalers (MDI) and Dry Powder Inhalers (DPI)
- n FDA CBER
  - 1999 Container Closure Systems for Packaging Drugs and Biologics
- n FDA CDRH
  - 1993 Reviewers Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators
- n FDA OCP
  - 1991 Intercenter Agreement
  - Updated 2006
    - n Selected Guidance Documents Applicable to Combination Products
    - n Jurisdictional Update: Metered Dose Inhalers, Spacers and Other Accessories



## **International Guidelines Extractable Recommendations**

- n EMEA
  - October 2006, Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products
  - May 2005, EMEA Guideline on Plastic Immediate Packaging Materials
- n Health Canada (HC)
  - October 2006, Guidance for Industry Pharmaceutical Quality of Inhalation and Nasal Products



## Universal Scope

These guidelines address new marketing applications with respect to the quality aspects of inhalation and nasal products.

Expected quality aspects related to changes in existing products are not outlined but the same general principles can be applied.



## OINDP Container Closure System

- n Canisters
- n Bottles
- n Blisters Packs
- n Pumps
- n Valves
- n Caps/Liners
- n Actuators
- n Protective Packaging
- n Devices
- n Labels



## FDA/EMEA/HC Contrast

### EMEA/HC

- n Organization
  - CTD Sections
  - Single Document
    - n Drug Product Categorization
- n Pharmaceutical Development Studies
  - Delivery Device Development
  - Extractables/Leachables
- n Drug Product Specifications
  - Leachables
- n Container Closure Systems
  - Compendial and Non-compendial
- n Stability
- n DPI Recommendations

### USFDA

- n Organization
  - CMC Information
  - Two Documents
- n Drug Product Specifications
  - MDI
  - DPI
  - Nasal/Inhalation
- n Container Closure Systems
  - MDI
  - DPI
  - Nasal/Inhalation
- n Stability



## Application

### EMEA/HC

- n Inhalation Products
  - Pressurized MDI
  - DPI
    - n Pre-metered/Device Metered
  - Product for Nebulization
    - n Single/multi dose
  - Non-pressurized MDI
- n Nasal Products
  - Pressurized Metered Dose Nasal Sprays
  - Nasal Powders (Device Metered)
  - Nasal Liquids
    - n Single Use Drops
    - n Multiple Use Drops
    - n Single Use Sprays
    - n Non-Pressurized Multiple use Metered Dose Sprays

### USFDA

- n Metered Dose Inhalers (MDI)
- n Dry Powder Inhalers (DPI)
  - Pre-metered/Device Metered
- n Nasal Sprays
- n Inhalation Solutions and Suspension
- n Inhalation Sprays
  - Pre-metered
  - Device metered



## **EMEA/HC Recommended Studies**

- n **Inhalation and Nasal Products**
  - **MDIs, Metered Dose Nasal Sprays, and Products for Nebulization**
    - n Extractable/Leachables
    - n Delivery Device Development
  - **Dry Powder Inhalers**
    - n Delivery Device Development
  - **Nasal Liquids**
    - n Extractable/Leachables
    - n Delivery Device Development




## **USFDA Recommended Studies**

- n **MDI, Nasal Sprays, Inhalations Solutions, Suspensions and Sprays**
  - **Drug Product**
    - n Appearance and Color
    - n Leachables
    - n Stability (Compatibility with Devices)
  - **Container Closure**
    - n Control Extraction
    - n Residue (MDI)
    - n Routine Extractable and Residue (MDI)
- n **DPI**
  - **Drug Product**
    - n Appearance and Color
    - n Stability (Compatibility with Devices)
  - **Container Closure**
    - n Control Extraction
    - n Routine Extractable



Drug Product	Leachables	Extractables
<b>EMA/HC</b>		
Metered Dose Inhalation and Nasal Sprays	Yes	Yes
Products for Nebulization	Yes	Yes
DPI	No	No
Nasal Liquids	Yes	Yes
<b>USFDA</b>		
MDI	Yes	Yes
DPI	No	Yes
Nasal Sprays	Yes	Yes
Inhalation Solution, Suspension and Sprays	Yes	Yes



## USFDA Recommendations Information for Drug Application

- n For assembled and individual components and attached accessories
  - Source(s) and Fabricator(s)
  - Item Numbers
  - Schematic Engineering Drawings
  - Precise Dimensional Measurements
  - Composition and Quality of the Materials
  - Control Extraction Studies
  - Toxicological Evaluation
  - Acceptance Criteria, Test Procedures, Sampling Plans
    - n Physicochemical Parameters and Dimensional Measurements
    - n Qualitative and Quantitative Extractable Profiles
    - n Performance Characteristics

## Additional Information

### n Specify

- Source and chemical composition of materials
- Appropriately referenced DMF
- Applicable citations to the indirect food additive regulation
- Submit assembled and disassembled components

### n Other Considerations

- Valve treatment procedures e.g., cleaning pre-extraction, washing, drying
- Canister residuals from washing and contamination
- Compatibility



## EMEA and Health Canada Extractables/Leachables (CTD 3.2.P.2.4)

### n Compendial Plastics

- Leachable Profile
  - n Safety Assessments
  - n Established Safety Thresholds
- Leachable Tests and Limits
- Correlation to Extractables
- Routine Extractable Testing
  - n Limits

### n Non-Compendial and Rubber Components

- Extractables Profile
  - n Study Design
- Leachables Profile
- Leachable Tests and Limits
- Correlation to Extractables
- Routine Extractable Testing
  - n Limits



**EMA and Health Canada  
Drug Product Container Closure System  
Delivery Device Development (CTD3.2.P.2.4)**

- n Identification
- n Composition of all Components
- n Resins and Additives for Non-compensial Components
- n Process Controls
- n Compliance with Relevant Standards
- n Specifications
  - Dimensions
  - Performance



**Quality Control**

- n Specifications and Acceptance Criteria
  - Dimensional measurements
  - Physicochemical parameters
  - Individual and total extractables
  - Performance attributes



## **Comments to OINDP Guidelines**

### **n FDA**

- Points to Consider
- Docket No. 02D-0254 October 2003
  - n Inhalation Drug Products Packaged in Semi Permeable Container Closure Systems
    - IPACS-RS

### **n EMEA**

- Doc. Ref. 103155/2006 June 2006
  - n Overview of Comments received on Draft Guideline on Pharmaceutical Quality of Inhalation and Nasal Products
    - IPAC-RS, EPAG, MEB, BAH, Pfeiffer, Trudell, Saint Gobain, TGA, Valois, EFPIA



## **Recommendation Document**

### **n Draft Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products**

- PQRI Leachables and Extractables Working Group
  - n Drafted November 2005
  - n Submitted to FDA September 21, 2006



## PQRI Recommendations

- n Threshold Concept
- n Controlled Extraction Studies
  - Qualitative
  - Quantitative
- n Correlation to Leachables
- n Acceptance Criteria and Specifications
- n Routine Testing



## Leachable Recommendations

Comprehensive Leachables Studies should always be accomplished for MDIs, Nasal Spray and Inhalation Spray drug products.

Leachables studies (stability studies or "one-time" characterization studies) are required for the to be marketed DPI drug products only if potential leachables, i.e. extractables, of safety concern are identified in the Controlled Extraction Studies.

For Inhalation Solution and Suspension drug products, Leachables Studies are not required if it can be scientifically demonstrated that:

- a. Aqueous and/or drug product formulation extracts of Inhalation Solution direct formulation contact container closure system materials yield no extractables, under appropriate stress conditions, at Final AET levels, or no extractables above final AET levels with safety concern; AND
- b. There is no evidence for migration of organic chemical entities through the unit dose container or protective packaging components into the drug product formulation.

PQRI Leachables and Extractables Working Group



## **Responsibilities**

### **n Applicant**

- **Supply Chain**
  - n Resin supplier
  - n Compounder
  - n Molder
  - n Assembly/Fill



## **Establish Reliability of Suppliers**

- n Applicant confirms suppliers extractable profile results by testing multiple incoming batches of individual components
  - Submitted batches
  - Clinical
  - Primary stability
  - Biobatch
  - Production
  - Post approval drug product



## **Good Manufacturing Practices Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products**

IPAC- RS 2006

A quality handbook that incorporates:

- *PS 9000:2001 Guideline for Pharmaceutical Packaging*
- *ISO 9001:2000 Quality Management System*
- *IPAC-RS Additional Recommendations for achieving GMP compliance for OINDP*



## **GMP Guideline for Suppliers**

- n **Measurement Analysis and Improvement**
  - Controlled Extraction Studies
  - Control of Extractables and Ancillary Materials
- n **Product Realization**
  - Change Control and Notification
  - Supply and Quality Agreements
  - Specifications
- n **Contamination Control**
  - Component and Equipment Cleaning
  - Material Change Over
  - Environment
  - Foreign Particulate



## Standards/Compendia

- n **USP Biological Reactivity<87> and <88>**
- n **USP Containers<661>**
- n **EP 3.1 Materials Used for the Manufacture of Containers**
- n **EP 3.2 Containers**
- n **ISO 10993 Biological Evaluation of Medical Devices Part 18 Chemical Characterization of Materials**
- § **ICH Q6A Test Procedures and Acceptance Criteria for New Drug Substances**
- n **ICH Q3C Impurities: Residual Solvents**
- n **[www.CFSAN.fda.gov](http://www.CFSAN.fda.gov) The List of "Indirect" Additives Used in Food Contact Substances**



## Questions

