



Tools for Suppliers

Regulation for Extractables in Materials/Components used in OINDP

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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 Legislation
 - GMP Global Status
 - EU and US Container Closure Requirements
- n OINDP Guidance Documents
- n PQRI Recommendations
- n IPAC-RS Suppliers Guideline
- n References
 - Standards/Compendia/CFR

Regulatory Mission

- n Marketed drugs are to be safe and effective, and are manufactured in accordance with current Good Manufacturing Practices (GMPs).

EU Legal Basis

- n Directive of the European Parliament and of the Council on the Community Code Relating to Medicinal Products for Human Use
 - Directive 2001/83/EC
 - Amended by Directives 2002/98/EC, 2003/63/EC, 2004/24/EC and 2004/27/EC
- n EudraLex Volume 4 - Good Manufacturing Practice
 - Commission Directive 2003/94/EC

United States Code

- n Federal Food Drug and Cosmetic Act
 - Section 501, 502, 505
 - n 1938/1968
 - n FDA Modernization Act 1997
- n Current Good Manufacturing Practice
 - 21 CFR Parts 210 and 211 and QSR Guideline
 - n GMP 1978/1996

EU Directive 2003/63/EC Container Closures

n Module 3

- 3.2.22 Suitability of a container closure system used for storage, shipping and use of finished drug product shall be documented. A possible interaction between medicinal product and container may need to be considered
- 3.2.27 A description of the container closure systems including the identity of each immediate packaging material and their specification shall be provided. The specification shall include description and identification. Non-pharmacopoeia methods (with validation) shall be included where appropriate

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, identity, 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.

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Legal Intent

n Consumer Protection

- GMP
 - n Mutual Recognition Agreements (MRA)
 - n USFDA legal authority for immediate suspension of imports based on appearance of violations
- Product Applications/Approvals
 - n Guidelines/CMC Information
 - Container Closure Systems
 - Medical Device

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Worldwide GMP

- n Mutual Recognition Agreements (MRA)
 - EC-Canada, 2006
 - EC-Japan, 2004
 - EC-Australia, 1999
 - n Australia- Singapore, 2001
 - US Agreements
 - n 21 CFR 10.90.(d), 20.108
- n Emerging Inspectorates
 - GMP Certification
- n Guidance Adoption
 - Australia - EMEA
- n Guidance Harmonization
 - EMEA – Health Canada

MRA

- § An agreement between two countries which provides for a reciprocal reliance upon facets of each others regulatory systems to the degree specified
- § Does not apply to review of product applications or approvals

Guidelines/Harmonization/Standards

n Reference Documents

- USFDA Guidance for Industry
- European Medicines Agency Inspections (EMA)
- International Organization for Standards (ISO)
- International Conference on Harmonization (ICH)
- World Health Organization (WHO)
- Compendia
 - n USP, EP, JP

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GMP

Safe and Effective Drug Products

- n 2006 Quality Systems Approach to Pharmaceutical cGMP Regulation
- n 2006 ICH Q9 Quality Risk Management

Risk Assessment
Preventative Action
Continuous Improvement

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GMP Guidance Document L&E Model

- Defining expectations early in the development process
- Evaluating appropriate container closure materials and components
- Communication and collaboration in early stages of drug development
- Understanding and applying the science involved
- Control and ensure a quality product

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OINDP Container Closure System

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

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Universal Scope

Container Closure 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.

Application

		EMEA	USFDA
n	Pressurized Inhalation and Nasal Products	✓	✓
	• Metered Dose Inhalers (MDI)		
	• Dry Powder Inhalers (DPI)		
	n Nasal Powders		
	n Pre-metered/Device Metered		
n	Inhalation Solutions and Suspension	✓	✓
	• Product for Nebulization		
n	Nasal Sprays	✓	✓
n	Nasal Liquids	✓	

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

US 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

OINDP Policy Comparison

	EMEA/HC	USFDA
Guidance Recommendations	One Document CTD Sections	Two Documents CMC Information
C/C Selection	Delivery Device Development	Composition and Quality Evaluation
Safety Assessment	Yes	Yes
Compendial Components	Yes	No
Leachable Specifications	Yes	Yes
Manufacture and Packaging	Impact to Product Performance	Drug Products = Formulation + C/C
Stability	Overview	Comprehensive
Labeling	Limited	Yes
Generics	Yes	No

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Drug Product	Leachables	Extractables
EMEA		
Metered Dose Inhalation and Nasal Sprays	Yes	Yes
Products for Nebulization	Yes	Yes
DPI	No	No
Nasal Liquids (local/systemic)	Yes	Yes
USFDA		
MDI	Yes	Yes
DPI	No	Yes
Nasal/Inhalation Sprays	Yes	Yes
Inhalation Solution and Suspension	Yes	Yes

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EMEA	USFDA
Delivery Device Development (CTD 3.2P.2.4 and 3.2.R)	<ul style="list-style-type: none"> • Source(s)/ Fabricator(s) • Item Numbers • Engineering Drawings • Dimensional Measurements • Materials Composition/Quality • Treatments, cleaning, residuals
Extractables/Leachables (CTD 3.2.P.2.4)	<ul style="list-style-type: none"> • Control Extraction Studies • Toxicological Evaluation • Acceptance Criteria, Test Procedures, Sampling Plans <ul style="list-style-type: none"> • Qualitative and Quantitative Extractable Profiles • Physicochemical Parameters • Performance Characteristics • Applicable CFR Citations
Compatibility (CTD 3.2.P.2.5)	<ul style="list-style-type: none"> • Compatibility



EMEA and Health Canada Extractables/Leachables (CTD 3.2.P.2.4)
<ul style="list-style-type: none"> n Compendial Plastics <ul style="list-style-type: none"> • Leachable Profile <ul style="list-style-type: none"> n Safety Assessments • Leachable Tests and Limits • Correlation to Extractables • Routine Extractable Testing <ul style="list-style-type: none"> n Limits n Non-Compendial and Rubber Components <ul style="list-style-type: none"> • Extractables Profile <ul style="list-style-type: none"> n Study Design • Leachables Profile <ul style="list-style-type: none"> n Safety Assessments • Leachable Tests and Limits • Correlation to Extractables • Routine Extractable Testing <ul style="list-style-type: none"> n Limits



Quality Control

n Specifications and Acceptance Criteria

- Dimensional measurements
- Physicochemical parameters
- Individual and total extractables
- Performance attributes

Comments to OINDP Guidelines

n FDA

- IPACS-RS
- Pharmaceutical Companies

n EMEA

- IPAC-RS, EPAG, MEB, BAH, PhRMA, TGA, EFPIA
- Pfeiffer, Trudell, Saint Gobain Calmar, Baxter, Valois

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

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PQRI Recommendations

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

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Extractables and Leachables CTD 3.2.P.2.4

- n For non-compendial plastic and for rubber container closure components in contact with formulation a study should be conducted to determine extractable profile
- n Determine if leachables are present in the formulation at the end of shelf life of the product
- n Leachables profile determined for compendial plastics and rubber container closure system
- n Leachables should be identified and safety assessments made.
- n Correlation and Specifications should be developed for leachables
- n Control of leachables may be established via testing of extractable limits

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Leachable Recommendations

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

Leachables studies are required for the to be marketed DPI drug products only if potential leachables are of safety concern.

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

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Applicant Responsibilities

n Supply Chain

- Resin supplier
- Compounder
- Molder
- 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*

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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


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Compatibility (CTD 3.2.P.2.5)	<ul style="list-style-type: none"> • Compatibility



Conclusion

Similarities



Legislation

Differences

Interpretation
Regulatory Expectations
Rational

Questions