



IPAC-RS Material Forum A Regulatory Perspective Barcelona 2009

Prasad Peri, Ph.D.
ONDQA
FDA



Overview

- General Introduction to Materials used for OINDPs- Importance
- Concepts of Extractables and Leachables
- Rationale for Controlling Materials
- Historical perspective
 - Extractables or As Leachables
 - Examples of materials changes impacting product performance
- Conclusion



Importance of Materials Selection and Optimization

- Device Drug Development of OINDP
- Packaging components ensure quality and stability of the API present in the formulation
 - Formulation under ambient or high pressure
- Delivery of Metered formulation from the Drug Product
- Devices designed to prevent moisture ingress in OINDPs but is unavoidable, more so with HFAs.
- Several Conferences Organized to highlight the importance of these topics

3



Materials used in OINDPs

- Plastics
 - PolyacetalABS, PBT, HDPE, LDPE
- Colorants-Actuators, Caps,
- Aluminum canisters, lined, annodized, foil overwrap
- Stainless steel-canisters, springs
- Elastomers-gaskets,
- Adhesives for foil overwraps, lidding

4



Extractables and Leachables-Definitions

- Extractable-Materials intentionally extracted from the OINDP components under simulated test conditions
- Leachables-Compounds that leach into the drug product formulation from the device or packaging components, during in-use/shelf life.

5



Rationale for Controlling Extractables and Leachables

- **Clinical Concerns**
 - Sensitive, compromised patient population
 - Paradoxical bronchospasm
 - Long-term safety for chronic use
- **Quality Control Issues**
 - Manufacturing process under control
 - Consistency in materials/components
 - Control for unintended contaminants

Leachables and Extractables in OINDP: An FDA Perspective
Alan C. Schroeder, Ph.D. ONDQA, CDER, FDA, PQRI L/E Workshop
December, 2005

6



Historical Perspective

- How did the importance of various Leachables/Extractables come to the attention of the FDA?
 - Reports of PNAs/Nitrosamines in elastomers in MDIs
 - 2-Mercaptobenzothiazole (2-MBT) in elastomers
 - Other classes of L/Es
 - Parenterals
- MDIs are worst case for L/E
 - Rubber and plastic in continual contact with propellant(s)/cosolvents under pressure

7



Examples to Illustrate Importance of evaluation Leachables

- PNAs Case Studies
- Nitrosamines Case Studies
- 2-MBT Case Studies
- Other polymeric extractables
- Metal component residues
- Migration of extraneous organics through wall
- Leachables seen in other dosage forms such as parenterals, infusion bags etc.

8

Leachables Case Study 1

- Effect of change in fabrication procedure on the drug product performance characteristics
- Certain batches of MDI drug product were found to have significant failures in acceptance criteria for aerodynamic particle size distribution (APSD)
- Manufacturer performed an extensive multi-factorial study to determine whether a change in a specific drug product component was responsible.
- The problem was traced to MDI lots containing certain batches of particular valve components
- Discussions with the valve manufacturer revealed that a change in the manufacturing process left a residue on the surface of the valve component

9

Leachables Case Study Cont...

- MDIs were made, spiked with varying levels of this residue (a processing aid) and tested for APSD
- Change in APSD was found to be linked to levels of this processing aid
- Valve manufacturer returned to original manufacturing process and the problem was resolved.
- Problem caused by unintentional surface residue (processing change), unknown to the applicant
- This problem resulted in the loss of substantial developmental time, resources and drug product stability batches.
- Lessons learned: better communication with supplier is needed, as well as agreement to avoid changes in materials or processes without first discussing proposal with applicant

10

Leachables Case Study 2

- **Migration from protective overwrap through LDPE container walls**
 - Inhalation solution drug product
 - Primary packaging materials did not contribute extractables to a hot water extract
 - However, product stability testing for leachables indicated the formulation contained a constituent of the polymer on the inside of the aluminum foil layer of the overwrap
 - A new overwrap was developed to avoid the migration of this constituent into the drug formulation on stability
- **Lessons Learned:**
 - Loss of time for drug product approval, additional resources expended
 - Protective overwrap should minimize constituent volatiles/semi-volatiles that could migrate into formulation, particularly those of safety concern.

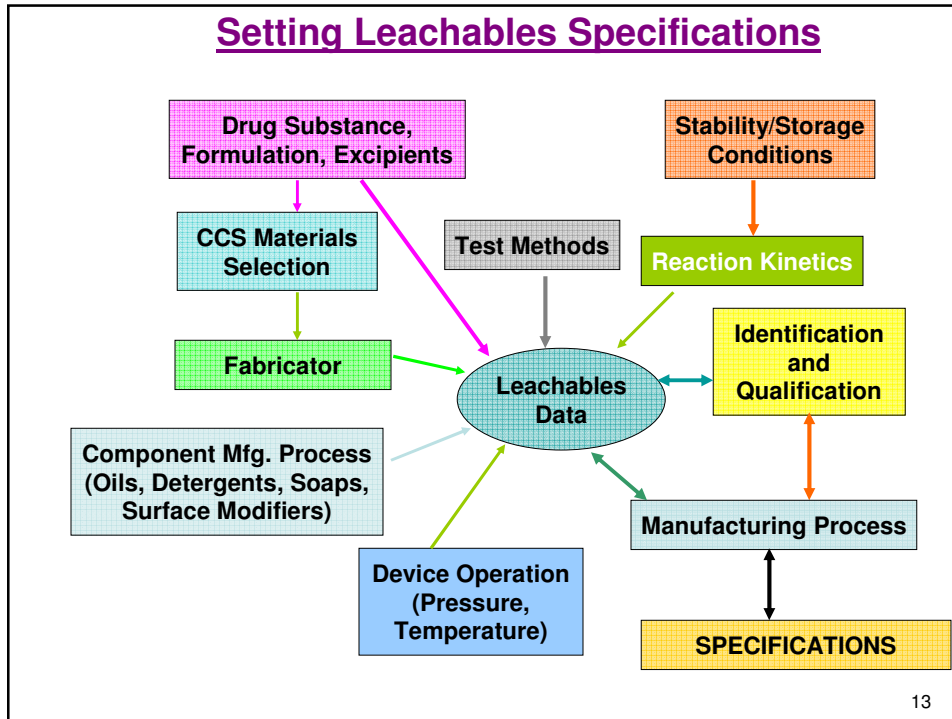
11

Leachables Case Study 3

- **Problem of poor method validation**
- A manufacturer planned a proposed change of test site for leachables in the drug product
- Approved method was found to be not reproducible at the new site
- New method for leachables was developed with site to site reproducibility.
- The downside of all this was that the results with the new method did not support the approved leachables acceptance criteria
- The firm had to develop a new body of data to reestablish leachable acceptance criteria.
- **Lessons learned:**
- Loss of time and resources due to inadequately validated analytical procedure

12

Setting Leachables Specifications



13



Summary

- Select materials designed to minimize leachables
- Know the compositions of the container closure system components and their surface treatments
- Design protection for product against migration of contaminants from outside the container closure system
- Conduct appropriate extractable/leachable studies with validated sensitive and specific analytical methods
 - Include methods for special case compounds
 - Develop risk assessments for L & E
- Develop and implement appropriate controls for extractables & leachables
- Work closely with your suppliers
- Obtain agreements pertaining to change control.

14



Acknowledgements

- Ali Al Hakim, Ph. D
- Alan Schroeder, Ph. D
- Craig Bertha, Ph. D
- Christine Moore, Ph. D

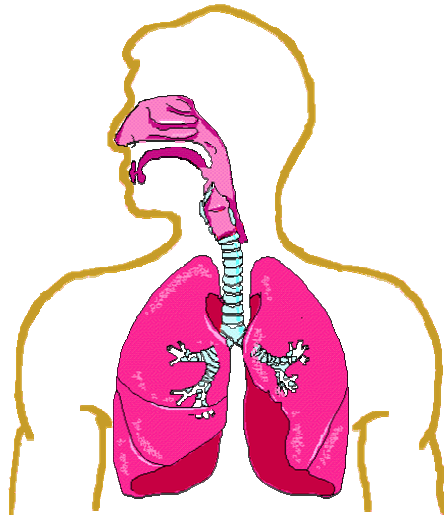
15



Office of New Drug Quality Assessment

10903 New Hampshire Ave. WO21
Silver Spring, MD 20993-0002

Phone: 301-796-1730
Fax: 301-796-9747



16