Leachables and Extractables in OINDP: An FDA Perspective

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PQRI L/E Workshop
December 5-6, 2005

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Extractables/Leachables – Why Are They Important?

- **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

Regulation of Extractables & Leachables for OINDP

- Evolutionary process for L/E
  - Problems observed in specific drug products
  - Increasing knowledge about materials and manufacturing processes
  - Data based

MDIs - L/E Concerns

- Worst case for L/E
- Rubber and plastic components in constant contact with formulation
- Formulation is primarily propellant, an organic solvent
- Increased extraction potential relative to aqueous formulations or solid formulations

Historical Perspective for L/E Regulation in OINDP

- How did the importance of various Leachables/Extractables come to the attention of the FDA?
  - Reports of PNAs in elastomers
  - PNAs in MDIs
  - Nitrosamines in elastomers
  - 2-Mercaptobenzothiazole (2-MBT) in elastomers
  - Other classes of L/Es

PNAs/Case Study (1)

- Reports of PNAs in elastomers
- In addition, one drug firm suspected a rubber formulation change in their MDI valve
- They investigated by analyzing a rubber extract
- Several unknown peaks observed

PNAs/Case Study (2)

- Firm raised this issue with supplier
- Supplier used processing oil which was linked to new contaminants
- PNAs observed in MDI drug product
- Risk assessment performed by drug firm and FDA
- Led to a program to replace the valve component with an alternative elastomer

PNAs/Case Study (3)

- Important lessons learned
  - Applicants should have full knowledge of necessary information (e.g., component manufacturing process and composition)
  - Component materials should be carefully selected
  - DMFs for components and materials should be up-to-date with adequate information

PNAs/Case Study (4)

- Important lessons learned (cont'd)
  - DMF holder shouldn't make changes without applicant's knowledge
    - Unintended contamination introduced here
  - Carbon black is one potential source, but not the only one, of PNAs in MDI elastomeric components

PNAs/Case Study (5)

- PNAs should be minimized (e.g., by selecting appropriate rubber components, by appropriate processing)
- Controls include total and individual PNA limits
- Limits based on safety and data
- Need sensitive and specific method for the individual target PNAs

Nitrosamines (1)

- Volatile N-nitrosamines were reported to be present in baby bottle rubber nipples
- FDA investigated
- Original action level established by FDA was 60 ppb total N-nitrosamines in rubber nipples (as of 1/1/84)
- Rubber nipples sold after 1/1/84 were sampled – total levels observed then were n.d. to 36.9 ppb

Nitrosamines (2)

- FDA Action Level reduced to 10 ppb for individual volatile nitrosamines for rubber baby bottle nipples sold on/after 1/1/85*
- This was due to manufacturers response to FDA concerns
  - Product formulas and manufacturing processes were altered to reduce nitrosamine formation

*FDA/ORA Compliance Policy Guide Section 500.450 (CPG 7117.11)

Nitrosamines (3)

- Based upon the nitrosamine contamination of rubber nipples, FDA contacted MDI manufacturers to request product-specific data
- MDI controls for nitrosamines in MDI drug products were developed, based upon data and toxicological safety assessment

Nitrosamines (4)

- Controls for nitrosamines in MDI elastomeric components are tighter than for baby bottle rubber nipples
- Volatile nitrosamines are controlled both individually and in total
- Safety limits depend upon MDI drug product characteristics (e.g., design, fill, total daily dose)

Nitrosamines (5)

- Nitrosamines should be reduced to the lowest possible levels
- Use sensitive, specific analytical procedure

2-MBT (1)

- 2-Mercaptobenzothiazole has been used as a vulcanization accelerator in the manufacture of rubber
- Known to be a dermal sensitizer and a relatively weak carcinogen in National Toxicology Program bioassays
- Past concern about its presence in rubber stoppers for parenteral drugs

2-MBT (2)

- Manufacturers of rubber parenteral components have reformulated their products to reduce/eliminate 2-MBT
- 2-MBT is also controlled/minimized in MDIs due to concerns about its toxicity and sensitization potential

Other Polymeric Extractables (1)

- Control of other polymeric extractables and leachables has been established both for safety and product quality reasons
- Complexity of elastomer (composition, manufacturing process), for example, needs to be taken into consideration in materials selection, safety assessment and L/E controls

Other Polymeric Extractables (2)

- These extractables may include the following, for example: plasticizers, antioxidants, lubricants, vulcanizers, peroxides, monomers, oligomers, catalysts, residual solvents, pigments, filler contaminants

Metal Component Residues (1)

- Metal components not as clean as first thought
- Example: The MDI canister manufacturing process was suspected of leaving residues which could become leachables
- Investigation found that this process has used drawing oils in making the canister, followed by washing with detergents to reduce residual oils on the surface

Metal Component Residues (2)

- Characterization studies for residues, and, if they are present, toxicological assessment and controls are now requested for such processing contaminants on metal components
- Actually this applies to any material and intentional & unintentional surface residues, not just metal surfaces

Migration of extraneous organics through container wall (1)

- Example: Inhalation solutions in primary LDPE container closure system
  - Vanillin was observed in drug formulation of product without protective overwrap
  - Apparent origin: packaging (cardboard)
  - Vanillin levels increased on storage

Migration of extraneous organics through container wall (2)

- Subsequently, numerous marketed inhalation solutions packaged without overwrap were surveyed for extraneous contaminants
- 5 known chemical contaminants detected in various lots of the products

- Addition of a protective overwrap (e.g., aluminum foil laminate) is recommended to prevent such migration into the drug formulation.

Case Studies

- Several case studies will be described to illustrate problems linked to leachables and extractables, and their effect on drug product quality and drug applications.

Case Study A (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

Case Study A (2)

- 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

Case Study A (3)

- 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

Case Study A (4)

- 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

Case Study A (5)

- 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

Case Study B (1)

- **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

Case Study B (2)

- 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

Case Study B (3)

- Lessons learned:
- Loss of time and resources due to inadequately validated analytical procedure

Case Study C (1)

- **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 presence of a constituent of the polymer on the inside of the aluminum foil layer of the overwrap

Case Study C (2)

- 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/semivolatiles that could migrate into formulation, particularly those of safety concern

Summary (1)

- 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

Summary (2)

- 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 with your suppliers
  - Obtain agreements pertaining to change control