Leachables and Extractables in OINDP: An FDA Perspective

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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
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
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
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.
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

Lesson 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