

IPAC-RS Conference

Rockville, Maryland

March 31, 2011

Leachables and Extractables: Evolution of Regulatory Aspects and Perspectives on PQRI Recommendations

Guirag Poochikian, Ph.D.

Poochikian Pharma Consulting

Poochikian@comcast.net

Outline

- Evolution
- Definitions
- Sources and types of leachables/extractables
- Illustrative case examples
- Summary/Material selection considerations

Historical Evolution

- 12/1986 - Reports
- 1987/1989 – Prewash and Baby Bottle
- June 1991 - University of Kentucky Conference
- 1994 - NDA
- 1998 - MDI/DPI Draft Guidance
- 1999 - Nasal/Inhalation Draft Guidance
- 1999/2001 - AAPS ITFG/IPAC
- June 2002 - LDPE Draft Guidance
- July 2002 – Nasal/Inhalation Guidance
- 2003 - DPTC/PQRI
- 2006 - PQRI Report/Recommendations
- 2011 – Quarter of a Century

IPAC-RS 2011 Conference

Extractables/Leachables Why Are They Important?

- Clinical/Safety Concerns
 - Sensitive/compromised patient population (INH)
 - Paradoxical bronchospasm (INH)
 - Other safety (Tox) considerations of L&E
 - Systemic Toxicity (e.g., QTH 100ng/kg/d; 5 mcg/d)
 - Route specific (local) toxicity
 - Mutagenic/carcinogenic potential
- Quality Control Concerns/Issues
 - Ensure consistency in materials/components
 - Ascertain part of manufacturing process under control (safety and effectiveness)
 - Minimize and control unintended contaminants

IPAC-RS 2011 Conference

Definitions

- **CCS:** The sum of packaging components that contain, protect, meter, deliver, modify, and count the doses. It includes
 - Primary packaging components
 - Secondary packaging components if they are intended to provide additional protection, e.g., foil overwrap
 - Associated accessories (e.g., integrated spacer, dose counter/indicator)
 - Indirect packaging components

IPAC-RS 2011 Conference

Definitions

- **Extractables:**
 - Compounds that can be extracted from elastomeric and plastic components, coatings of, and residues on a CCS component
 - when in presence of appropriate solvent(s) and under stressed extraction conditions
- **Leachables:**
 - Compounds that may migrate into the formulation from the elastomeric, plastic, coating of, or residues on CCS component,
 - Contaminants from processing aids (e.g., lubricants, cleaning and washing agents) used during
 - Processing of CCS components
 - Manufacture of the drug product
 - Contaminants from environment

IPAC-RS 2011 Conference

Drug Products of Concerns

- Inhalation drug products (e.g., MDIs, DPIs, Inhalation Sprays, Solutions, and Suspensions)
- Nasal drug products (e.g., N-MDIs, N-Sprays, N-Solutions/Suspensions)
- Parenteral drug products (e.g., SVPs/LVPs/PBPs)
- Implants
- Ophthalmic and Otic drug products
- Transdermal system drug products
- Topical preparations
- Oral non-solid drug products

IPAC-RS 2011 Conference

Potential Sources of L&E (1)

- **CCS components: Direct** - examples include:
 - Containers, closures, valve components, blisters,
 - Coatings on inner surface of containers & valves
 - Delivery units, tubing, etc
 - Additives (chemicals) to CCS components and/or base polymers
- **CCS components: Indirect (e.g., LDPE Units)**
 - **Paper label components**
 - Volatile compounds, adhesive components, varnish/over lacquer, inks, residual volatile solvents
 - **Foil overwrap components**
 - Volatile components, residual volatile solvents, adhesive
 - **Cartons**
 - Volatile components, residual volatile solvents, adhesive

IPAC-RS 2011 Conference

Potential Sources of L&E (2)

- **Processing aids (CCS/DP) and CCS surface treatment materials**
 - Lubricants, mould release, antistatic, antislip agents, etc
 - Cleaning/washing agents and other surface treatment reagents
 - Drug product contamination during manufacture (leachables)
- **Environment (leachables)**
- Thus, leachables could not always be predicted from limited extractable studies

IPAC-RS 2011 Conference

Types of L&E

- Monomeric units, oligomeric fragments
- Chemicals used as primary additives in elastomers and plastic components (e.g., antioxidants, plasticizers, lubricants, vulcanization accelerators, peroxides, catalysts, filler contaminants, retarders, UV stabilizers, pigments, residual solvents)
- Trace levels in additives, e.g., PNAs, N-nitrosamines, mercaptobenzothiazole
- Processing aid components (e.g., lubricants, mould release, antistatic, and antislip agents) and cleaning and washing agents
- Volatile components from paper label and carton box
- Environmental contaminants

IPAC-RS 2011 Conference

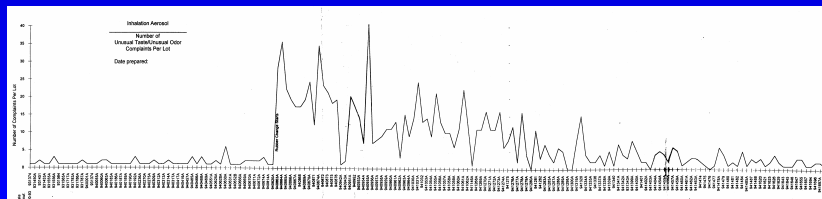
EXAMPLES

CASE REPORTS

IPAC-RS 2011 Conference

Examples 1 and 2: MDI Gasket Replacement (composition) or Process change

- Drug “Y” Inhalation Aerosol contamination
- Drug “Z” Inhalation Aerosol “off-taste” and “skunk-like odor” complaints



IPAC-RS 2011 Conference

Example 3: Effect of Leachables (Packaging Component) in Inhalation Solution - Respiratory Irritant

- A packaging component found in D.P. in trace amounts
- Skin irritant
- Long-term toxicological effects were unknown
 - carcinogenicity and mutagenicity
 - Inhalation toxicity
- Irritation to the respiratory tract may result in bronchospasm, a concern in COPD, bronchitis, emphysema, and asthma patients
- Product Recall

13

IPAC-RS 2011 Conference

Guidance for Industry – Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – CMC Documentation

- “...The levels of the leachables originating from indirect exposure to labels or related materials should be determined with validated methodology that has suitable detection and quantitation limits for the potential leachables. The levels of leached compounds should be appropriately qualified and documented and acceptance criteria established” (Section III.G)

IPAC-RS 2011 Conference

FDA Analytical Survey*

- Initiated by OGD & DPADP/OND in coordination with OC/ORR Field Offices and Pacific Regional Laboratory
- 7 ANDAs and 1 NDA for Inhalation solutions covering five different drug substances
 - 38 samples representing 37 Lots of various drug products in LDPE vials without a protective overwrap foil-pouch
 - Samples screened for potential volatile chemicals such as *vanillin*, *2-phenoxyethanol*, and *1-phenoxy-2-propanol* by GC-MS (sensitivity ~ 0.5 ppm) and HPLC methods

*Drug Safety and Risk Management Advisory Committee, May 2004

IPAC-RS 2011 Conference

FDA Analytical Survey*: Results

- **29** out of **38** samples tested positive for chemical contamination originating from packaging.
- Detected **5** known chemical contaminants originating from packaging.
 - *Benzophenone* (2 lots)
 - *Polyethylene glycols* ($n = 4-8$), (3 lots)
 - *2-(2-Butoxyethoxy)ethanol* (DEGBE), (24 lots)
 - *2-(2-Ethoxyethoxy)ethanol acetate* (DEGEEA), (3 lots)
 - *2-Hydroxy-2-methylpropiophenone* (2-HMPP), (5 lots)

*Drug Safety and Risk Management Advisory Committee, May 2004

IPAC-RS 2011 Conference

FDA Analytical Survey*: Conclusion

- Potential for these chemicals to cause bronchospasm at levels detected is unknown, especially, in patients with respiratory diseases
- Concentration of these chemicals might be greater at the end of expiry than what was detected
- Ingress/Leaching of chemical contaminants into drug product formulations from packaging components demonstrates that **permeation** through LDPE is a **real phenomenon**
- Additional chemicals may be present, but may not get detected by the analytical procedures used
- Changes in the materials used in labeling and packaging may result in potential contamination with different chemicals.

*Drug Safety and Risk Management Advisory Committee, May 2004

IPAC-RS 2011 Conference

Example 4: Selection of Protective packaging

- Inhalation solution DP in LDPE container
 - Primary packaging materials did not contribute Es to a hot water extract
 - DP stability testing for Ls indicated the presence of a constituent of the polymer on the inside of the Al foil layer of the overwrap
 - Migration from protective overwrap through LDPE container walls
- A new overwrap was developed to avoid the migration of this constituent into the drug formulation on stability
- Lessons Learned:
 - Additional resources, loss of time for drug product approval
 - Protective overwrap should minimize constituent volatiles/semi-volatiles that could migrate into formulation, particularly those of safety concern

IPAC-RS 2011 Conference

Metal component Residues

- Metal components not as clean as first thought
- Example: The MDI canister fabrication processes may result into residues which could become leachables
 - Canister fabrication process may use drawing oils, followed by washing (e.g., detergents) to reduce residual oils on the surface
- Characterization studies for residues, and if they are present, toxicological assessment and controls are to be considered for such processing contaminants on metal components
 - Same approach applies to any material and intentional and unintentional surface residues, not just metal surfaces

IPAC-RS 2011 Conference

Example 5: Effect of change in fabrication procedure on DP performance (1)

- Significant **failures in APSD** of a MDI - DP
- Extensive multi-factorial study traced the problem to MDI lots containing certain batches of particular valve components
- APSD failures were attributed to a change in the manufacturing process that left a residue on the surface of the valve component
- MDIs spiked with varying levels of this residue (a processing aid) demonstrated change in APSD that was found to be linked to residue levels

IPAC-RS 2011 Conference

Example 5: Effect of change in fabrication procedure on DP performance (2)

- Problem caused by unintentional **surface residue**, unknown to the applicant
- Consequences: Loss of substantial developmental time, resources and drug product stability batches
- Lessons learned:
 - Better communication with supplier(s)
 - Agreement with supplier(s) to avoid changes in materials or processes without first discussing proposal with applicant
 - Communicate significance of “simple” changes to supplier(s)
 - Surface extraction studies to identify and quantify processing residues, e.g., on uncoated canisters, metallic valve components

IPAC-RS 2011 Conference

Example 6: Change in Procedure (material treatment) and Lack of Control

- An HFA-based suspension MDI:
 - A change in the rinsing procedure of the valve spring
 - changed the APSD FPM results (ACI stages 3-5) to OOS at release as follows:
 - **Before procedure change: x mcg**
 - **After procedure change: 2x mcg**
 - **Root cause: Increased surface active residue**

22

IPAC-RS 2011 Conference

Example 7: Change in material (e.g., change in device colorant)

- HFA-based suspension MDI:
 - A change in the carrier for the actuator colorant
 - The actuator fabricator (n-1) buys the colored resin from a supplier (n-2) who in turn buys the carrier from yet another upstream supplier (n-3)
 - APSD changed abruptly and substantially prompting investigations to find and correct the root cause.

23

IPAC-RS 2011 Conference

Example 8: Significance of appropriate and relevant method validation

- A manufacturer proposed change in test site for Ls
- Approved method was found to be not reproducible at the new site
- New method(s) for leachables was developed with site to site reproducibility
- Consequences:
 - New method did not support the approved leachables AC
 - Firm had to develop a new body of data to reestablish leachable AC
- Lessons learned: Loss of time and resources due to inadequately validated analytical procedure

IPAC-RS 2011 Conference

Considerations in Material Selection (1)

- Materials should comply with accepted standards for food contact and/or GRAS materials, when possible
- Materials should meet the indirect food additive regulations in Title 21 CFR, when possible
- Materials containing sources of known carcinogens or mutagens should be avoided/minimized, e.g.:
 - PolynuclearAromatic Hydrocarbons (PNAs)
 - N-nitrosamines
 - Mercaptobenzothiozole (MBT)

IPAC-RS 2011 Conference

Other considerations for materials/components (2)

- Applicants accessibility to full knowledge of necessary information (e.g., material composition, component composition and fabrication process)
- Establishment of appropriate specifications for incoming critical materials/components
- Availability of relevant DMFs for materials and components with up-to-date and adequate information
- Better communication with supplier(s)
- Agreements with suppliers [DMF holder(s)] to avoid changes without prior applicant's concurrence
- Awareness of suppliers and fabricators (DMF holder) of consequences of material and process changes and unintentional cross contamination

IPAC-RS 2011 Conference

Acknowledgement

- Craig Bertha Ph.D.
- Dale Koble Ph.D.
- Prasad Peri Ph.D.
- Brian Rogers Ph.D.
- Alan Schroeder Ph.D.
- Vibhakar Shah Ph.D.

IPAC-RS 2011 Conference

Thank You ?

IPAC-RS 2011 Conference