Regulatory Perspectives on Extractables and Leachables

Prasad Peri, ONDQA, FDA
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Structures of potential leachables

Bisphenol A (known teratogen)

(1-hydroxycyclohexyl)phenyl-Methanone, suspected leachable

Benzophenone Known photo initiator

PVC monomers

2 2,4-bis(1,1-dimethylethyl) -phenol (DTBP) Leachable, toxicity to be determined

Would you want these in your drug products?
Definitions

• **Extractables**
  – Compounds that can be extracted from the container closure system (CCS) when in the presence of a solvent

• **Leachables**
  – Compounds that leach into the dosage form from the container closure as a result of direct contact with the formulation
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Outline

- Regulatory Background/Importance
- Recommendations
- Current Status
- QbD Approaches to Extractables and Leachables
- Conclusion
Background

• How did the importance of extractables/leachables come to FDA’s attention?
• In the early 1990s.
  – Nitrosamines in metered-dosed inhalers elastomers (MDIs)
  – 2-Mercaptobenzothiazole in elastomers
  – Other classes of E/L’s
  – Processing aid residues
  – Vanillin in inhalation solution
  – Aluminum in large volume parenterals
Why the Concern?

• Safety concerns
  – MDIs
    • Sensitive, compromised patient populations
    • Paradoxical bronchospasm
    • Long-term safety for chronic use
  – Parenterals
    • Direct exposure to leachables

• Quality concerns
  – Lack of knowledge/control of source materials
  – Lack of understanding of potential risks from extractables and leachables
  – Lack of control of extractables and leachables
Relevant Recent Meetings/Courses

- PDA Extractables and Leachables Nov 6-8, 2007, Bethesda, MD.
- PharmaEd’s Extractables and Leachables 2010, May 2010, San Francisco
- Leachables and Extractables Testing and Assessment, Nov. 2010, Prague Czech Republic.
- IPAC RS Workshop on Extractables and Leachables 2011 March.
- Extractables-Leachables Forum 2011, May 17-18, 2011 in Goettingen, Germany
Potential for Extractables and Leachables

<table>
<thead>
<tr>
<th>N-4</th>
<th>N-3</th>
<th>N-2</th>
<th>N-1</th>
<th>(N) End user</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomer Synthesis</td>
<td>Polymer Manufacturing</td>
<td>Masterbatcher</td>
<td>Molding Shop (Converter)</td>
<td>Packaging Containers/Device Components</td>
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</tbody>
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Bulk Chemicals
Storage Stabilizers
Catalysis
Stabilizers
Antioxidants
Processing aids
Others
Stabilizers
Antioxidants
Processing aids
Antistatic
Others
Lubricants
Colorants

Trade Secret Protected
Present and Future

• Only in the past 15 years have attempts been made to proactively design materials fit for use based on increased knowledge about container closure system (CCS) materials and manufacturing processes.
• There is room for a risk-based approach for ophthalmic and some parenteral drug products regarding E/L studies
  • Likelihood of CCS – formulation interaction
  • Potential risk to the patient based on the route of administration.
• If risks not known, can use conservative approaches (e.g., MDI/DPI)
Extractables Studies – Why?

- For qualification of CCS components
- Used to screen for and monitor presence of toxic materials (e.g., nitrosamines etc.)
- Used for quality control for acceptance of CCS components
- Extractables limits ensure limitations on leachables when extractables are correlated to leachables.
Extractables Studies—How?

- Use knowledge of component composition as an initial guide to developing the extraction techniques and analytical methods
- Use solvents of varying polarity, multiple extraction techniques and analytical techniques
- Estimate daily exposure, and safety concern threshold
- Involve toxicologists in assessment
Extractables Studies—How?

- Extraction
- Water
- Polar solvents
- Organic Solvents
Leachables Studies – How?

• Conduct leachables studies (during drug product stability testing) based on methods used for controlled extractables studies.

• When possible establish a correlation between extractables & leachables
  – Could be possible to eliminate leachables testing and develop routine extractables testing.
QbD Approach

QbD
A systematic approach, predefined objectives, product and process understanding and process control, science, quality risk management.

Proactive Approach
Enhanced Assessment of Product Quality.

Quality Risk Management
Pharm. Quality System
Process Understanding

Reactive Approach
ICH Quality Roadmap

Q8, Q9, and Q10 work together as a foundation for Pharmaceutical Quality
ICH Q8(R2) Concepts

- Quality should be built in by design
- Enhanced product knowledge and process understanding
  - Facilitates establishment of design space
  - Provides opportunities for flexible regulatory approaches
    - Risk-based regulatory decisions (review & inspection)
Role of Quality Risk Management

• Role of risk assessment
  – Early identification of risk
  – Risk analysis and evaluation
  – Risk reduction as needed

• Risk communication for continuity between
  – Development and manufacturing
  – Industry and regulators
  – Multiple manufacturing sites

• Review of risk can be incorporated
  – On periodic basis
  – As part of investigations of deviations
  – As part of change control and continuous improvement
QbD Approach to Extractables and Leachables

- Desired product profile
- Critical quality attribute (CQA)
  - Minimum level or absence of leachables
    Formulation and CCS selection and design to consistently meet CQA
- Risk assessment to identify source of variability (material, process) on CQAs
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement
QbD Approach to Extractables and Leachables

- **QTPP** - Acceptable levels of leachables
- **Considerations**
  - Dosage form and route of administration
  - Patient population
  - Chronic vs. short-term use
  - Patients daily exposure
  - Formulation that is stable and not reactive
  - Delivers consistent product performance
  - Container closure systems with low and safe levels of leachables
“CCS Understanding”

- Not all extractables are leachables
- Not all leachables are extractable
- When possible, develop a correlation between extractables and leachables
- Control and/or characterize the leachables that are not-correlated.

Anthony Grilli, Leachables and Extractables Testing, A Primer on Regulations and Methods
Risk Assessment

• Understand risks of E/L
  – Dosage form risk
    • Inhalation, parenteral > ophthalmic > transdermal > oral > topical
  – Patient population
    • For example, highly sensitive or immune compromised patients
  – Use prior knowledge for selecting and studying CCS
    • For example, high pH formulations and glass
Risk Assessment – E/L’s

- Understand potential contributing factors toward E/Ls
Designing the Product

• Material selection for CCS components is driven by
  - Safety assessment of extractables/leachables
  - Desired performance parameter outcomes
  - Formulation compatibility considerations

• Primary vs. secondary packaging components
  - Elevated risks for packaging components in contact with drug or patient

• Work with supplier
  - Understand CCS manufacturing process and composition, as much as possible, especially for higher risk components

• Make safety assessment of materials to guide the choice of materials and to decrease risk later in development
Understanding the Process

- Understand sources of variability for each material, component, and processing used in the CCS
- Evaluate the impact of this variability on CCS performance and safety as it pertains to drug product
  - Rational experiments
  - Determine who (NDA applicant or supplier) will do experiments
- Work with supplier(s) to ensure appropriate raw material quality, in-process/release controls for CCS components to maximize chances for successful development
While it is possible to have a Design space for CCS, it is not necessary as part of a QbD approach.
Control Strategy

• Prior knowledge useful as a starting point.
• The planned set of controls, derived from current product and process understanding that assures process performance and product quality.
• Control strategies can include
  – parameters and attributes related to materials and components,
  – facility and equipment operating conditions
  – in process controls
  – finished product specifications
  – associated methods and frequency of monitoring/control
  – move the control upstream (extractables) to where the source of variability is likely.
  – Leachables testing when necessary
Setting Leachables Specification

- Drug substance, formulation, excipients
- CCS materials selection
- Fabricator
- Component mfg. process (oils, detergents, soaps, processing aids)
- Device operation (pressure, temp)
- Analytical methods
- Stability/storage conditions
- Reaction kinetics
- Identification & qualification
- Drug product manufacturing process
- Specification
Control Strategy – Specifications

• Setting leachables specification is a circular, labor-intensive process if a proactive approach is not adopted

• Specifications are usually based on data; however, amount of research and development plays a significant role
  – Formulation
  – CCS material
  – Analytical methods

• If extractable studies are performed ahead of time, the burden of setting leachables specifications becomes easier as
  – an extractables-leachables correlation can be accomplished in a single stability study
Lifecycle Management

- Lifecycle monitoring and improvement in CCS material and process
- Work with supplier related to changes in CCS process
  - Business decisions
  - Alternate sites for better access
  - Better knowledge of materials
- Development of libraries for alternate CCS materials to be interchanged ahead of time since the component marketplace is constantly changing
Summary

• Extractables and leachables (E/L’s) pose a safety and quality concern to certain types of products
• The QbD approach can provide a framework for a more scientific, risk-based approach to E/L’s
• Risk understanding and management is key
• Specification is only part of quality control strategy
• Higher level of understanding can facilitate continual improvement during product lifecycle
Available References

- ICH Q9 *Quality Risk Management* (Nov 2005).
- FDA Guidance to Industry (draft), *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products* (November 1998).
- PQRI Recommendation (draft), *Safety Thresholds and Best Practices for E/L in Orally Inhaled and Nasal Drug Products* (September 2006).
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