Extractables & Leachables

Ophthalmic Drug Products: A Regulatory Perspective
Current Industry Challenges and Case Studies

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Thresholds and Best Practices for
Parenteral and Ophthalmic Drug Products (PODP)
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Overview

• Background
  - Rise of Leachables
  - Regulatory Landscape – Industry Perspective

• Product Experience & Challenges

• Where are we going

• Conclusion
Container Product Compatibility – The Past

• Initial focus on container closures were:
  ▪ Does it work with the formulation?
  ▪ Ability to deliver the dose?
  ▪ Maintain sterility?

• Development of a multitude of formulation and container closure combinations

• Parallel evolution of regulatory concerns
  ▪ Risk posed is no longer “basic”

• Processes and drug related impurities well controlled
  ▪ Next thing to worry about?
The Rise of Leachables

- Greater focus on the role of packaging components and interaction with drug product
  - Do they pose a risk to the patient?
  - Tylenol, Kellogg's
- Food industry has dealt with leachable issues for decades
  - FDA guidance
- Regulatory assumption
  - All leachables are genotoxic impurities
  - Can you prove otherwise?
Regulatory Background

• Regulatory guidance on impurities focus on process related/degradation impurities
  ▪ The topic of leachables falls outside of their scope.

• Guidance on genotoxic impurities (EMA; guidelines final; FDA; guidelines currently in draft)
  ▪ Again do not specifically cover the topic of leachables.
Regulatory Background

- Beginning in the late 1990s, the FDA gradually increased scrutiny on packaging materials and components used for drug products.
- Initial focus was on inhalation devices, and FDA draft guidance (1998) called for the identity and concentration profiles of the leachables in the drug product.
- Followed in 1999 by the FDA container closure guidance.
# Regulatory Background

## Table 1. Examples of Packaging Concerns for Common Classes of Drug Products. (1)

<table>
<thead>
<tr>
<th>Degree of Concern Associated with the Route of Administration</th>
<th>Likelihood of Packaging Component-Dosage Form Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest</strong></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Inhalation Aerosols and Solutions; Injections and Injectable Suspensions&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Topical Solutions and Suspensions; Oral Lingual Aerosols and Oral Solutions and Suspensions</td>
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<td></td>
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</tbody>
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Notes: (1) From Guidance for Industry. Container Closure Systems for Packaging Human Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration; Rockville, MD, May, 1999.<sup>2</sup>  
<sup>a</sup> For the purpose of this table, the term suspension is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.
Regulatory Background

• Broadened the scope of products included, and outlined the highest risk dosage forms as a function of the route of administration.

• More recent guidance on the use of plastics in primary packaging:
  ▪ European Medicines Agency
  ▪ Health Canada

• Biologics – Ability of leachables triggering formation of agglomerates
Regulatory Landscape

• Regulators have divergent views on L&E
• US – strong focus on leachables
  ▪ Particularly Ophthalmics division
• EU – Aware but more pragmatic on levels
  ▪ e.g. application of genotoxic limit
• Seeing added scrutiny from other countries
  ▪ Japan, Israel
• Starting to see queries relating to veterinary products
• Biologics – Ability of leachables triggering formation of agglomerates
Product Experience – Ophthalmics

- Most common packaging is a semi-permeable polyethylene bottle that does not provide a barrier to migrating chemical moieties

- Examples:
  - Label leachables (direct contact w/bottle)
  - Adhesive
  - Inks
  - Varnish

- Carton leachables (migrate through air)
  - Adhesive
  - Inks
  - Varnish

- Environmental (fleeting contact)
  - Sanitization
Product Experience – Ophthalmics (US)

• Historically leachables were treated as quality issues
• Application of ICH impurity “thinking”
• Set specification based on batch data
  ▪ Specified impurity limit of 1 ppm
• Control based on batch data
  ▪ Have a limit in the registered DP specification
  ▪ Limit exceeded, batch failure
  ▪ Challenge is no fingerprint
Product Experience – Ophthalmics

- Benzophenone from UV-based inks/labels
  - Found in numerous products via field alert reports
  - Causes eye irritation

- Individual unspecified leachable acceptance criteria: - Linked to active
  - For DPs > 0.01% strength: NMT 0.1%
  - For DPs <0.01% strength: Incremental increase
  - For DPs 0.001% strength: NMT 1%

- Exclude in specification if observed at 1000-fold lower than level of toxicological risk

*Ravi S. Harapanhalli, PDA 2007 Extractables and Leachables Forum*
Quality Limit vs. Safety Limit
Example

• Benzophenone Limit NMT 1%
  ▪ ~60-fold lower than normal range of benzalkonium chloride
  ▪ Considered one of the more irritating preservatives.
  ▪ >150K times lower than the minimally irritating dose (20 mg/eye)

• More recently:
  ▪ Acceptable threshold levels would be 1 ppm for reporting, 10 ppm for identification, and 20 ppm for toxicological qualification
Product Experience – Ophthalmics

• Move to TDI argument
  ▪ Safety (TDI of 0.15µg) rather than quality (1ppm)
  ▪ Successful with Inhalation products – Product Quality Research Institute (PQRI)

• Will continue to be a challenge for the foreseeable future
  ▪ Absence of formal guidance
  ▪ Acceptance of scientific and toxicological approaches
Where are We Going?

• PQRI issued Safety Thresholds and Best Practices for Extractables and Leachables in OINDP (Sept 2006)
• PQRI working group on PODPs
  ▪ Help frame a consistent approach
• Improved understanding - Regulators and Industry
  ▪ Improve engagement with regulators
  ▪ Greater dialogue
  ▪ Move to a safety risk argument
  ▪ Away from ICH mentality
Conclusion

• Area continues to evolve
  ▪ Greater regulatory scrutiny

• Improved regulatory understanding and interaction
  ▪ Greater dialogue/interaction with Health Authorities
  ▪ Greater guidance availability
  ▪ Understanding of expectations for submissions

• Balance control with benefit of new medicines to patients