Current Regulatory Recommendations for Leachables in Ophthalmic Products

Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products.
February 22-23, 2011
Hyatt Regency Bethesda, Maryland
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Definitions

- Extractable
  Any chemical compound that can be removed from packaging components using laboratory procedures

- Leachable
  An extractable that has migrated into the drug product formulation under storage conditions
What will be covered

- Will cover leachables for solutions, suspensions and emulsions in low density polyethylene (LDPE) container closure system (C/C)
- Will not address leachables in injectables in glass container or syringe
- Will not address leachables in other dosage forms

Ophthalmic Products

- Commonly present as solution or suspension
- Stored in LDPE bottle and tip, with cap or blow-fill-seal vial
- Container has to be squeezable to allow delivery as drops to the eye
- LDPE containers are squeezable but also are semi-permeable to volatile compounds
Leachables

- Container closure:
  - Plasticizer
  - Lubricant
  - Pigment
  - Stabilizer
  - Antioxidant
  - Binding agent

- Outer carton
  - Sterilization agent
  - Preservatives
  - Sealant
  - Ink

- Labelling:
  - Ink
  - Adhesive
  - Varnish

- H₂O

Leachables Affected by

- Headspace in semi-permeable bottle
- Environmental humidity
- Temperature
- Time
- Composition of product
Leachables Testing in New & Old Products

- Use a scientific approach to detect, quantitate and qualify unknowns
- Compounds type, level & properties unknown
- Penetration level and rate unknown
- Low molecular weight volatile compounds type unknown

What & when leachables appear in formulation?
How to evaluate such leachables?

Leachables in Ophthalmic Products

- Migrate through semi-permeable containers into formulated product through time
- Could originate from adhesive, paper, ink on primary and secondary packaging
- Information on composition of packaging and labeling components not available to the drug product developer
- Information submitted by suppliers as part of Type III DMF
A Potential Solution

• Ink, adhesive, paper suppliers provide names of only the low molecular weight compounds to NDA/ANDA/BLA holder
• Molecular weight cut-off determined between supplier and applicant
• Then volatile compounds are known to the applicant

Potential Solution (cont’d)

• Applicant designs procedure to detect specific compounds and has reduced method development burden
• Supplier can use DMF to maintain confidentially the composition of the item of sale
• Reviewer has access to composition of potential leachables for confirmation of observed peaks
Evaluation of Leachables

• One-time study until next C/C change
• Use appropriate control e.g. sealed glass vial with same product under identical storage conditions
• Test at least one batch 6 months at accelerated, and recommended storage temperature through expiry concurrent with the stability program

Evaluation (cont’d)

• Select and use screening techniques such as gradient GC and/or gradient HPLC, with detection techniques appropriate for maximum coverage of potential leachables
• Leachable analytes could be compared to established in-house standards or matched to compounds in commercially available libraries
How to Report

• Leachables should be reported in ppm that refers to weight of leachable per unit volume or mass of the drug product
• Impurities (process and degradation) are reported as percent of the drug substance

Reporting, Identification and Qualification

• Leachables should be identified when possible and toxicology assessment evaluated as necessary
• Typically, leachables are
  – Reported at above 1 ppm
  – Identified at 10 ppm
  – Qualified at 20 ppm
  – Not included in the drug product specification if detected at levels 1000 fold lower than level posed toxicological risk
Summary

• Leachables are usually low molecular weight volatile compounds that migrate through semi-permeable containers
• Process and degradation impurities are recorded in %; leachables in ppm
• Appropriate testing should be designed to monitor leachables
• Working with the suppliers may reduce method development of leachable testing

Conclusion

Aim for clear understanding, with good science approach, for potential leachables from interaction of the primary and secondary packaging, labeling components with the drug product