Quality Considerations for Topical Ophthalmic Drug Products – Guidance for Industry

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Learning Objectives

- Provide an overview of the draft guidance
- Explain current practices on assessment of key topics discussed in the guidance

Scope of the Guidance

- Ophthalmic drug products intended for topical delivery
  - Gels, ointments, creams
  - Liquid formulations
    - Solutions, suspensions, and emulsions
  - NDAs, ANDAs, BLAs, OTC

Topics Covered

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- Microbiological Considerations
- Visible Particulate Matter
- Extractables and Leachables
- Impurities and Degradation Products
- In Vitro Drug Release/Dissolution Testing for Quality
- CCS Design and Delivery and Dispensing Characteristics
- Stability

Microbiological Considerations

- Provides for microbiological considerations related to product sterility for all ophthalmic drug products
- Emphasis on complying with CGMP requirements to ensure product quality
- Guidance for Industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (September 2004) and
- *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994)

Microbiological Considerations

- Multidose Drug Products - Should remain free from harmful contamination following potential microbial ingress
- Use of preservative if drug product does not have inherently antimicrobial activity
- Using silver sulfate or other silver containing compounds as preservative – not recommended
- Multidose preservative free formulations
  - Robust protection for each unit from incidental contamination during multiple use
  - Validation of all aseptic and sterilization processes

Visible Particulate Matter

- Visual inspection to ensure products are not adulterated
- Drug products packaged in opaque container – use of non-destructive (e.g., X-ray) or destructive testing
- Suspensions and emulsions – stability testing to evaluate changes in particle size over the shelf life

Extractables and Leachables

- Assessment for extractables and leachables for primary, secondary and tertiary packaging components (including labeling) of CCS
- Framework for Extractable and Leachable studies
  - USP<1663> *Assessment of Extractables Associated With Pharmaceutical Packaging/Delivery Systems*
  - USP<1664> *Assessment of Drug Product Leachables Associated With Pharmaceutical Packaging/Delivery Systems*
  - *Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation (May 1999)*

Extractables and Leachables

- Leachable Studies for CCS
- **Safety Thresholds**
  - Reporting threshold: 1 ppm
  - Identification threshold: 10 ppm
  - Qualification threshold: 20 ppm
- Analytical Method: LOQ ≤ IT

Impurities and Degradation Products

- NDA/ANDA/OTC Monograph Drugs generally to follow ICH Q3B(R2)*
  - Each specified identified degradation product or impurity as a percent of the API
  - Each specified unidentified degradation product or impurity as a percent of the API
  - Any individual unspecified degradation product or impurity
  - Total degradation products or impurities

**Acceptance criteria for specified degradation products in generic drug products should be established according to the guidance for industry ANDAs: Impurities in Drug Products (November 2010)*

Impurities and Degradation Products

- **Individual unspecified degradation products or impurities** – different than corresponding thresholds in ICH Q3B(R2)
  - Potential for high local concentration in the eye
  - Lack of data on potential effects

FDA's Recommended Thresholds for Unspecified Degradation Products or Impurities in Ophthalmic Drug Products*

Drug Product Strength (% w/v)	Recommended Identification and Qualification Threshold
Greater than 0.1% to less than or equal to 1%** (> 0.1% to ≤ 1%)	0.1%
Less than or equal to 0.1% (≤ 0.1%)	1% or 1 ppm***

*These recommended thresholds apply to OTC monograph ophthalmic drug products and ophthalmic drug products submitted under NDAs and ANDAs.
** Limits above 1% will be evaluated on a case-by-case basis.
*** Whichever is higher; ppm=parts per million (i.e., parts of a leachable per unit mass of the ophthalmic drug product).

  - **For impurities above IT/QT – Safety information should address both local ocular toxicity as well as general systemic toxicity**

In Vitro Drug Release/Dissolution

- Rate and extent of drug release – quality criteria to ensure consistency for suspensions, emulsions and semi-solids
- In vitro drug release/dissolution – part of quality control strategy
- Alternatively, using one or more CQAs sensitive to the formulation and process variants

Challenge Question #1

For leachables study in topical ophthalmic drug products, threshold at or above which the observed leachable should be qualified for safety is:

A. 1 ppm

B. 10 ppm

C. 20 ppm

D. 0.1%

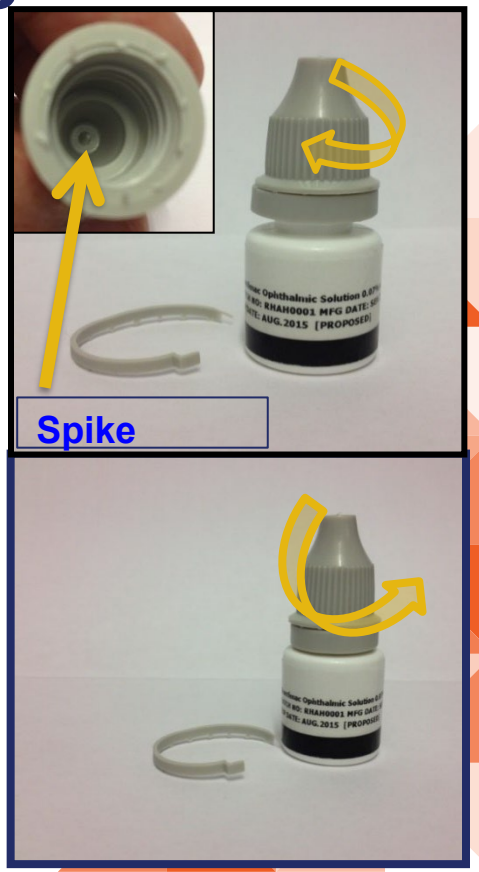
CCS Design and Delivery and Dispensing Characteristics

- **Tamper-Evident Packaging**
  - For non-retaining tamper-evident ring
  - Consumer complaints – rings slip off bottle neck

- Recommendation: Positive-retention mechanism to prevent rings from coming off during use

CCS Design and Delivery and Dispensing Characteristics

- **Tips**
  - CCS designs with tip sealed until opening – multistep procedure to unseal the tip is discouraged
  - Complex procedure leads to confusion
  - Recommend use of single-step procedure with simple directions and twisting the cap without removing it



CCS Design and Delivery and Dispensing Characteristics

- **Torque Specification**
  - Consideration for patient population
  - Low enough for elderly to open caps without undue difficulty
  - High enough to remain in place during manufacturing, storage, shipping and handling
- **Color Coding**
  - Caps color to characterize therapeutic class
  - Recommend to use uniform color-coding system as described in the American Academy of Ophthalmology's *Color Codes for Topical Ocular Medications* policy statement

CCS Design and Delivery and Dispensing Characteristics

- **Unit Dose Containers**
  - Maximum fill volume (non-preserved): Solutions, suspensions and emulsions – no more than 0.5 mL
  - Maximum fill: Ointment or gel – no more than 1 gram
  - Not be able to be recapped
- **Multidose Containers**
  - Drop size: between 20 and 70 µL
    - ANDAs – within ±10% of drop size of the RLD AND within recommended drop size of 20 and 70 µL
    - Deviations from RLD – justification to demonstrate similar number of delivered doses

CCS Design and Delivery and Dispensing Characteristics

- **Multidose Containers – Suspensions**
  - Resuspendability/Redispersibility
    - Qualitative test – performed per labeling instructions to mimic actual patient use conditions
    - Acceptance criteria – time for resuspension of drug product after storage: e.g., NMT 15 – 30 seconds
  - Dose Uniformity of Suspension drug products
    - One-time dose uniformity study
    - Quantitative test – unit dose samples from top, middle and bottom of container – after shaking per labeling instructions
    - From at least three pilot or exhibit batches
    - Samples tested for assay – using assay acceptance criteria
    - Ensure drop homogeneity within the entire container throughout product shelf life

Stability

- Appropriate Storage Conditions
- Ophthalmic drug products packaged in semi-permeable containers (e.g., LDPE), should be kept in low relative humidity conditions.
- Recommended ICH Q1A(R2) conditions
  - Long Term: 25°C± 2°C/40% RH ± 5% RH or 30°C± 2°C/35% RH ± 5%
  - Intermediate: 30°C± 2°C/65% RH ± 5%
  - Accelerated: 40°C± 2C/NMT 25% RH
- Higher RH may be employed – deriving water loss at the reference RH through calculation – ICH Q1A(R2)

Stability

- Container Orientation During Storage
  - NDAs: Preliminary development work to evaluate storage conditions – two different orientations – upright and inverted or horizontal
  - Worst-case orientation for batches representing commercial manufacturing process
  - ANDAs: Two different orientations – primary stability batches – upright and either inverted or horizontal
  - Data from both orientations
  - Worst-case orientation for routine stability
  - BLAs: Primary stability studies to determine storage under real-time conditions

Stability

- Water Loss
  - Moisture transmission properties of the CCS and protective properties of any secondary packaging
- Freeze/Thaw Study
  - One-time study for suspensions and emulsions
  - Three cycles – freezing (-20°C to 0°C) and ambient (25°C – 35°C) for a cumulative minimum of 3 days
  - Alternative conditions and durations should be adequately justified
- In-Use Stability
  - To support labeling claims – storage conditions that may change after opening
    - Change in temperature
    - Light exposure

Challenge Question #2

Which of the following studies is most suitable to mitigate the risk to drug product quality for ophthalmic suspensions and emulsions due to temperature variations during shipping and storage?

A. In-Use stability study

B. Photostability study

C. Water loss study

D. Freeze/Thaw study

Take Home

- The draft guidance provides recommendations for certain quality considerations for topical ophthalmic drug products
- The draft guidance also provides recommendations on the documentation
- Adequate supporting data in ANDA applications to ensure smooth and timely assessment of applications

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Questions?

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