Quality Considerations for Topical Ophthalmic Drug Products

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)

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Pharmaceutical Quality/CMC

Revision 1

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Quality Considerations for Topical Ophthalmic Drug Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance discusses certain quality considerations for ophthalmic drug products[2] (i.e., gels, ointments, creams, and liquid formulations such as solutions, suspensions, and emulsions) intended for topical delivery in and around the eye. Specifically, the guidance discusses:

- Microbiological considerations.
- Approaches to evaluating visible particulate matter, extractables and leachables, and impurities and degradation products.
- Use of in vitro drug release/dissolution testing as an optional quality control strategy for certain ophthalmic dosage forms.
- Recommendations for design, delivery, and dispensing features of container closure systems (CCSs).[3]
- Recommendations for stability studies.

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] The term *drug product*, as used in this guidance, refers to drugs approved pursuant to new drug applications (NDAs) and abbreviated new drug applications (ANDAs) under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act; 21 U.S.C. 355); biological products licensed under section 351(a) or (k) of the Public Health Service Act (PHS Act; 42 U.S.C. 262(a) or (k)) that are regulated as drugs; and other drugs that, while also subject to CGMP requirements, are not marketed pursuant to an approval or licensure, including products marketed pursuant to section 505G of the FD&C Act (often referred to as *over-the-counter (OTC) monograph drugs*) and drugs compounded by outsourcing facilities pursuant to section 503B of the FD&C Act. The term also encompasses such drugs or biological products when they are included as a constituent part of a combination product, as defined in FDA regulations at 21 CFR 3.2(e).

[3] Some ophthalmic products that are the subject of this guidance may be combination products (see 21 CFR 3.2). See section VII for more information. Contact the Office of Combination Products at Combination@fda.hhs.gov with questions regarding the classification of a specific product.

This guidance provides information regarding quality considerations for ophthalmic drug products consistent with the current good manufacturing practice (CGMP) requirements outlined in section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR parts 210 and 211 for all drug products, part 601 for biological products, and part 4 for combination products.[4] For ophthalmic drug products with a United States Pharmacopeia (USP) monograph, this guidance provides information about applicable criteria from the USP.[5] This guidance also provides recommendations to industry on the documentation that should be submitted in the chemistry, manufacturing, and controls (CMC) section of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs), including BLAs for biosimilar and interchangeable biosimilar products.[6] The CMC section of NDAs, ANDAs, and BLAs must be included as required by 21 CFR 314.50, 21 CFR 314.94, and 21 CFR part 601, respectively. Relevant records and other information that demonstrate compliance with CGMP requirements must be made available for FDA review during an inspection conducted under section 704(a)(1) of the FD&C Act or when requested by FDA in advance or in lieu of an inspection as described in section 704(a)(4) of the FD&C Act.[7] This guidance does not apply to biological products regulated by the Center for Biologics Evaluation and Research.

This guidance revises the draft guidance of the same name issued in October 2023. This revision adds microbiological considerations related to product sterility for all ophthalmic drug products and the prevention of contamination of ophthalmic drug products packaged in multidose containers.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. MICROBIOLOGICAL CONSIDERATIONS

A. Product Sterility

Product sterility is a critical quality attribute (CQA) for ophthalmic drug products.[8] Recent cases of microbially contaminated ophthalmic drug products leading to serious injury and death, as

[4] In addition, applicants, manufacturers, and outsourcing facilities should ensure that drug products subject to this guidance comply with other applicable provisions of the FD&C Act, including sections 501(a)(2)(A), 501(a)(1), 501(c), 502(a), and 502(j).

[5] See section 501(b) of the FD&C Act.

[6] For topical ophthalmic biological products, including biosimilars and interchangeable products, we recommend that applicants consult with FDA before submitting their application.

[7] See also 21 CFR 211.180(c).

[8] See 21 CFR 200.50(a)(1).

well as recent recalls, highlight the importance of product sterility.[9] Manufacturers[10] of sterile drug products must comply with CGMP requirements to ensure product sterility.[11] Failure to comply with these requirements will cause affected products to be deemed adulterated under section 501(a)(2)(B) of the FD&C Act.

For recommendations on how to meet CGMP requirements for product sterility, see guidances 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).[12]

B. Multidose Drug Products

Ophthalmic drug products should be appropriately designed and controlled to prevent harmful microbial contamination throughout their shelf life and in-use period, which must be supported by stability data.[13] Unit-dose CCSs prevent the hazards associated with in-use contamination and growth of microorganisms between doses that can occur with multidose CCSs that are opened multiple times over the course of their shelf life. Liquid ophthalmic drug products packaged in multidose containers should contain one or more suitable substances that will preserve the product and minimize the hazard of injury resulting from incidental contamination during use.[14] If a multidose drug product does not possess inherent antimicrobial activity adequate to preserve the formulation, it should be formulated with an appropriate preservative.[15] Preservatives are critical to ensuring that the multidose drug product remains free from harmful contamination following potential microbial ingress. Such ingress could occur, for example, if surrounding air is introduced into the multidose drug product following administration, if the tip of a dropper is contaminated by a nonsterile surface (i.e., the fluid path is contaminated), or if a contaminated drop returns to the product reservoir. Regardless of whether a multidose drug product possesses inherent antimicrobial activity or contains one or more added preservatives, manufacturers

[9] See FDA's alerts and warnings about eye drops at https://www.fda.gov/drugs/buying-using-medicine-safely/what-you-should-know-about-eye-drops.

[10] For the purposes of this guidance, we use the term *manufacturer* to refer to entities that produce the drug products defined in footnote 2. Where applicable, this guidance uses the term *applicant* to refer to manufacturers and other parties who are NDA, ANDA, and BLA applicants or application holders.

[11] See, e.g., 21 CFR 211.22(a), 211.94(b), 211.113(b), 211.160, 211.165, 211.166, and 211.167.

[12] Although the latter guidance on sterilization process validation is intended for the submission of documentation for application products, its principles are also instructive for OTC monograph drugs. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[13] See 21 CFR 211.137 and 211.166.

[14] See 21 CFR 200.50(b)(1). If such substance(s) are not included in the drug product, other packaging and labeling recommendations apply. See 21 CFR 200.50(b)(2).

[15] For further discussion about the use of preservatives, see draft guidance for industry *Microbiological Quality Considerations in Non-Sterile Drug Manufacturing* (September 2021) at page 6. When final, this guidance will represent the FDA's current thinking on this topic.

should implement a well-designed and rigorous antimicrobial effectiveness testing program that covers the product's shelf life.[16]

FDA does not recommend using silver sulfate or other silver-containing compounds as a preservative in ophthalmic drug products because of the significant safety concerns associated with applying silver directly to the eye, including argyria (an irreversible discoloration of the skin and eyes) and granular deposits of silver in the conjunctiva and cornea.[17]

Some manufacturers have sought to use a preservative-free formulation for a multidose liquid drug product in conjunction with a CCS design intended to eliminate the potential for in-use microbial contamination.[18] These formulations and associated presentations should afford robust protection for each unit produced to prevent the hazard of injury resulting from exposure to incidental contamination during multiple uses of the product.[19] There are numerous ways in which such presentations might fail to prevent microbial contamination. Any ophthalmic drug product that lacks adequate preservative properties, when exposed to in-use contamination, is especially vulnerable to proliferation of microbes that can pose severe harm to consumers. CCSs must provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination.[20]

For information on delivery and dispensing characteristics of multidose containers, see section VII.B.2 of this guidance.

III. VISIBLE PARTICULATE MATTER

The use of a robust visual inspection program and the implementation of CGMP requirements are important to ensure products are not adulterated. For topical ophthalmic drug products packaged in opaque containers, appropriate technologies (e.g., X-ray spectroscopy) or destructive testing should be used to identify particulates within the accepted visible size range.[21]

Ophthalmic drug products with names recognized in the USP are generally required to also meet the particulate matter requirements in USP General Chapter <771> *Ophthalmic Products—*

[16] See USP General Chapter <51> *Antimicrobial Effectiveness Testing*.

[17] FDA also does not recommend using silver in CCSs for ophthalmic drug products because silver may continually leach into the drug product.

[18] Liquid ophthalmic preparations packed in multidose containers that do not contain one or more suitable and harmless substances that will inhibit the growth of microorganisms should be packaged and labeled with necessary warnings to minimize injury from contamination during use. See 21 CFR 200.50(b).

[19] Ibid. Furthermore, appropriate written procedures designed to prevent microbial contamination of sterile products must be established and followed, including validation of all aseptic and sterilization processes. See 21 CFR 211.113(b).

[20] See 21 CFR 211.94(b).

[21] For topical ophthalmic drug products that include inherent visible particulates by design, such as suspensions and emulsions, stability testing can be used to evaluate any changes in the particle size over the shelf life of the product. See USP General Chapter <771> *Ophthalmic Products—Quality Tests*.

Quality Tests.[22] Noncompendial ophthalmic drug products should also follow the above USP General Chapter. Adherence to compendial standards can assist applicants and manufacturers in complying with CGMP regulations (e.g., 21 CFR 211.165(e), 211.167(b), and 211.194(a)(2)).

IV. EXTRACTABLES AND LEACHABLES

Ophthalmic drug products should be evaluated for extractables and leachables from the CCS. Leachables have the potential to interact with the formulated drug product, which could compromise product quality and therapeutic effect. The assessment of extractables and leachables should consider the primary, secondary, and tertiary packaging components of the CCS, including the labeling components.

Semipermeable CCSs can, over time, leach low molecular weight compounds (e.g., plasticizers, lubricants, pigments, stabilizers, antioxidants, binding agents) from CCS components or from labeling components (e.g., inks, adhesives, varnishes) into the drug product. However, this is less of a concern for products packaged in glass containers (e.g., biological products).

General tests for CCSs are described in USP General Chapters, such as <87> *Biological Reactivity Tests, In Vitro*; <88> *Biological Reactivity Tests, In Vivo*; <660> *Containers—Glass*; and <661> *Plastic Packaging Systems and Their Materials of Construction*. For more information about testing extractables and leachables, applicants and manufacturers should consult USP General Chapters <1663> *Assessment of Extractables Associated With Pharmaceutical Packaging/Delivery Systems* and <1664> *Assessment of Drug Product Leachables Associated With Pharmaceutical Packaging/Delivery Systems*. Applicants should also refer to the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation* (May 1999).

A. Extractables Studies

Where extractables testing is conducted to comply with CGMP requirements, manufacturers should document the following information about their extractables studies, and applicants should provide this information in their application (see 21 CFR 211.194(a)).

- A risk assessment in support of their study approach.
- Data from their extractables studies, which generally should be conducted following the framework provided in USP General Chapter <1663> and should take into account the primary, secondary, and tertiary packaging components.
- Information on the use of extraction conditions (e.g., media, temperature, time, analytical techniques).

[22] See section 501(b) of the FD&C Act.

- Information on the use of analytical procedures (e.g., gas or liquid chromatography–mass spectrometry), including method validation information.

- An assessment of the resultant extractables profiles.

Where a CCS has been used in an approved ophthalmic drug product, an applicant can refer to previously submitted information to address the recommendations above, when feasible and with adequate justification.

B. Leachables Studies

Because leachables can stem from different sources and be formulation dependent, applicants and manufacturers should have adequate data to identify and characterize the potential risks associated with the leachables from the CCS and describe how these risks are mitigated, such as by conducting leachables studies.

Where leachables testing is conducted to comply with CGMP requirements, manufacturers should document the following information about their leachables studies, and applicants should provide this information in their application (see 21 CFR 211.194(a)).

- Data from three primary stability batches, each of which generally should be followed through expiry as described in USP General Chapter <1664>.

- Information on the use of analytical procedures (e.g., gas or liquid chromatography–mass spectrometry), including method validation information.

- An assessment of the resultant leachables profiles.[23]

- The acceptance criteria contained in drug product specifications.[24]

In addition to the leachables studies, a separate toxicological risk assessment of the leachables should be conducted.

C. Safety Thresholds

Because of the variety of chemical species and the enormous capability of modern analytical techniques in detecting trace amounts of chemicals, it is neither practical nor necessary to identify all detected leachables for safety qualification. However, because ophthalmic drug products are applied directly to the eye, applicants and manufacturers should assess compatibility and safety concerns of any potential leachables exceeding the qualification threshold discussed below. The safety assessment should address the ocular toxicity and irritancy potential of such leachables, in addition to systemic safety, as appropriate.

[23] See section IV.C of this guidance.

[24] Ibid.

Applicants and manufacturers can use a safety threshold approach to assess the potential of leachables and extractables to leach into and/or interact with the formulated drug product. The following recommended leachables thresholds are expressed in parts per million (ppm) (i.e., the parts of a leachable per unit mass of the ophthalmic drug product)[25]:

- Reporting threshold: 1 ppm.
- Identification threshold: 10 ppm.
- Qualification threshold: 20 ppm.

Manufacturers should document information about their safety thresholds, and applicants should list leachable impurities above the reporting threshold along with other impurities in the drug product specification section of NDAs and ANDAs, but not in BLAs (see 21 CFR 211.194).[26]

V. IMPURITIES AND DEGRADATION PRODUCTS

A. NDA, ANDA, and OTC Monograph Drugs

The establishment of scientifically sound and appropriate specifications to comply with 21 CFR 211.160(b) includes identifying test methods and acceptance criteria for impurities and degradation products. NDA and ANDA applicants should generally follow the principles of reporting, identifying, and qualifying degradation products and impurities outlined in the International Council for Harmonisation (ICH) guidance for industry *Q3B(R2) Impurities in New Drug Products* (August 2006).[27] Manufacturers should generally establish thresholds and acceptance criteria for impurities and degradation products according to USP General Chapter <1086> *Impurities in Drug Substances and Drug Products*. Manufacturers should document the following information and applicants should include it in the drug product specification section of NDAs or ANDAs (21 CFR 211.194(a)):

- Each specified identified degradation product or impurity as a percentage of the active pharmaceutical ingredient (API).
- Each specified unidentified degradation product or impurity as a percentage of the API.
- Any individual unspecified degradation product or impurity.
- Total degradation products or impurities.

However, FDA's recommended thresholds for individual unspecified degradation products or impurities are different for ophthalmic drug products than the corresponding thresholds provided

[25] These thresholds are based on historical data from approved drug products. For topical ophthalmic drug products, ppm is used instead of a limit on concentration because of the risk of local toxicity to the eye.

[26] See section V.B of this guidance for an explanation of this recommendation for BLAs.

[27] 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).

in ICH Q3B(R2) for the same dose range (see table below for these different thresholds, which are based on historical data from FDA-approved drug products). There are two reasons for the differences in recommended thresholds compared to the ICH recommendations: First, ophthalmic drug products are directly administered to the eye, and direct, local application has the potential to produce high local concentrations in the eye. In contrast, the recommendations in ICH Q3B(R2) are generally used to support safety determinations for drug products that act systemically. Second, these differences also account for the fact that less is known about the potential effects of individual unspecified degradation products or impurities than specified degradation products or impurities.

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 individual unspecified degradation product or impurity limits that exceed the recommended thresholds in the table above, manufacturers should document identification and safety information for the degradation product or impurity, and applicants should provide such information in their application. Safety information should address both local ocular toxicity as well as general systemic toxicity.

B. BLAs

For ophthalmic biological products, degradation products or product impurities can be controlled by specific acceptance criteria at release and under storage based on historical ranges in pivotal clinical trials. However, some ophthalmic biological products include product-related substances (including some that form under storage) that retain biological activity. Moreover, individual quantitation of each of these individual species may not always be technically feasible. For this reason, impurity considerations for ophthalmic biological products should include product-related substances in addition to degradation products and product-related impurities. Therefore, for ophthalmic biological products, specifications should be established for attributes (e.g., charge variant profile) that are known to be reflective of the mixture of product-related substances and product-related impurities. Other impurities, such as process impurities, can be controlled by using (1) drug product release criteria based on risk assessments for each impurity or impurity class (i.e., host cell proteins), and (2) historical process clearance. Applicants should establish acceptance criteria for impurities, including leachables and process impurities, as

required to control product quality, safety, and efficacy.[28] Impurity amounts should be clearly defined as a percentage of the active ingredient or in current conventional units for ophthalmic biological products (e.g., milligram/milliliter (mg/mL), microgram/milliliter (µg/mL), nanogram/milligram (ng/mg)).

VI. IN VITRO DRUG RELEASE/DISSOLUTION TESTING FOR QUALITY CONTROL

The rate and extent of drug release from ophthalmic drug products are quality criteria that may reflect aspects related to formulation and process variants that are important to control to ensure consistent quality. One approach that applicants can consider as part of the quality control strategy for certain ophthalmic dosage forms (e.g., suspensions, emulsions, semi-solids) is the use of in vitro drug release/dissolution testing. Other approaches are also acceptable, such as using one or more CQAs that are sensitive to the formulation and process variants. The applicant should provide scientific justification for how the control strategy will ensure consistent product quality.

VII. CCS DESIGN AND DELIVERY AND DISPENSING CHARACTERISTICS

This section describes recommendations regarding design elements and delivery and dispensing characteristics that applicants and manufacturers should consider for ophthalmic drug product CCSs. When the CCS that holds or contains an ophthalmic drug also delivers it, it may also be a device constituent part and, together with the drug contained within, a combination product (see 21 CFR 3.2(e)). Combination products are subject to the CGMP requirements under 21 CFR part 4, subpart A.[29]

A. CCS Design

1. Tamper-Evident Packaging

All containers of ophthalmic drug products must be sterile at the time of filling and closing and sealed to prevent product use without destruction of the seal.[30] Additionally, ophthalmic drug products that are OTC drugs must comply with the tamper-evident packaging requirements of 21 CFR 211.132. If the CCS has a nonretaining tamper-evident ring (e.g., collar or band) to seal the bottle and cap, special care should be taken so that the ring does not detach from the bottle during use, which could cause an eye injury. OTC drugs with tamper-evident rings should also

[28] See ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999).

[29] For further information, see the guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017). See also the guidance for industry *Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4* (March 2022) for more information regarding ophthalmic drugs and biological products packaged with eye cups, eye droppers, or other dispensers.

[30] See 21 CFR 200.50(a)(3).

include a positive-retention mechanism similar to those on disposable plastic beverage bottles to prevent the rings from coming off during use.

2. Tips

For CCS designs in which the tip is sealed until opening, multistep procedures are discouraged because a patient may touch and contaminate the tip with their hands while attempting to unseal it. FDA recommends use of single-step procedures that involve simple directions and twisting the cap without removing it.

3. Torque Specifications

Applicants and manufacturers should consider the torque specifications for drug product CCSs because some patients may have difficulties twisting off CCS caps that require extra effort to open. FDA recommends that torque be low enough so that special populations, including the elderly, can open caps without undue difficulty but high enough so that caps remain in place during manufacturing, storage, shipping, and handling.

4. Color Coding

Color coding the caps of ophthalmic drug products is an effective tool in characterizing their therapeutic class.[31] FDA recommends that applicants and manufacturers use a uniform color-coding system as described in the American Academy of Ophthalmology's *Color Codes for Topical Ocular Medications* policy statement.[32]

B. Delivery and Dispensing Characteristics

1. Unit Dose Containers

For all topical ophthalmic drug products,[33] FDA recommends that the maximum fill volume of a unit dose (nonpreserved) container be no more than 0.5 mL for solutions, emulsions, and suspensions. FDA also recommends that the maximum fill for a unit dose ointment or gel be no more than 1 gram. Unit dose containers should not be able to be recapped.

2. Multidose Containers

a. Drop size

For all topical ophthalmic drug products,[34] FDA recommends that the drop size in a multidose CCS be between 20 and 70 microliters.

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[31] See guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).

[32] See https://www.aao.org/about/policies/color-codes-topical-ocular-medications.

[33] See footnote 2.

[34] Ibid.

For ophthalmic drug products submitted for approval under an ANDA, applicants should conduct a one-time drop volume/drop weight study to determine drop size during delivery or dispensing. The drop size of the generic product should be within ±10% of the drop size for the reference listed drug (RLD) and within the recommended drop size of 20 to 70 microliters. For any deviations from the RLD, the ANDA applicant should provide a justification to demonstrate that there will be a similar number of delivered doses as the RLD. ANDA submissions should include information on the measurement of drop volume/drop weight and testing conditions, such as the number of drops in the container and its holding angle during dosing.

b. Dose uniformity of suspension drug products

As recommended in USP General Chapter <771> *Ophthalmic Products—Quality Tests,* a resuspendability/redispersibility test should be performed for all ophthalmic suspension drug products. For multidose containers, data for a one-time dose-uniformity study (from top, middle, and bottom of the container) should be provided from at least three pilot or exhibit batches to demonstrate that the drug substance is uniformly dispersed and the labeled dose can be consistently delivered throughout the shelf life. Alternatively, applicants may consider providing data from development batches (such as investigational new drug batches) that represent the to-be-marketed formulation to demonstrate dose uniformity.

VIII. STABILITY

Manufacturers of drug products must establish a program to evaluate the stability of drug products and to use the results of the stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166). The following stability recommendations should be considered when developing a stability testing program.[35]

A. Container Orientation During Storage

The stability of ophthalmic drug products can be affected when they are stored under different orientations. Before conducting primary stability studies, NDA applicants should conduct preliminary development work[36] to evaluate storage conditions in two different orientations—an upright position and either an inverted or horizontal position. Data from this preliminary work should be used to capture and characterize differences in quality attributes, if any, and determine the worst-case orientation. NDA applicants should use this worst-case orientation when conducting stability tests using batches that represent the commercial manufacturing process.

[35] For detailed information on the stability protocol, annual stability testing, and data reporting, refer to the FDA guidances for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003); *ANDAs: Stability Testing of Drug Substances and Products* (June 2013) and *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* (May 2014). For BLA products, refer to the ICH guidance for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996).

[36] See guidance for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information* (May 2003).

Products submitted under a BLA do not rely on preliminary development work to establish storage conditions during stability. Rather, these products rely on primary stability studies, frequently including process validation batches, to determine storage under real-time conditions. Where interactions between a formulated liquid biological product and the CCS (other than sealed ampules) cannot be excluded, applicants should place stability samples in an upright position and in either an inverted or horizontal position (i.e., in contact with all CCS surfaces) to determine the effect of all product-contact CCS components on product quality.[37]

For products submitted for approval under an ANDA, applicants should place primary stability batches in an upright position and either an inverted or horizontal position, and data from both orientations should be provided in the original submission. The determination of worst-case orientation from this comparison should be used to justify use of that orientation for routine stability batches following approval.[38]

Manufacturers must have a written stability testing program that includes the storage conditions for samples retained for testing (see 21 CFR 211.166(a)(2)), and should generally follow similar principles to determine the worst-case orientation for stability studies.

B. Water Loss

For ophthalmic drug products packaged in semipermeable CCSs, applicants and manufacturers should conduct a water loss test to assess the moisture transmission properties of the CCS and the protective properties of any secondary packaging used. Where water loss testing is conducted to comply with CGMP requirements, manufacturers should document information on the test methods and acceptance criteria used, and applicants should include such information in their application (see 21 CFR 211.194(a)).

C. Freeze/Thaw Study for Emulsions and Suspensions

For ophthalmic drug products that are emulsions or suspensions, applicants and manufacturers should perform a one-time freeze/thaw thermal cycling study to evaluate the effects of any high and low temperature variations that may be encountered during shipping and handling, which could affect the quality and performance of the drug product.[39] FDA recommends this study consist of three cycles, with temperatures cycling between freezing (-20 °C to 0 °C) and ambient (25 °C to 35 °C) temperatures for a cumulative minimum of 3 days. Periodically throughout the study, and at the end of a predetermined number of cycles, the samples should be analyzed for all quality attributes and compared with the control drug product. Applicants that use alternative conditions and durations for their tests should provide a justification for the test conditions used.

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[37] See ICH guidance for industry *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (July 1996).

[38] See guidance for industry *ANDAs: Stability Testing of Drug Substances and Products Questions and Answers* (May 2014).

[39] See guidance for industry *Drug Stability Guidelines* (December 2008). This guidance was published by the Center for Veterinary Medicine, but FDA recommends that its thermal cycling study recommendations also be applied to drugs intended for human use.

D. In-Use Stability Studies

In-use stability studies are used to determine expiration dates and support labeling claims for appropriate storage conditions that may change after opening, such as a change in temperature or light exposure (see 21 CFR 211.166, 21 CFR 211.137(b)). Manufacturers should document information on in-use stability studies, and applicants should submit such information in their application.

Under 21 CFR 211.137(h), OTC drugs that do not bear dosage limitations in their labeling and are stable for at least 3 years, as supported by appropriate stability data, are exempt from the expiration date labeling requirement. Accelerated testing programs can be appropriate to establish stability for the purposes of meeting this requirement.

IX. GLOSSARY

Container closure system (CCS): For the purpose of this guidance, the CCS includes primary packaging components (e.g., bottles, drug-dispensing tips, tubes with liner, caps), secondary packaging components (e.g., overwrap), and tertiary packaging components (e.g., shipping boxes).

Critical quality attribute: "Physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."[40]

Degradation product: "An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the new drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system."[41]

Extractables: "Organic and inorganic chemical entities that are released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction and into an extraction solvent under laboratory conditions.[42]

Impurity: "Any component of the new drug product that is not the drug substance or an excipient in the drug product."[43]

Leachables: "Foreign organic and inorganic chemical entities that are present in a packaged drug product because they have leached into the packaged drug product from a packaging/delivery system, packaging component, or packaging material of construction under

[40] ICH guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

[41] ICH Q3B(R2).

[42] USP General Chapter <1663>.

[43] ICH Q3B(R2).

normal conditions of storage and use or during accelerated drug product stability studies."[44]

Preservative: A substance added to a drug product to protect it from the growth of microorganisms.

Semipermeable CCS: CCSs that permit the passage of solvent or foreign volatile materials through the CCS wall.

Specified degradation product: "A degradation product that is individually listed and limited with a specific acceptance criterion in the new drug product specification. A specified degradation product can either be identified or unidentified."[45]

Specified impurity: An impurity that is individually listed and limited with a specific acceptance criterion in the new drug substance specification. A specified impurity can be either identified or unidentified.

Unidentified degradation product: "A degradation product for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time)."[46]

Unidentified impurity: An impurity for which a structural characterization has not been achieved and is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Unspecified degradation product: "A degradation product that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug product specification."[47]

Unspecified impurity: An impurity that is limited by a general acceptance criterion but not listed with its own specific acceptance criterion in the new drug substance specification.

[44] USP General Chapter <1664>.

[45] ICH Q3B(R2).

[46] Ibid.

[47] Ibid.