

〈771〉 OPHTHALMIC PRODUCTS—QUALITY TESTS

INTRODUCTION

Ophthalmic products are sterile products that are intended for application to any ocular structure, including any space adjacent to an ocular structure and its immediate surrounding spaces.

The routes of administration of ophthalmic products fall into three general categories: topical, intraocular injections, and extraocular injections. Topical drug products are intended to be administered to an ocular surface component, such as the eyelid, conjunctiva, or cornea, and can produce local or systemic effects. Intraocular and extraocular injections are administered through external boundary tissue. The ophthalmic routes of administration include, but are not limited to: topical, subconjunctival, sub-Tenons, subretinal, subchoroidal, intracorneal, intrascleral, suprachoroidal, intravitreal, intracameral, juxtasceral, and retrobulbar routes (see Figure 1). Ophthalmic products are administered to the eye in a wide variety of dosage forms, including but not restricted to: solutions, suspensions, ointments, gels, emulsions, strips, injections, inserts, and implants.

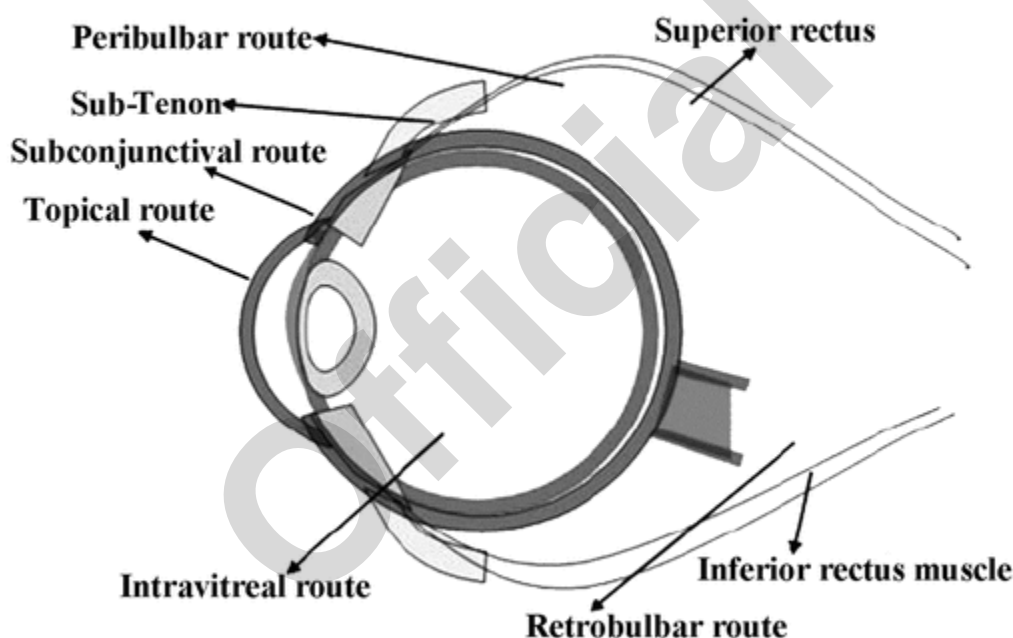


Figure 1. Some of the routes of administration in the eye.

This chapter provides lists of consolidated common product quality test requirements in a concise and coherent fashion. This chapter applies, in part or in its entirety, when referenced in a drug product monograph (see *General Notices, 3.10 Applicability of Standards*). The chapter includes the quality tests for the specific route of administration. The quality tests listed can be used, as appropriate, by manufacturers toward the development of new drug product monographs for submission to the *USP–NF*.

[NOTE—All references to chapters above 〈1000〉 are for information purposes only, for use as a helpful resource. These chapters are not mandatory unless explicitly called out for application.]

OPHTHALMIC DOSAGE FORMS

This chapter discusses the specific characteristics of dosage forms that are administered to any structure in the eye. See *Pharmaceutical Dosage Forms* (1151) for additional information pertaining to the description and manufacturing of pharmaceutical dosage forms.

Ophthalmic products have the same or similar requirements as injectables and implants. For more information on the requirements for these dosage forms, see *Injections and Implanted Drug Products* (1).

Depending on the formulation, container–closure system, and sterilization process, degradation and/or morphological changes can occur during the sterilization step of the manufacturing process and should be minimized. Temperatures required for autoclaving can cause irreversible damage to certain dosage forms such as suspensions, semisolids, emulsions, and others, whereas filtration is applicable only to formulations containing particulates with particle sizes $<0.2\ \mu\text{m}$. An alternative is to manufacture the product from sterile ingredients in an aseptic environment.

For multidose products, a suitable antimicrobial preservative is required, and its effectiveness over the shelf life of the product must be verified.

Solutions

[NOTE—Included in this section are those solid products that, when reconstituted according to the label instructions, result in a solution.] The corneal contact time of topical ophthalmic solutions increases with the viscosity of the formulations. Several synthetic polymers, including but not limited to polyvinylalcohol, polyvinylpyrrolidone, polyethylene glycol, polyacrylic acid, and many cellulose derivatives such as hypromellose and hydroxyethylcellulose, are commonly used as viscosity enhancers because of their physiologic compatibility and satisfactory physicochemical properties.

Another approach to increase the corneal contact time involves the use of polymers that provide the liquid formulation with semisolid consistency only when it is placed in the conjunctival or corneal area. In this way, easy instillation of the solution is followed by prolonged permanence as a result of the viscoelastic properties of the formed hydrogel. “Hydrogel”, or “water-based gels”, are three-dimensional networks of polymer chains containing water within the network. The network can be either physically or chemically cross-linked (a covalent bonding) structures between polymer chains. The water content of hydrogels can be adjusted by modulating the composition and conformation of polymers, such as the hydrophilic/hydrophobic balance of polymer chains and pendant groups, and the degree of cross-linking. The in situ gelling phenomenon is caused by a change in the conformation of the polymer(s) that can be triggered by external stimuli such as temperature, pH, ionic content, and lacrimal fluid, upon delivery to the eye. Additionally, some polymers can interact, via noncovalent bonds, with conjunctival mucin and maintain the formulation in contact with corneal tissues.

Solutions can be injected not only by the intravitreal route but also by other routes, such as subconjunctival, sub-Tenons, retrobulbar, suprachoroidal, and subretinal routes.

Suspensions

[NOTE—Included in this section are those solid products that, when reconstituted according to the label instructions, result in a suspension.] Use of aqueous or oily suspensions may be considered for a number of reasons such as the following: 1) for drugs that are poorly water soluble, 2) for drugs that have poor aqueous stability, and 3) in cases where there is a need to increase contact time with the eye and to increase wetting of the eye. The drug particle size is often reduced to levels $<10\ \mu\text{m}$ in an attempt to avoid excessive lacrimation.

After topical instillation, particles are expected to be retained in the cul-de-sac, and the drug slowly dissolves or is released from the polymeric structures by diffusion, dissolution, polymer degradation, or ion-exchange.

Suspensions can be injected not only by the intravitreal route but also through other routes, such as subconjunctival, sub-Tenons, retrobulbar, suprachoroidal, and subretinal.

Ointments

Eye ointments are semisolid products usually intended for application to the conjunctiva, cornea, or eyelid. They have longer contact time when compared to many solutions. A suitable ophthalmic ointment base is nonirritating to the eye and permits diffusion of the drug substance throughout the secretions bathing the eye.

The majority of water-free, oleaginous eye ointment bases are composed of white petrolatum and liquid petrolatum (mineral oil), or the eye ointment base is a modification of the petrolatum-based formula. They are designed to melt at body temperature. Other types of lipophilic ointment bases can also be used. An anhydrous vehicle can be advantageous for moisture-sensitive drugs.

Gels

Semisolid gel-type products are an alternative to traditional ointments and are based on the effect of increasing the viscosity to prolong the retention of the drug in the eye. Several types of gelling agents can be used, such as polyacrylic acid derivatives, carbomer, and hypromellose.

Emulsions

Topical ophthalmic emulsions are generally prepared by dissolving or dispersing the drug substance into an oil phase, adding suitable emulsifying and suspending agents, and mixing with water vigorously to form a uniform oil-in-water emulsion. Each phase is typically sterilized before or during charging into the mixing vessel. High-shear homogenation may be used to reduce oil droplet size to submicron size, which may improve the physical stability of the oil micelles so that they do not coalesce. The resulting dosage form should contain small oil droplets, uniformly suspended.

Limited aqueous solubility of the drug substance(s) is the most common rationale for developing an ophthalmic emulsion. The drug substance(s) can be added to the phase in which it is soluble at the beginning of the manufacturing process, or the drug substance can be added after the emulsion is prepared by a suitable dispersion process.

The physical stability of the emulsion can be measured by light-scattering techniques that characterize oil-phase, globule-size distribution. Suitable surfactants may be added to improve emulsion stability.

Strips

Ophthalmic strips can have different ophthalmic uses including, but not limited to, use as a diagnostic tool to visualize defects or aberrations in the corneal epithelium or to measure the amount of tear production. They are made of filter paper, and they can contain compounds such as fluorescein sodium. They are individually packed to preserve sterility until the moment of use.

Injections

Although injections are considered a dosage form for nomenclature purposes, they are not treated as a dosage form in this chapter. Instead, refer to the appropriate physical form, such as solution, suspension, or others, for general information.

Inserts

Ophthalmic inserts and ocular systems are solid dosage forms of appropriate size and shape that are placed in the conjunctival fornix, in the lacrimal punctum (*Figure 2*), or on the cornea. Inserts can usually be removed, if adverse effects develop, and provide extended release of the drug over a certain period of time. Inserts can be classified as erodible (soluble) or nonerodible (insoluble). Drug release from soluble inserts involves two steps: 1) fast release of a portion of the drug as the tear fluid penetrates into the system, and 2) slow release as a gel layer is formed on the surface of the insert. Collagen shields made from porcine sclera collagen or bovine corium tissue—and devices obtained by molding, extrusion, or compression (minitables) of gelling polymers—belong to this category of soluble inserts. Bioerodible polymers (e.g., cross-linked gelatin derivatives and polyesters) can be used to prepare erodible inserts; these matrices act as reservoirs or interact with the drug molecules through labile bonds.

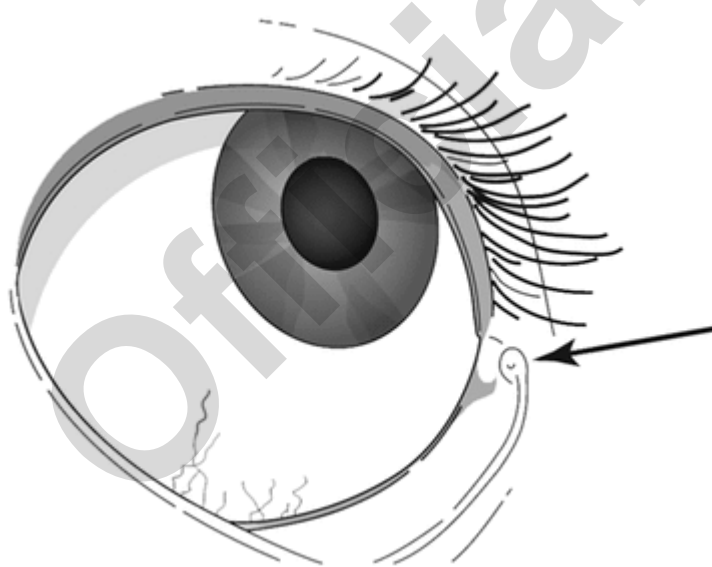


Figure 2. Lacrimal punctum.

Soluble inserts can have the drug incorporated into an erodible matrix, such as hydroxypropyl cellulose, hyaluronic acid, carbomer, or polyacrylic acid. Soluble inserts may be placed in the lower cul-de-sac and generally dissolve within 12–24 h. Eroderible polymeric products undergo gradual dissolution while releasing the drug, and the patient does not have to remove the erodible polymeric insert after use.

Insoluble inserts can have a reservoir or matrix structure. Their mechanism of action is based on diffusion of a fluid into the device, dissolving of the drug, and the creation of a saturated solution released to the medium by diffusion out of the insert. These insoluble inserts need to be removed after a certain period of time.

Implants

Implants are injected or implanted into the anterior segment (intracameral, subconjunctival, sub-Tenon, or other parts of the anterior segment) or intravitreal cavities, and the implants can be in different shapes, such as a disk or a thin rod. Implants can be made of nonbiodegradable or biodegradable polymers.

Among the types of nonbiodegradable solid (polymer) implants are reservoir-type implants anchored to the sclera, in which the drug is released across a nonbiodegradable, semipermeable polymer. The reservoir-type implants can be made of a variety of materials, including polyvinyl alcohol–ethylene vinyl acetate. Biodegradable polymers can be used to form injectable solid implants.

Drug–Device Combination Products

An ophthalmic drug–device combination product is constituted, in most cases, of two components. One is a pharmaceutical dosage form containing the drug substance(s), and the other is a device that will activate or facilitate the penetration of the drug substance(s) from the dosage form into a particular region of the eye. Some examples of the devices are those that generate waveforms (heat or light).

This chapter is applicable only to the pharmaceutical dosage form component of the ophthalmic drug–device combination product. The appropriate FDA regulations regarding medical devices should be used for the device component.

Change to read:

DRUG PRODUCT QUALITY

Procedures and acceptance criteria for testing ophthalmic products are divided into two categories: 1) those that assess general quality attributes, e.g., identification, potency, purity (and impurities), sterility, and particulate matter; and 2) those that assess in vitro product performance, i.e., dissolution or drug release of the drug substance from the drug product. Quality tests assess the integrity of the dosage form, whereas the performance tests assess drug release and other attributes that relate to in vivo drug performance. Taken together, quality and performance tests ensure the identity, strength, quality, purity, and efficacy of the drug product. This chapter addresses the quality tests for ophthalmic products. The performance tests (dissolution/drug release) are addressed by *Ophthalmic Products—Performance Tests* (1771).

Universal Tests

In this chapter, the division of the product quality tests into universal and specific tests does not strictly follow the ICH guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (available at www.ich.org). Universal tests in this chapter mean the tests that are applicable to all ophthalmic products, regardless of the dosage form type.

DESCRIPTION

A qualitative description of the drug product should be provided. The acceptance criteria should contain the final acceptable appearance, including clarity and color, of the dosage form and packaging. If the color changes during storage, a quantitative procedure may be appropriate. This is not a compendial test but is part of the manufacturer's specification of the drug product.

IDENTIFICATION

Identification tests are discussed in *General Notices, 5.40 Identification*. Identification tests should establish the identity of the drug or drugs present in the article and should discriminate between compounds of closely related structures that are likely to be present. Identity tests should be specific for the drug substance(s) [e.g., infrared (IR) spectroscopy]. If the test is nonspecific, at least two orthogonal nonspecific tests should be used. Near-infrared (NIR) or Raman spectrophotometric methods could be acceptable for the identification of the drug product. The most widely used identification procedures for drug substance(s) contained in pharmaceutical dosage forms are chromatographic procedures with comparison to the appropriate standards (see *Chromatography* (621) and *Thin-Layer Chromatographic Identification Test* (201)). Identification by use of a single chromatographic retention time does not constitute a specific test.

ASSAY

A specific and stability-indicating test should be used to determine the strength (content) of the drug product. In cases where the use of a nonspecific assay test is justified, other supporting analytical procedures should be used to achieve overall specificity. A specific procedure should be used when there is evidence of excipient interference with the nonspecific assay test. Additional information on specific assays may be found in *Antibiotics—Microbial Assays* (81), (621), and *Ion Chromatography* (1065).

IMPURITIES

Process impurities, synthetic byproducts, and other inorganic and organic impurities may be present in the drug substance and excipients used in the manufacture of the drug product. These impurities are controlled by the drug substance and excipient monographs. Organic impurities arising from the degradation of the drug substance in the drug product and those impurities arising during the manufacturing process of the drug product should be monitored. All articles meet the requirements in *Elemental Impurities—Limits* (232) and *Residual Solvents* (467).

pH

See *pH* (791). Normal tears have a pH of about 7.4. The eye can tolerate products over a range of pH values from about 3.0 to about 8.6, depending on the buffering capacity of the formulation. The pH value of the formulation should be the one where the drug product is the most stable. Formulations that target the extremes of the acceptable pH range will have better patient acceptability if the formulations have a low buffering capacity.

OSMOLARITY

See *Osmolality and Osmolarity* (785). Ophthalmic products may be tolerated over a fairly wide range of tonicity (0.5%–5% sodium chloride, equivalent to about 171–1711 mOsm/kg). Hypotonic solutions are better tolerated than hypertonic solutions. Precautions should be taken to ensure that the product maintains its osmolality during shelf life. Any possible contributions or interferences from the packaging system should be considered.

PARTICULATE AND FOREIGN MATTER

All ophthalmic products should be inspected for package integrity and, to the extent possible, for the presence of observable foreign and particulate matter (visible particulates). These unwanted particles arise from two sources: extrinsic (i.e., foreign matter); and intrinsic, or product-related matter. Extrinsic matter cannot be associated with the product or process. Intrinsic particles are added during assembly of the product or result from a change over time. A third category, inherent matter, describes a physical state or particles that are an expected attribute of the product.

One hundred percent inspection of injectable products in clear packages is required to remove final packages with visible particles. When 100% inspection of the injectable product in the final package is difficult, such as in opaque containers, alternative methods may be used to determine acceptability. *Visible Particulates in Injections* (790) provides further guidance for general inspection methods and a definition of “essentially free of visible particles” for batch compliance.

Two general categories apply for product administration to the tissues in the eye. Intraocular administration includes all ophthalmic products that cross (penetrate) boundary tissue, such as the cornea and sclera. Extraocular administration of ophthalmic products includes all other ocular components and spaces. For subvisible particle content, USP guidance is followed. Products for intraocular use must comply with *Particulate Matter in Ophthalmic Solutions* (789). Products for extraocular use must comply with *Particulate Matter in Injections* (788). Considerations for product evaluation and the background for both subvisible methods are found in ▲*Methods for the Determination of Subvisible Particulate Matter* (1788)▲ (CN 1-May-2021).

STERILITY

Ophthalmic dosage forms must meet the requirements of *Sterility Tests* (71). If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described in (71), along with aseptic manufacture, may be used. The immediate container for ophthalmic products shall be sterile at the time of filling and closing. See also *Universal Tests, Container–Closure Integrity*.

ANTIMICROBIAL PRESERVATIVES

Antimicrobial agents must be added to products that are packaged in containers that allow for the withdrawal or administration of multiple doses, unless one of the following conditions prevails: 1) there are different directions in the individual monograph; 2) the substance contains a radionuclide with a physical half-life of <24 h; and 3) the drug product, without additional agents, is sufficiently microbicidal to meet the requirements of *Antimicrobial Effectiveness Testing* (51). Substances must meet the requirements of (51) and *Antimicrobial Agents—Content* (341). Acceptance criteria for antimicrobial preservative content in multiple-unit products should be established.

BACTERIAL ENDOTOXINS

All injected ophthalmic drug products shall be prepared in a manner designed to minimize bacterial endotoxins as defined in *Bacterial Endotoxins Test* (85). The limits are NMT 0.5 EU/mL for ophthalmic irrigation products and NMT 2.0 EU/dose/eye for injected or implanted drug products. Typically, this test is not required for topically applied ophthalmic products. This chapter does not address the endotoxin limits for devices that are injected or implanted.

UNIFORMITY OF DOSAGE UNITS

This test is applicable to dosage forms packaged in single-unit containers. It includes both the mass of the dosage form and the content of the drug substance(s) in the dosage form. The test can be performed by either content uniformity or weight variation (see *Uniformity of Dosage Units* (905)).

CONTAINER CONTENTS

Container contents of ophthalmic products should be determined (see *Minimum Fill* (755)).

LEACHABLES AND EXTRACTABLES

The packaging system should not interact physically or chemically with the product in any manner to alter the strength, quality, or purity of the drug product. The packaging system should meet the requirements in *Elastomeric Components Used in Injectable Pharmaceutical Packaging/Delivery Systems* (381), *Containers—Glass* (660), *Plastic Materials of Construction* (661.1), and *Plastic Packaging Systems for Pharmaceutical Use* (661.2). Further information regarding packaging systems testing can be found in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* (1663) and *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* (1664). The assessment of possible leachables and/or extractables and the establishment of any acceptance criteria for these compounds should take into account the risk assessment of the product, its indication, and its packaging system. This assessment is done in a case-by-case approach during product development and re-evaluated when any changes are made to the product including, but not restricted to, changes in manufacturing process, formulation, and packaging material.

Furthermore, it should be noted that a risk assessment of extractable/leachable impact on topical or intraocular route of administration is a challenging undertaking. Toxicological or safety assessments of primary or secondary packaging component extractables and leachables are not typically available for ophthalmic routes of administration. A risk assessment may include evaluation of toxicology and safety from other routes of administration and an assessment of the Total Daily Intake of the extractable/leachable being evaluated. The preponderance of such assessments leads to an estimate of extractable/leachable risk via ocular delivery to the patient.

CONTAINER—CLOSURE INTEGRITY

The packaging system should be closed or sealed in such a manner as to prevent contamination or loss of contents and should provide evidence of being tamper proof. Validation of container integrity must demonstrate no penetration of microbial contamination or of chemical or physical impurities (see *Package Integrity Evaluation—Sterile Products* <1207>).

Specific Tests

VISCOSITY

An increase in viscosity increases the residence time in the eye. However, drug diffusion out of the formulation into the eye may be inhibited due to high product viscosity. Ophthalmic ointments are designed to be of very high viscosity to prolong the residence time in the eye. The inclusion of viscosity evaluation in the specification of the product should be based on the type of dosage form and whether changes in product viscosity will affect its performance. This is not a compendial test but is part of the manufacturer's specification of the drug product. See *Viscosity—Capillary Methods* <911>, *Viscosity—Rotational Methods* <912>, and *Viscosity—Rolling Ball Method* <913>.

ANTIOXIDANT CONTENT

If antioxidants are present in the drug product, tests of their content should be established, unless oxidative degradation can be detected by another test method such as impurity testing. Acceptance criteria for antioxidant content should be established. They should be based on the levels of antioxidant necessary to maintain the product's stability at all stages throughout its proposed usage and shelf life.

RESUSPENDABILITY/REDISPERSIBILITY

Consideration must be given to establishing good physical stability of a suspension. If the particles settle and eventually produce a cake at the bottom of the container, they must redisperse readily at the time of use to achieve dosage uniformity.

PARTICLE SIZE AND PARTICLE SIZE DISTRIBUTION

The potential for any changes in the particle size of ophthalmic suspensions and emulsions needs to be evaluated through stability testing (see *Light Diffraction Measurement of Particle Size* <429>).

DROP SIZE

For ophthalmic drug products dispensed as drops, drop sizes may typically range from 20 to 70 μL . Drop size can be controlled by weight or by volume, and it is typically evaluated during product development. Drop size can be determined by any appropriated validated procedure.

ADDED SUBSTANCES

Suitable substances may be added to ophthalmic products to increase stability, unless proscribed in the individual monograph, provided they are harmless in the amounts administered and do not interfere with therapeutic efficacy or with responses to the specified assays and tests. Typically, they should be evaluated during product development. The use of ingredients solely to impart a color, odor, or flavor is prohibited.