⟨4⟩ MUCOSAL DRUG PRODUCTS—PRODUCT QUALITY TESTS

INTRODUCTION

The mucosal route of drug administration is subdivided into seven membrane surfaces for the purposes of taxonomic distinction of dosage forms by route of administration. These membrane surfaces are characterized as otic, ophthalmic, nasal, oropharyngeal, urethral, vaginal, and rectal. This grouping does not include the pulmonary mucosal route addressed in *Inhalation and Nasal Drug Products—General Information and Product Quality Tests* ⟨5⟩. A drug product is administered to any of these seven mucosal surfaces to effect either local action or systemic absorption. Local action is to the area proximate to application. Where local action is intended, systemic absorption is not typically desired and is unnecessary for therapeutic effect. In some cases, however, the mucosal delivery of a drug for systemic absorption is used because it avoids first-pass metabolism, it provides more rapid systemic delivery, or it provides an alternative when oral delivery (to the gastrointestinal tract) is not possible due to a disease state. A large number of the dosage forms listed in *Pharmaceutical Dosage Forms* ⟨1151⟩ can be delivered by way of the various membrane surfaces in the mucosal category. [NOTE—All references to chapters above 1000 are for informational purposes only, for use as a helpful resource. These chapters are not mandatory unless explicitly called out for application.]

Analytical procedures and acceptance criteria for testing drug products are divided into two categories: those that assess general product quality attributes and those that assess product performance. Drug product quality tests assess attributes such as identification, assay (strength), dose content uniformity, and impurities and are usually part of the compendial monograph. Product performance tests include the dissolution test for a solid oral dosage form, *Dissolution* ⟨711⟩, and the drug release test, *Drug Release* ⟨724⟩. Taken together, quality and performance tests ensure the identity, strength, quality, and purity of a mucosal drug product.

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 quality tests listed can be used, as appropriate, by manufacturers toward the development of new drug product monographs for submission to the *USP*.

PRODUCT QUALITY TESTS FOR MUCOSAL DRUG PRODUCTS

This chapter provides product quality tests that are generally necessary, tests that apply to specific products, and tests that apply to one or more of the specific mucosal routes. Quality tests listed under a specific mucosal route in this chapter represent expectations for any dosage form administered by that specific route.

Generally Necessary Tests

Product quality attributes for mucosal dosage forms should reflect acceptable requirements for marketed products. The following tests should be generally applied to all dosage forms intended for mucosal delivery. Tests that are generally necessary for any article include: *Definition*, *Identification*, *Assay*, and *Impurities* (organic, inorganic, and residual solvents). *Uniformity of Dosage Units* ⟨905⟩ is typically included in a *USP* product monograph.

DEFINITION

The definition section (see *General Notices, 4.10 Monographs*) in a *USP* monograph describes the drug product and specifies the range of acceptable assayed content of the drug substance(s) present in the dosage form. For certain products, the definition includes any relevant additional information, such as the presence or absence of other components, excipients, or adjuvants, and cautionary statements on toxicity and stability. Appearance information is used in a regulatory submission to aid in product identification. Because the size, shape, color, and other attributes are attributes of individual marketed products, a qualitative description is typically not required as part of a *USP* monograph (see ⟨1151⟩).

IDENTIFICATION

Identification is included in a monograph as an aid in verifying the identity of the article (see *General Notices, 5.40 Identification*.)

ASSAY

The assay is used to determine the strength (content) of the drug product. Typically, the assay is specific and stability-indicating. When a nonspecific assay is justified, other supporting analytical procedures should ensure that any interfering species will be detected and can be limited. Assay results are often reported as a percentage of the label claim, with acceptance criteria that are typically in the range from 90.0% to 110.0%. For some antibiotic products, the range may be wider. The width of these limits is intended to allow for manufacturing variability, including changes in stability, as well as analytical variation. The narrower acceptance range of 95.0%–105.0% is used less often and with justification.

IMPURITIES

Process impurities include those arising from starting materials, synthetic byproducts, and other inorganic and organic impurities that may be present in the drug substance and in the excipients used in the manufacture of the drug product. These impurities are limited, as specified within the drug substance and excipient monographs. Impurities in the drug product may also result from degradation of the drug substance or excipients, from interactions between the drug substance and an excipient, or from interactions between the drug substance and the packaging components. The procedures and acceptance criteria should specifically limit toxic degradation products as well as degradation products that compromise the quality of the article if they exceed certain levels. A more complete discussion of impurities is provided in *Impurities in Drug Substances and Drug Products* ⟨1086⟩ [1] and in ICH Q3B Impurities in New Drug Products.[1]

UNIFORMITY OF DOSAGE UNITS

Chapter ⟨905⟩ is used to ensure the consistency of drug substance content in dosage units within a narrow range around the label claim. The test is applied only to dosage forms containing a single dose or a part of a dose of the drug substance in each unit. Uniformity of dosage units may be demonstrated by one of two methods: content uniformity or weight variation. Content uniformity is based on the assays of a number of individual dosage units. Weight variation can be used to estimate content uniformity under certain conditions.

Dosage Forms by Specific Mucosal Route and Product-Specific Tests

In addition to the generally necessary product quality tests already discussed, the dosage form may require specific quality tests that are common across routes of administration. *Injections and Implanted Drug Products* ⟨1⟩ provides testing requirements common to injectable and implantable products. *Oral Drug Products—Product Quality Tests* ⟨2⟩ provides testing requirements for tablets and lozenges. *Topical and Transdermal Drug Products—Product Quality Tests* ⟨3⟩ provides testing requirements common to semisolids (creams, ointments, and gels). Chapter ⟨5⟩ presents testing requirements for sprays and aerosols. Where a dosage form has no specific test given in this chapter, no additional test is required unless included in the individual monograph specification.

OTIC ROUTE

The otic route is characterized by administration of a preparation into, or by way of, the ear. Demonstration of sterility (see *Sterility Tests* ⟨71⟩) is not always required for products delivered to the ear. Typically, sterility is required where the product is administered to the inner ear or where the eardrum is damaged. Where sterility is not required, the quantitative enumeration of mesophilic bacteria and fungi that grow under anaerobic conditions, *Microbial Enumeration Tests* ⟨61⟩, or the determination of the absence or limited occurrence of specified organisms, *Tests for Specified Microorganisms* ⟨62⟩, may be required.

If an antimicrobial preservative is used, *Antimicrobial Effectiveness Testing* ⟨51⟩ and *Antimicrobial Agents—Content* ⟨341⟩ may be required.

Dosage forms given by the otic route include liquids, solutions, and suspensions.

OPHTHALMIC ROUTE

The ophthalmic route is to the eye. In addition to the generally necessary tests, the following specific tests for ophthalmic drug products should be considered (see *Table 1*). For products that are injected or implanted into the eye, see ⟨1⟩. Some of the important product quality tests for products administered by the ophthalmic route are listed below. See *Ophthalmic Products—Quality Tests* ⟨771⟩ for details and other product quality information.

- Particulate and Foreign Matter
- Sterility
- Particle Size and Particle Size Distribution
- Antimicrobial Preservative

Table 1. Drug Products Administered by the Ophthalmic Route, with Product-Specific Tests

Ophthalmic Route	
Dosage Form	**Product-Specific Tests**
Gels	*Minimum Fill* ⟨755⟩
	⟨3⟩

[1] ICH Q3B (R2) Impurities in New Drug Products, 2006, http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html. Accessed 28 May 2015.

Table 1. Drug Products Administered by the Ophthalmic Route, with Product-Specific Tests *(continued)*

Ophthalmic Route	
Dosage Form	**Product-Specific Tests**
Emulsions	*Osmolality and Osmolarity* ⟨785⟩ *pH* ⟨791⟩ Surface tension *Viscosity—Capillary Methods* ⟨911⟩ *Viscosity—Rotational Methods* ⟨912⟩ Zeta potential
Inserts	*Bacterial Endotoxins Test* ⟨85⟩
Ointments	⟨755⟩ ⟨3⟩
Solutions	*Particulate Matter in Ophthalmic Solutions* ⟨789⟩ ⟨791⟩ ⟨911⟩ ⟨912⟩ *Viscosity—Rolling Ball Method* ⟨913⟩ ⟨785⟩
Strips	Currently no specific tests (additional specific monograph requirements may apply)
Suspensions	⟨791⟩ ⟨785⟩ Particle size and particle size distribution ⟨911⟩ ⟨912⟩ ⟨913⟩

NASAL ROUTE

The nasal route is administration to the nose, or by way of the nose, for local or systemic effect (see *Table 2*).

Table 2. Drug Products Administered by the Nasal Route, with Product-Specific Tests

Nasal Route	
Dosage Form	**Product-Specific Tests**
Aerosols	⟨5⟩
Gels (Jelly)	⟨755⟩ ⟨3⟩
Ointments	⟨755⟩ ⟨3⟩
Sprays	⟨5⟩
Solutions	⟨5⟩

OROPHARYNGEAL ROUTE

The oropharyngeal route is into the oral cavity and/or pharyngeal region. The oropharyngeal route is subclassified by the specific intra-oral surfaces, such as buccal or sublingual. Buccal and sublingual administrations are typically intended to promote systemic absorption by permeation through the respective mucosa. However, in this context, oral administration may mean topical application for local action (see *Table 3*). Product quality tests for products administered to oropharyngeal surfaces often conform to those for oral administration to the gastrointestinal tract (see ⟨2⟩).

Table 3. Drug Products Administered by the Oropharyngeal Route, with Product-Specific Tests

Oropharyngeal Route	
Dosage Form	**Product-Specific Tests**
Buccal patches	See ⟨3⟩ for testing requirements common to patches.
Films	Currently no specific tests (additional specific monograph requirements may apply)
Gels	⟨755⟩
	⟨3⟩
Gums	Currently no specific tests (additional specific monograph requirements may apply)
Lozenges	Currently no specific tests (additional specific monograph requirements may apply)
Ointments	⟨3⟩
	⟨755⟩
Solutions (Rinses)	Currently no specific tests (additional specific monograph requirements may apply)
Sprays	⟨5⟩
Tablets	⟨2⟩

URETHRAL ROUTE

The urethral route is into the urethra, typically for local action, but systemic distribution is also possible. Chapters ⟨61⟩ and ⟨62⟩ may apply. Drug products in this category include urethral inserts.

VAGINAL ROUTE

The vaginal route is into the vagina, typically for local action, but systemic distribution is also possible. Chapters ⟨61⟩ and ⟨62⟩ may apply (see *Table 4*).

Relative foam density: Determine relative foam density by weighing a mass of foam (*m*) and a mass of the same volume of water (*e*) in a flat-bottom dish. Relative foam density = *m*/*e*.

Volume of foam expansion: Estimate the volume of foam expansion at 25° using a graduated buret and a foam-generating container equipped with a dose-actuating device and fitted to the buret.

Table 4. Drug Products Administered by the Vaginal Route, with Product-Specific Tests

Vaginal Route	
Dosage Form	**Product-Specific Tests**
Creams	⟨755⟩
	⟨3⟩
Foams	⟨755⟩
	Physical appearance (of the foam and of the collapsed foam) *Relative foam density* *Volume of foam expansion*
Gels	⟨755⟩
	⟨3⟩
Inserts	Currently no specific tests (additional specific monograph requirements may apply)

RECTAL ROUTE

The rectal route is into the rectum. Rectally administered products may produce local effect(s) or delivery to the systemic circulation.

Softening time of lipophilic suppositories: The test is intended to determine, under defined conditions, the time that elapses until a suppository maintained in water at 37 ± 0.5° softens to the extent that it no longer offers resistance when a defined weight is applied (see *Table 5*).

Table 5. Drug Products Administered by the Rectal Route, with Product-Specific Tests

Rectal Route	
Dosage Form	**Product-Specific Tests**
Foams	⟨755⟩
	Physical appearance (of the foam and of the collapsed foam)
	Relative foam density
	Volume of foam expansion
Ointments	⟨755⟩
	⟨3⟩
Suppositories	Softening time of lipophilic suppositories
Solutions	Currently no specific tests (additional specific monograph requirements may apply)
Suspensions	Currently no specific tests (additional specific monograph requirements may apply)