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⟨4⟩ MUCOSAL DRUG PRODUCTS—PRODUCT QUALITY TESTS

Change to read:

INTRODUCTION

The mucosal route of drug administration is subdivided into ▲eight▲ (USP 1-May-2024) membrane surfaces for the purposes of taxonomic distinction of dosage forms by route of administration. These membrane surfaces are characterized as ▲nasal, ophthalmic, otic, oropharyngeal, pulmonary, rectal, urethral, and vaginal.▲ (USP 1-May-2024) A drug product ▲may be▲ (USP 1-May-2024) administered to any of these ▲eight▲ (USP 1-May-2024) 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. ▲Many▲ (USP 1-May-2024) 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 ▲(see *Mucosal Drug Products—Performance Tests* ⟨1004⟩)▲ (USP 1-May-2024) 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.

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▲SCOPE▲ (USP 1-MAY-2024)

This chapter provides lists ▲and references of▲ (USP 1-May-2024) common product quality test requirements ▲for mucosal drug products▲ (USP 1-May-2024) 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*.

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PRODUCT QUALITY TESTS FOR MUCOSAL DRUG PRODUCTS

This chapter provides product quality tests that are ▲universal▲ (USP 1-May-2024) , 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.

▲Universal▲ (USP 1-May-2024) Tests

Product quality attributes for mucosal dosage forms should reflect acceptable requirements for marketed products. The following ▲universal▲ (USP 1-May-2024) tests should be generally applied to all dosage forms intended for mucosal delivery▲ (USP 1-May-2024) : *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 ▲(see *General Notices, 5.50 Assay*).▲ (USP 1-May-2024)

IMPURITIES

Process impurities ▲▲ (USP 1-May-2024) may be present in the drug substance. ▲▲ (USP 1-May-2024) 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. ▲See *General Notices, 5.60 Impurities and Foreign Substances*,▲ (USP 1-May-2024) *Impurities in Drug Substances and Drug Products* ⟨1086⟩▲, *Elemental Impurities—Limits* ⟨232⟩, *Nitrosamine Impurities* ⟨1469⟩,▲ (USP 1-May-2024) 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. ▲▲ (USP 1-May-2024)

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). *Inhalation and Nasal Drug Products—General Information and Product Quality Tests* ⟨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.

▲Microbiological examination of nonsterile drug products is performed according to the methods given in *Tests for Burkholderia Cepacia Complex* ⟨60⟩ (as appropriate for aqueous formulations), *Microbial Enumeration Tests* ⟨61⟩, and *Tests for Specified Microorganisms* ⟨62⟩, unless the formulation itself is demonstrated to have antimicrobial properties. Recommended acceptance criteria for nonsterile pharmaceutical products based on total aerobic microbial count and total combined yeasts and molds count are given in *Microbiological Acceptance Criteria for Nonsterile Pharmaceutical Preparations and Substances for Pharmaceutical Use* ⟨1111⟩. If acceptance criteria for antimicrobial preservative content in multiple-unit products should be established see *Antimicrobial Effectiveness Testing* ⟨51⟩ and *Antimicrobial Agents—Content* ⟨341⟩.

NASAL ROUTE AND PULMONARY MUCOSAL ROUTE

The nasal route is administration to the nose, or by way of the nose, for local or systemic effects. See *Table 1* for specific tests required for nasal gel and nasal ointment. For other nasal dosage forms and pulmonary route administration dosage forms, see ⟨5⟩.

OPHTHALMIC ROUTE

See *Ophthalmic Products—Quality Tests* ⟨771⟩.

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. Product quality tests for products administered to oropharyngeal surfaces often conform to those for oral administration to the gastrointestinal tract (see ⟨2⟩).▲ (USP 1-May-2024)

OTIC ROUTE

The otic route is characterized by administration of a preparation into, or by way of, the ear. ▲Otic products may be nonaqueous, with no measurable pH, or aqueous. The normal pH of the ear is slightly acidic with a pH of about 5–6, but otic products may have pH values of about 2.9–7.8.▲ (USP 1-May-2024) 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, ⟨61⟩, ▲and▲ (USP 1-May-2024) the determination of the absence or limited occurrence of specified organisms, ⟨62⟩, ▲is▲ (USP 1-May-2024) required.

If an antimicrobial preservative is used, ⟨51⟩ and ⟨341⟩ may be required.

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

▲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.▲ (USP 1-May-2024)

URETHRAL ROUTE

The urethral route is into the urethra, typically for local action, but systemic distribution is also possible. ▲The pH of the urethra is controlled by the pH of the urine. The pH of urine is normally in the range of 5.5–7 with an average of 6.2.▲ (USP 1-May-2024) Chapters ⟨61⟩ and ⟨62⟩ may apply. ▲The most common bacterial cause of urinary tract infections is *Escherichia coli* and so urethral and intravesical products should be free of *E. coli* contamination.▲ (USP 1-May-2024) 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. ▲The pH of the healthy vagina is in the range of 3.8–4.5.▲ (USP 1-May-2024) Chapters ⟨61⟩ and ⟨62⟩ may apply.

▲*Table 1* summarizes the drug product dosage forms and product quality tests for mucosal route administration.

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

Dosage Form	Administration Route	Product-Specific Tests
Creams	Vaginal	*Minimum Fill* ⟨755⟩
Films	Oropharyngeal	Currently no specific tests (additional specific monograph requirements may apply)
Foams	Rectal; vaginal	*Pharmaceutical Foams—Product Quality Tests* ⟨607⟩
Gels	Nasal; oropharyngeal; vaginal	⟨755⟩
Gums	Oropharyngeal	Currently no specific tests (additional specific monograph requirements may apply)
Inserts	Urethral; vaginal	Currently no specific tests (additional specific monograph requirements may apply)
Lozenges	Oropharyngeal	Currently no specific tests (additional specific monograph requirements may apply)
Ointments	Nasal; oropharyngeal; rectal	⟨755⟩
Solutions	Oropharyngeal; otic; rectal	Currently no specific tests (additional specific monograph requirements may apply)
Sprays	Oropharyngeal	⟨5⟩
Suppositories	Rectal	Softening time of lipophilic suppositories[a] (additional specific monograph requirements may apply)

Dosage Form	Administration Route	Product-Specific Tests
Suspensions	Otic; rectal	Currently no specific tests (additional specific monograph requirements may apply)
Tablets	Oropharyngeal	⟨2⟩

[a] Currently there is no test procedure available in *USP–NF*.

[NOTE—For dosage forms other than gel and ointment in nasal route and pulmonary mucosal route products, see ⟨5⟩; for ophthalmic products, see ⟨771⟩.]▲ (USP 1-MAY-2024)

REFERENCES

1. International Council for Harmonisation. ICH Q3B (R2) Impurities in new drug products. 2006. *https://database.ich.org/sites/default/files/Q3B%28R2%29%20Guideline.pdf*. Accessed 8 April 2022.

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Topic/Question	Contact	Expert Committee
<4> MUCOSAL DRUG PRODUCTS-PRODUCT QUALITY TESTS	Ravikiran Kaja Senior Principal Scientist	GCDF2020 General Chapters - Dosage Forms 2020

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