Water Activity
USP <795> Changes

Beyond-use dating in the USP <795> guidelines set to go into effect November 2023 have made big changes to the recommended maximum beyond-use dates for different types of formulations.

One of the biggest changes is a new focus on microbial growth and preservative efficacy. The guidelines specify aqueous preparations as those having a water activity (a_w) equal to or greater than 0.6, and only preparations with an a_w less than 0.6 are considered nonaqueous or solid dosage forms.[1]

What is Water Activity?

Water activity is a measurement for the ratio of vapor pressure of the substance in question when at equilibrium with the surrounding air to the vapor pressure of distilled water under identical conditions.[2] For example, a water activity of 0.6 means that the vapor pressure of the substance in question is 60% of that of pure water. Water activity should not be mistaken for water content. Water content is a measure of how much water is in a particular substance by weight or volume, whereas water activity is a measure of water that is available for reaction or accessible to microbes. Even items with relatively low water content can still have relatively high a_w.

Why Does Water Activity Matter?

Water activity is a fairly reliable measure of a microbe's ability to grow in a particular substance. Generally, bacteria can grow at a_w greater than 0.85, and fungi such as yeasts and molds at a_w greater than 0.6.[3,4] Newly published USP <795> guidelines consider anything with an a_w less than 0.6 to be nonaqueous, and therefore can be given longer recommended maximum beyond-use dates without necessarily having a preservative.' Water activity is also a useful reference parameter when considering how much water is available in a substance to act in chemical reactions, potentially resulting in degradation of active ingredients in that substance.[5]

What Does This Mean for My Practice?

This new focus on a_w not only means a change in beyond-use dating guidelines, but also a new focus on preservatives and how to select one for a particular compounded preparation. The guideline clarifies in section 10.3 that these new guidelines do not require compounders to measure a_w for particular compounds, and that these markers are intended to be used as a guide.[6] The guideline contains a helpful table (table 3) of expected a_w for a variety of compounded preparations and refers to General Chapter <1112> (Application of Water Activity Determination to Nonsterile Pharmaceutical Products) which also provides a list of approximated a_w for various products.[6,7] If a_w is not tested for a water containing preparation such as a cream or suspension, the a_w should be assumed to be ≥0.6 and, in the absence of an appropriate study, the beyond-use date should be consistent with the maximum beyond-use date listed in table 4 of new USP 795 guidelines.[1] In the absence of explicit data on a particular compound, General Chapter <1112> provides a good resources for justifying an assigned beyond-use date.

Anhydrous Base Options (Aw <0.6)

TOPICAL PREPARATIONS

	VEHICLE BENEFITS
Jelene® Topical base	• Plasticized ointment base containing polyethylene and mineral oil • Can be applied topically or mucosally and is commonly used in dental gel preparations • Water repellant, so preparations applied mucosally are resistant to removal by saliva, allowing time for drug delivery to a specific area • Compatible with a wide range of APIs
Nourisil™ Anhydrous Silicone Base	• Anhydrous silicone base with a silky skin feel • Contains vitamin E and silicone to confer improved hydration • Frequently used topically for wound and scar type preparations or added in concentrations of ~10% to other creams to improve feel and silkiness Compatible with a variety of APIs • Compatible with a variety of APIs
Occluvan™ Hydrophilic Ointment Base	• Anhydrous hydrophilic ointment base with vitamin E and natural oils for hydration • Often used topically but safe for rectal use as well • Compatible with a wide range of APIs and solvents
TrichoOil™ Oil base	• Anhydrous oil base that exists as part of the Tricho hair care line • Natural oils including avocado oil and vitamin E confer hydration benefits and a smooth feel • Intended for use as part of the Tricho hair care line

TRANSDERMAL PREPARATIONS

	VEHICLE BENEFITS
Lipopen Anhydrous Anhydrous penetrating vehicle	• Nonaqueous penetrating vehicle • Contains penetration enhancers found in PLOs such as isopropyl myristate, isopropyl palmitate, and lecithins • Designed to feel more like a cream than ointment • Works well with a wide variety of solvents and APIs
Versatile Anhydrous Anhydrous penetrating vehicle	• Anhydrous, multipurpose base for topical compounding • Viscosity adjustable by adding solvents • Slightly occlusive skin-feel with rapid absorption • Built-in antioxidants protect oxidation prone APIs • Solvent selection can enhance skin feel and reduce tackiness

MUCOSAL PREPARATIONS

	VEHICLE BENEFITS
Troche Base SF with Bitter-Bloc Troche & lozenge base	• Intended for use in troche sublingual or buccal preparations • Sweetened with stevia and contains bitter-bloc to improve palatability • Compatible with water miscible flavors • Compatible with a wide range of APIs

ORAL PREPERATIONS

	VEHICLE BENEFITS
Unispend™ Anhydrous Oral suspending vehicle	• Oral anhydrous suspension base composed mainly of plant based, medium chain triglycerides Sweetened with stevia and fortified with a natural bitterness masker for optimal palatability Acceptable for oral use in human and veterinary patients • Compatible with oil miscible flavors and some water miscible flavors • Can be used as is (i.e. no need to add additional silica or other thickeners as you would when making your own fixed oil base) • Available in sweetened and unsweetened version
Gelatin Troche Base Gelatin Troche Vehicle	• A ready-made gelatin base that may be used for the formulation of gummies, gelatin troches, or as a basis for animal treats • Contains water, but the water activity is below 0.6, which qualifies this vehicle for anhydrous beyond use dating per USP <795> guidelines to be official November 2023

RECTAL AND VAGINAL PREPARATIONS

	VEHICLE BENEFITS
Cocoa Butter Anhydrous suppository base	• Anhydrous suppository base • Melts at low temperatures for quick rectal and vaginal dissolution (~31-35C) • Can also be used in some lip balm formulations
Fattyblend Anhydrous suppository base	• Anhydrous mix of palm kernel oil and coconut oil triglycerides • Melts at low temperatures for quick rectal and vaginal dissolution (~35C) • Can also be used in some lip balm formulations or as an ingredient in troches or anhydrous animal treats
PEGblend Anhydrous suppository base	• Anhydrous suppository base, mix of polyethylene glycols of various weights • Higher melting temperature confers higher room temperature stability than other fatty based sup- pository options • Can be used rectally or vaginally, also used in some lip balm preparations
Supposiblend Anhydrous suppository base	• Anhydrous suppository base composed of palm kernel oil triglycerides • Melts at low temperatures for quick rectal and vaginal dissolution (-35C) • Can also be used in some lip balm formulations
Supposibase F Anhydrous suppository base	• Anhydrous suppository base composed of palm kernel oil triglycerides • Melts at low temperatures for quick rectal and vaginal dissolution (-35C) • Can also be used in some lip balm formulations
Witepsol Anhydrous suppository base	• Anhydrous hard fat suppository base • Melts at low temperatures for quick rectal and vaginal dissolution (~35-37C)

Resources:

1. United States Pharmacopeia and National Formulary (USP 41-NF 36). Rockville, MD: United States Pharmacopeial Convention; 2019. https://online.uspnf.com/uspnf/document/GUID-98DCB48D-DC23-4A63-AD2E-01CA8979FB7E_3_en-US. Accessed August 13th, 2019.
2. Food and Drug Administration. 2014 Aug 27th. Water Activity (aw) in Foods. https://www.fda.gov/inspections-compliance-enforce- ment-and-criminal-investigations/inspection- technical-guides/water-activity-aw-foods. Accessed 7/30/2019
3. Sperber W. Influence of water activity on foodborne bacteria - a review. Journal of Food Production.1983; 46(2): 142-150.
4. Beuchat L. Influence of water activity on growth, metabolic activities and survival of yeasts and molds. Journal of Food Production. 1983; 46(2): 135-141.
5. Maltini E, Venir E. Relevance of physical properties in the stability of plant-based food products. Indian Journal of Experimental Biology. 2013; 51:895-904.
6. United States Pharmacopeia. 2019 May 31st. FAQs: <795> Pharmaceutical Compounding - Nonsterile Preparations. https://www.usp. org/frequently-asked-questions/compounding. Accessed 8/13/2019.
7. United States Pharmacopeia and National Formulary (USP 1112) GCM2015 General Chapters- Microbiology; 2015. https://online.uspnf.com/uspnf/document/GUID-088FEEB1-8BD8-4120-AC2A-106AAE5E8E4E_1_en-US. Accessed 8/13/2019.