

Allergen Extract Temperature Excursions

ALK TECHNICAL MEMO
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ALK Medical Scientific Affairs

ALK entered the U.S. allergenic extract market in 1985 after more than 50 years of successful business in Europe. Since that time, ALK has grown to be one of the top U.S. extract suppliers, providing consistent, quality products to numerous markets offering allergy testing and treatment. The potency of allergen extracts is critical for diagnostic and therapeutic management of allergic disease. Occasionally allergen extracts can undergo excursions from the recommended storage temperatures of 2-8°C (or 34-48°F) as specified in their respective package inserts. ALK is dedicated to providing scientific technical support and assistance with unexpected temperature excursions effecting allergen extracts. There are several important considerations when evaluating the condition of allergy extract vials exposed to temperatures outside the recommended storage (e.g. mailing and shipping, power outages, appliance failures, and left at room temperature for extended periods). Among these factors include the concentration of the extract, the diluent used in the patient vial formulation, and whether extracts are freeze dried. This technical memo is intended to serve as a guidance document to assist practices with temperature excursions for North American ALK extracts. Medical Scientific Affairs is available to personally assist your practice, and answer specific questions related to allergen extract temperature excursions.

Technical Considerations

Temperature excursions outside the recommended storage conditions can prompt questions related to the safety and efficacy of the allergen extracts and effects on expiration dating. The labeled temperature storage range specified for extracts manufactured in the US is 2-8°C. This range has been determined to be optimal for the storage of allergenic extracts and was originally mandated by the FDA in the 1970s. Limited studies have been conducted to establish the potency of different standardized and non-standardized allergen extracts outside the recommended storage of 2-8°C. Since allergen extracts are biological solutions containing protein as active ingredients, elevated temperatures can cause denaturation of the protein binding structure. Allergen extracts exposed to temperatures at 40-48°C (104-118°F) for a few days have been shown to cause instability in some protein^{1,2}. Additionally, extracts and patient vials exposed to freezing temperatures have also demonstrated detrimental effects (decreased potency) in some allergenic extracts^{1,2}.

Standardized products sold in the US have verified expiration dating determined by manufacturer-driven formal potency studies and approved by the FDA (for ALK under US License 1256). These potency studies include elevated temperatures to justify shipping at ambient temperatures. According to these internal studies, ambient temperature excursions of up to a week have no detrimental effect on the potency of standardized products formulated in 50% glycerin. Extrapolation of this potency data to non-standardized allergenic extracts is reasonable for those formulated in 50% glycerin. However, non-standardized aqueous extracts are less stable than glycerinated products, and more susceptible to detrimental effects of temperature excursions. It is also important to recognize that aqueous allergenic extracts are more susceptible to freezing due to malfunctioning refrigerators. ALK recommends that all frozen extracts and patient vials be discarded.

The potency of all allergy extracts decreases with time and is due to additional factors beyond temperature, such as the diluent used and dilution strength of patient vials. Expiration dating for diluted patient vials

is up to the physician and depends on the concentration and diluent utilized. Manufacturers do not have diluted patient vial potency recommendations specified in package inserts with the exception of venom treatment vials. In general more dilute patient vials have shorter expiration dating, due to lower protein concentrations, but the effect on temperature excursions for diluted vials above 2-8°C is not well studied. A review of studies indicate that 1:100 w/v patient vials remain stable for 6 days at room temperature, or 2-3 days at 40°C (104°F) for several allergenic extracts. Additionally these studies showed that patient vials diluted in Human Serum Albumin are more stable than patient vials diluted with Normal Saline with Phenol, 10% glycerin and 50% glycerin^{2,3}.

In summary, short temperature excursions of allergy extract concentrates and diluted patient vials above 2-8°C are common during allergy diagnosis and immunotherapy treatment. The decision to administer or discard allergy extracts and patient vials exposed to temperature excursions outside of the recommended storage is at the discretion of the prescribing physician. The information contained in this technical memo is provided to support these decisions in the office.

ALK Commitment

ALK is committed to helping physicians maintain uniformity of care with immunotherapy for their patients. Please do not hesitate to contact your Allergy Consultant, Customer Service (800-325-7354), or Medical Scientific Affairs (855-782-9323, science@alk.net, or submit your scientific questions to our 24/7 online helpdesk in a support ticket at: <https://alkinc.freshdesk.com>) should you have additional questions or concerns regarding ALK allergy extract temperature excursions.

This technical memo is not intended to replace physician judgment with respect to the clinical diagnosis and treatment of patients. All decisions regarding potential patient care are solely at the discretion of the treating physician.

References

1. Plunkett, G. Update: Stability of allergen extracts to establish expiration dates. *Curr Opin Otolaryngol Head Neck Surg.* 2016;24(3):261-269.
2. Plunkett, G. Stability of allergen extracts. *Curr Opin Otolaryngol Head Neck Surg.* 2008;16(3):285-291.
3. Nida, A, Leatherman B, Plunkett G, Mire B. Allergen stability of testing/treatment boards and immunotherapy vials with various diluents. *Int Forum Allergy Rhinol.* 2015;5(11):1028-1035.



Glycerin—Manufacturer's Concentrate*				
<24 hours	24-48 hrs	48-96 hrs	4-7 days	1-2 weeks
35 - 46°F 2-8°C				
46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C
77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C
90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C
over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C
Frozen	Frozen	Frozen	Frozen	Frozen

Aqueous—Manufacturer's Concentrate*				
<24 hours	24-48 hrs	48-96 hrs	4-7 days	1-2 weeks
35 - 46°F 2-8°C				
46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C
77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C
90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C
over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C
Frozen	Frozen	Frozen	Frozen	Frozen

Legend
Recommended Storage per Package Insert
Okay to Use
Discard

*ALK Data on File.

Diluted Patient Vials— <i>Normal Saline with Phenol (NSP)*</i>				
<24 hours	24-48 hrs	48-96 hrs	4-7 days	1-2 weeks
35 - 46°F 2-8°C				
46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C
77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C
90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C
over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C
Frozen	Frozen	Frozen	Frozen	Frozen
Diluted Patient Vials— <i>Human Serum Albumin (HSA)*</i>				
<24 hours	24-48 hrs	48-96 hrs	4-7 days	1-2 weeks
35 - 46°F 2-8°C				
46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C	46 - 77°F 8 - 25°C
77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C	77 - 90°F 25 - 32°C
90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C	90 - 104°F 32 - 40°C
over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C	over 104°F over 40°C
Frozen	Frozen	Frozen	Frozen	Frozen

Legend
Recommended Storage per Package Insert
Okay to Use
Discard

*ALK Data on File.