Mold Conversion

ALK TECHNICAL MEMO
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ALK Medical Scientific Affairs

Molds are present throughout our environment and cause nonseasonal allergies in a significant proportion of the U.S. population. ALK is committed to helping physicians maintain a high standard and continuity of care for these patients. In keeping with this commitment, we are streamlining our manufacturing process to deliver a more readily available mold product line to our customers. This technical memo is intended as a guidance document to provide information about the changes made to the ALK mold line, as well as outline recommended extract substitutions and conversion considerations.

Mold Raw Material

Mold used for immunotherapy extract generation is grown in a laboratory using mold culturing techniques. Optimal growing conditions vary from species to species; however, common growth requirements include oxygen, water and a carbohydrate source[1]. Growing molds can be a complicated and involved process, with many factors influencing growth initiation and propagation. Furthermore, bacterial or fungal contamination can occur, rendering a mold culture unusable for manufacturing. Taking these concerns into account, ALK has transitioned from growing mold source material in our New York production facility to utilizing mold source materials grown at OKC Crystal Laboratory Inc., an ALK subsidiary. This sourcing change involves a transition from mold extract production using a combination of mold mat and media to utilization of a powdered, mold-only source material, which allows for longer storage, expanded production and shorter production turn-around times. Importantly, this powdered mold source material corresponds with other industry suppliers of mold allergy extracts, thereby reducing manufacturer differences among these products.

Nomenclature Harmonization

The FDA has requested that the nomenclature (i.e., common name, genus and species) of all extracts be harmonized across manufacturers. To comply with this request, U.S. extract manufacturers have collectively created an extract nomenclature list, which reflects all U.S. available species. This creates industrywide nomenclature standardization and species composition transparency. While the timeline for implementing this request is unknown, ALK is adopting the new mold nomenclature on all newly formulated mold extracts, so as to eliminate the need for additional future changes. Table 1 outlines the changes in mold nomenclature, which will be reflected on the labels of newly formulated mold and fungal extracts.

Mold Species Availability & Cross-reactivity

Table 1 outlines the mold extracts that will be available from ALK moving forward. Medical Scientific Affairs has made recommendations to simplify the ALK mold extract offerings, based on recent literature evaluating mold cross-reactivity[2,3]. These cross-reactivity considerations are outlined in the third column of Table 1. The cross-reactive mold extract substitute reflects what is being recommended for both testing and treatment. Cross-reactivity was considered for comprehensive mold mixes, as well. In an effort to simplify and reduce the number of individual components, new comprehensive mixes will be available. These mixes are outlined in Table 2. Several previous ALK mixes (i.e., Airborne Mold Mix 1, FAPP Mix, Midwest Molds) will not have commercially available substitutes, but instructions for preparation have been included in Table 3.

Table 1. Mold Extract Cross-Reactivity Recommendations

Previous Fungal Extract Nomenclature	Updated Fungal Extract Nomenclature	Cross-reactivity (May substitute for these)
Acremonium strictum	*Sarocladium strictum*	*Cephalosporium, Chaetomium, Nigrospora*
Alternaria alternata	*Same*	*Stemphylium*
Aspergillus fumigatus	*Same*	*Mixed Aspergillus, Aspergillus niger*
Aureobasidium pullalans	*Same*	
Drechslera sorokiniana	*Bipolaris sorokiniana*	*Helmithosporium, Bipolaris, Curvularia, Stemphylium*
Botrytis cinerea	*Same*	
Candida albicans	*Same*	
Cladosporium cladosporioides	*Same*	*Cladosporium sphaerospermum*
Epicoccum nigrum	*Same*	*Phoma*
Fusarium roseum	*Gibberella pulicaris*	
Mucor plumbeus	*Same*	*Rhizopus*
Penicillium notatum	*Same*	*Mixed Penicillium*
Rhodotorula rubra	*Rhodotorula mucilaginosa*	
Saccharomyces cerevisiae	*Same*	
Trichophyton mentagrophytes	*Same*	

Table 2. Available Fungal Mixes, Composition and Cross-Reactivity

Comprehensive Fungal Mix	Composition	Cross-Reactivity (May substitute for these)
Mold Mix A	Alternaria, Aspergillus, Cladosporium, Penicillium	Mixed Molds, Mold Mix 1, HASH Mix
Mold Mix B	Epicoccum, Gibberella, Mucor	Mold Mix 2
Mold Mix C	Botrytis, Candida, Rhodotorula, Trichophyton	

Table 3. Mixing Instructions for Comprehensive Mixes

Comprehensive Fungal Mix	Components Needed	Mix Composition (%)	Volume for 50 mL Vial (mL)
Airborne Mold Mix 1 Alternaria, Aspergillus, Aureobasidium, Bipolaris, Cladosporium, Gibberella, Mucor, Penicillium, Epicoccum	Mold Mix A	33	16.7
	Mold Mix B	33	16.7
	Mold Mix C	33	16.7
FAPP Mix	Gibberella pulicaris	25	12.5
	Aspergillus fumigatus	25	12.5
	Penicillium notatum	25	12.5
	Epicoccum nigrum	25	12.5
Midwest Molds	Sarocladium strictum	15	7.5
	Bipolaris sorokiniana	25	12.5
	Gibberella pulicaris	15	7.5
	Mucor plumbeus	30	15
	Epicoccum nigrum	15	7.5

A change in extract labeling will also be reflected on the new mold extract vials. Moving forward, ALK mold extracts will be labeled as 1:10 w/v (Aqueous) and 1:20 w/v (Glycerinated), instead of adjusted PNU concentrations. PNU dilutions will no longer be performed prior to product release. All aqueous, 1:10 w/v mold extracts will contain the actual PNU concentration on the label, while the PNU concentration of 1:20 w/v glycerinated ALK mold extracts can be provided by Customer Service (800.325.7354). A mold PNU dilution calculator will be provided upon request, to aid in the conversion process.

Please note: all newly formulated molds will have a gold vial cap, as opposed to the silver cap utilized on our current mold extracts.

Conversion Recommendations

As outlined, ALK will no longer be offering PNU dilutions for newly formulated mold extracts. Given this change, additional precautions can be employed when transitioning current immunotherapy patients. Medical Scientific Affairs has generated a PNU dilution calculator, which can be employed for mold extract dilution, should this step be desired for patient transition. This calculator can be provided upon request to aid in the conversion process.

Recommendations for transition can be safely made using standard of care practices detailed in the Allergy Practice Parameters, published by the the American Academy of Allergy, Asthma and Immunology (AAAAI)[4]. When converting allergen dosage from one extract lot to another, a 50-75% dose reduction is encouraged to reduce the potential for an adverse reaction; this reduction is applied to the previous injection volume (e.g., if 0.5 cc is being given as a maintenance injection, reduce dosage volume to 0.25 or 0.13 cc). If no reaction occurs, dosage can be increased, incrementally, back to the dose injected prior to conversion (e.g., 0.25, 0.35 or 0.5 cc). The incremental increase in dosage utilized should correspond to the build-up regimen you are currently employing. In extremely sensitive patients, a 90% dose reduction can be implemented as a precautionary measure.

ALK Commitment

ALK is committed to helping your practice make this transition as seamless as possible. 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 this mold extract reformulation.

References

1. Simon-Nobbe B, Denk U, Poll V, Rid R, Breitenbach M. The spectrum of fungal allergy. *Int Arch Allergy Immunol*. 2008;145(1):58-86.
2. Levetin E, Horner WE, Scott JA. Taxonomy of allergenic fungi. *J Allergy Clin Immunol Pract*. 2016;4(3):375-385.
3. Portnoy J, Jara D. Mold allergy revisited. *Ann Allergy Asthma Immunol*. 2015;114(2):83-89.
4. Cox L, Nelson H, Lockey R et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127(1 Suppl):S1-S55.