

Allergen Immunotherapy

FINAL ENVIRONMENTAL SCAN REPORT

September 2015

Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the Allergen Immunotherapy Drug Class Review.

Acknowledgments

The Ontario Drug Policy Research Network (ODPRN) is funded by grants from the Ontario Ministry of Health and Long-term Care (MOHLTC) Health System Research Fund. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources and supporting organizations.

A special thank you to all of the provincial and territorial representatives in Canada from the respective Ministries of Health as well as the representative from the Non-Insured Health Benefits for First Nations and Inuit (NIHB) who participated in the telephone survey.

Study Team

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Executive Summary

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

In Canada, allergen immunotherapy is available either for sublingual administration (SLIT) or for subcutaneous administration (SCIT). There are three commercialized products available for SLIT administration: Oralair, Ragwitek and Grastek. Most SCIT products are formulated specifically for the allergic patient (one exception is Pollinex R, which is available as a commercially formulated product). The compounding of patient-specific serums is done by commercial laboratories, pharmacies or in the physician's office. The cost of these compounded products is not standardized nor is it publically available.

In Ontario, Oralair and Ragwitek are listed as Limited Use products on the Ontario Drug Benefit formulary. Allergenic extracts for SCIT are available for ODB eligible patients under the special "Allergy Product" program. Across Canada, most public drug programs (with the exception of Yukon Territories) provide coverage for allergen immunotherapy, in particular the SCIT products. SLIT products are listed on five public drug plans. Only one jurisdiction (Nova Scotia) has developed clinical criteria for SCIT and SLIT products in Canada. In the US, most drug plans reviewed provide coverage for SCIT for patients with specific conditions. Australia and New Zealand provide coverage through the public plan programs only for subcutaneous venom immunotherapy.

Part B: Guidelines for the use of allergen immunotherapy

There have been several guidelines and consensus statement published by various organizations on allergen immunotherapy including the American Academy of Allergy, Asthma and Immunology (AAAAI), Canadian Society of Allergy and Clinical Immunology (CSACI), British Society for Allergy and Clinical Immunology and the German, Austrian and Swiss professional associations (S2K group). Recommendations for allergenic extract preparation, use of diluents, dosing and compatibility for allergy immunotherapy were reviewed.

Part C: Impact of different drug reimbursement schemes for allergen immunotherapy

There is a lack of literature investigating various reimbursement schemes for allergen immunotherapy.

Part D: Rapid review of selected topics

- *Venom immunotherapy*: Venom immunotherapy is an effective therapy for prevention of future allergic reactions to Hymenoptera stings, and also improves quality of life. However, venom immunotherapy is not without risk, and patients may develop local reactions or more rarely, systemic reactions.
- *Duration of therapy*: Although the optimal duration of immunotherapy is unknown, three to five years duration for SCIT has been recommended. Patients receiving venom immunotherapy may require life-long administration. For SLIT, three years of therapy (pre- and co-seasonal) is recommended.
- *Sublingual immunotherapy (drop formulation)*: In meta-analyses that have compared SLIT tablets and drops, SLIT tablets are more effective than drops in terms of symptom improvement. The use of multi-allergen SLIT administration has not been well studied and may not be as effective as single-allergen SLIT.
- *Immunotherapy for food allergies*: Use of subcutaneous allergen immunotherapy for food allergies is not recommended due to safety concerns. Although sublingual allergen

immunotherapy has been studied for some food allergies, the evidence for its efficacy and safety is still limited and cannot be recommended for routine use at this time.

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Introduction

Allergen immunotherapy involves the administration of gradually increasing doses of a specific allergen to a patient with a history of allergy; the goal of allergen immunotherapy is to reduce sensitivity and minimize future symptomatic reaction on natural exposure to the causative agent.¹ Traditionally, allergen immunotherapy has been administered subcutaneously (SCIT: subcutaneous immunotherapy), although more recently the sublingual route has also been used (SLIT: sublingual immunotherapy).

Allergen immunotherapy is used for a number of different conditions, although it is used most commonly for treatment of patients with allergic rhinitis. Other indications for allergen immunotherapy is for patients with allergic asthma and in patients with stinging insect (Hymenoptera) hypersensitivity.²

Allergic rhinitis, characterized by rhinorrhea, nasal obstruction, nasal itching and sneezing, is associated with decreased quality of life, work and educational performance.^{3,4} It is a global health problem, and affects approximately 10-20% of the Canadian population.⁵ Allergic rhinitis and asthma frequently co-exist.⁶ Longitudinal data indicate that children with allergic rhinitis have a two- to sevenfold increased risk of asthma later in life.⁷ As well, allergic rhinitis is associated with significantly worse asthma control in adults and children.⁸

The treatment goal for allergic rhinitis is relief of symptoms. Options include avoidance measures of triggers (e.g., dust mites, grass pollen), pharmacotherapy and allergen immunotherapy. Pharmacotherapeutic options include intranasal corticosteroids, oral antihistamines, and leukotriene receptor antagonists.³ Allergen immunotherapy is used in patients with allergic rhinitis who have poor relief with standard pharmacotherapy or in those who experience adverse effects. Allergen immunotherapy may have persistent benefits after immunotherapy is discontinued, may decrease the development of new sensitizations, and may reduce the development of asthma in patients with allergic rhinitis.⁹

The objectives of this report are:

- Part A: To summarize coverage of allergen immunotherapy through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- Part B: To summarize the guidelines allergen immunotherapy
- Part C: To review the evidence relating to the impact of different drug reimbursement schemes for allergen immunotherapy on patient access and/or utilization and costs
- Part D: To provide summary information on selected topics, as needed

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability of Allergen Immunotherapy in Canada

In Canada, allergen immunotherapy is available either for sublingual administration or for subcutaneous administration. There are three commercially available SLIT products in Canada: Oralair, Ragwitek and Grastek. Most SCIT products are generally formulated specifically for the allergic patient (one exception is Pollinex R, which is available as a commercially formulated product). The components of the serum extract are based on the results of skin testing, the patient's clinical symptoms and local and regional aerobiology and indoor and outdoor allergens.¹⁰ The compounding of patient-specific serums is done by commercial laboratories, pharmacies or in the physician's office. The cost of these compounded products is not standardized.

A list of commercial products licensed in Canada that are ready-to-use, either by the allergist or the patient, is found in Table 1. For a list of products that have associated drug identification numbers (DINs), see Appendix A. Many of these products are used in the compounding of patient-specific serums; once formulated for a specific patient, they have an associated product identification number (PIN). Standardized extract should be utilized whenever possible to prepare patient-specific serum since the efficacy and safety of immunotherapy are dependent on the quality of the allergen extracts used.¹⁰

Conventional SCIT treatment schedules involve a gradual increase in the allergen content of injections, usually involving one or two injections per week over a 3- to 6-month period.¹¹ Due to the risk of severe allergic reactions, SCIT must be administered in a clinical setting with full resuscitation facilities available. In contrast, SLIT has a large safety record and can be self-administered by the patient in a non-clinical setting, for example in their home. For the SLIT products, the administration needs to start 2-4 months prior to the pollen season, and continues throughout the pollen season. The grass pollen season in Ontario is typically June and July, and ragweed season is from August until October.

Summary

- Allergen immunotherapy is available either for sublingual or subcutaneous administration in Canada.
- Four products are available as ready-to-use formulations: Pollinex R, Oralair, Ragwitek and Grastek.
- Most subcutaneous products are formulated specifically for the allergic patient, based on the results of skin testing and clinical symptoms. The components of the patient-specific serum extract are available as Health Canada approved products with drug identification numbers (DINs).

Exhibit 1: Commercially available allergen immunotherapy in Canada

Brand name	Generic name	Manufacturer	Indication	Administration schedule	Cost (annual)	Date available in Canada
Pollinex R	Modified ragweed pollen allergen tyrosine adsorbate	Allergy Therapeutics (UK)	Pre-seasonal immunotherapy of ragweed allergic rhinitis in adults and children over the age of 8 years	SC as 4 weekly injections prior to ragweed season	\$387.72 [†]	December 1979
Oralair	Grass pollen allergen extract	Stallergenes Canada	Moderate to severe seasonal grass pollen allergic rhinitis in patients 5 to 50 years of age	SL daily starting 4 months prior to pollen season and maintained throughout pollen season	\$672.60*	July 2012
Grastek	Standardized allergen extract, Timothy grass	Merck Canada	Moderate to severe seasonal Timothy and related grass pollen induced allergic rhinitis in adults and children 5 years of age and older	SL daily starting 8 weeks before grass pollen season and maintain dosing throughout the season	\$481.10 ^{†*}	Jan 2014
Ragwitek	Standardized short ragweed pollen allergenic extract	Merck Canada	Moderate to severe seasonal short ragweed pollen-induced allergic rhinitis	SL daily starting 12 weeks prior to ragweed season and maintain dosing throughout the season	\$570.00*	April 2014

SC: subcutaneous

SL: sublingual

*Assuming 2 month of pollen season

[†]Price obtained from McKesson Wholesaler

Current as of July 20, 2015

Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. No review was completed for Ragwitek (see Exhibit 2).

Exhibit 2: Summary of Common Drug Review recommendations for sublingual allergen immunotherapy

Product	Recommendation	Reason for Recommendation
Grastek (Timothy grass standardized allergenic extract)(2014)	<i>Do not list</i>	CDEC considered the comparative clinical benefit of Grastek to be uncertain due to the variability of efficacy results across the included randomized controlled trials (RCTs) and the small magnitude of the absolute differences between Grastek and placebo.
Oralair (Grass pollen allergen extract) (2013)	<i>List with criteria/conditions</i>	<p><u>Clinical Criteria:</u></p> <ol style="list-style-type: none"> 1. Patients have not adequately responded to, or tolerated, conventional pharmacotherapy. 2. Treatment with Oralair should be initiated by an allergist. <p><i>Condition: Reduced Price: The cost of seasonal treatment for allergic rhinitis with Oralair should be no more than the cost of treatment with subcutaneous immunotherapy (SCIT).</i></p> <p><u>Reasons for the Recommendation:</u> Oralair was shown to be superior to placebo for the management of allergic rhinitis in four, double-blind, randomized controlled trials (RCTs). However, there was no evidence from RCTs to establish the comparative efficacy of Oralair relative to SCIT. At the submitted price, seasonal treatment with Oralair is more costly than SCIT for allergic rhinitis. Given the insufficient evidence to support the comparative efficacy of Oralair relative to SCIT, the Committee concluded that the cost of treatment with Oralair should not exceed that of SCIT.</p>

Product listing in Ontario

Sublingual allergen immunotherapy (SLIT)

Ragwitek and Oralair are listed as Limited use (LU) drugs on the Ontario Drug Benefit formulary. LU drugs have been deemed to have value in certain circumstances, although they may not be appropriate for general listing in the Formulary. Grastek is not listed on the ODB formulary, nor is it available through the Exceptional Access Program (EAP).

The Limited Use criteria are as follows:

Code 457 (Ragwitek):

For the seasonal treatment of short ragweed pollen induced allergic rhinitis in patients that have not adequately responded to, or tolerated, conventional pharmacotherapy.

Notes:

- Treatment with short ragweed pollen allergen extract must be initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases.
- Treatment should be initiated at least twelve (12) weeks before the onset of ragweed pollen season and should only be continued until the end of the season.

LU Authorization Period: 1 year.

Code 451 (Oralair):

For the seasonal treatment of grass pollen allergic rhinitis in patients that have not adequately responded to, or tolerated, conventional pharmacotherapy.

Notes:

- Treatment with grass pollen allergen extract must be initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases.
- Treatment should be initiated four (4) months before the onset of pollen season and should only be continued until the end of the season.
- Treatment should not be taken for more than three (3) consecutive years.

LU Authorization Period: 1 year.

Subcutaneous allergen immunotherapy (SCIT)

The program entitled “Ontario Drug Benefit Program: Allergy Products” covers the cost of allergen immunotherapy administered in a doctor’s office to treat severe allergy symptoms for patients who qualify for coverage under the ODB program (e.g., 65 years of age and older, living in a long-term care home or home for special care, registered in the Trillium Drug Program or receiving social assistance). A special form is completed by the prescriber or dispenser and authorization is granted once form has been approved (See Appendix B). There are no criteria (e.g., previous therapy, severity of disease) that need to be met prior to approval of SCIT for a patient.

Committee to Evaluate Drugs:

The Committee to Evaluate Drugs (CED) is the Ministry of Health and Long-term care’s independent expert advisory committee on drug-related issues. Oralair was reviewed and listed on the ODB formulary as a Limited Use product in March 2014. Ragwitek was listed on the ODB formulary as a Limited Use product in May 2015. Grastek was reviewed in

Summary

- In Ontario, SLIT (namely Ragwitek and Oralair) are listed as Limited Use products on the ODB formulary.
- SCIT is available for ODB eligible patients under the special “Allergy Product” program.

Public Plan Listings in Canada

Part 1: Listing Status

In order to determine the listing of allergen immunotherapy products across Canada, the relevant webpages of the provincial drug formularies were searched (See Appendix C). In Canada, allergen immunotherapy products are on all public plans (except for Yukon Territories). A summary of the various listings is found in Exhibit 3.

Exhibit 3: Public plan listings in Canada for allergen immunotherapy

Drug	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/ NU/ NW
Sublingual allergen immunotherapy												
Oralair	No	No	No	Res	Pas	Pas	No	Res	No	No	No	No
Ragwitek	No	No	No	No	Pas	No	No	No	No	No	No	No
Grastek	No	No	No	No	No	Pas	No	No	No	No	No	No
Subcutaneous allergen immunotherapy												
Pollinex R	No	No	No	No	SDP	No	No	Res	No	No	No	FB
Allergen extracts	FB	FB	Res	No*	SDP	FB	SA	Res	SA	FB	No	FB

No=not listed

Pas=restricted listing – passive (e.g., Limited Use in Ontario, Exceptional Medications in Quebec)

Res=restricted listing – enforced

FB=full benefit

SDP=Special drug program

SA=covered under Social Assistance program

*only cover stinging insect (Hymenoptera) immunotherapy

Current as of July 6, 2015

Restriction Criteria

In order for patients to be eligible for publically funded allergen immunotherapy, Nova Scotia uses restriction criteria as part of the special authorization process (see Appendix D).

Part 2: Telephone Interview with Public Drug Program Representatives

A representative from each public drug program invited to participate in a 30 minute telephone interview (see Appendix E) to gather further information about formulary listing of allergen immunotherapy. Exhibit 4 summarizes the information obtained in the interviews.

Exhibit 4: Summary of interviews with representative from public drug program

Province	Listing	Information on listing
British Columbia	Restricted	No SLIT product listed on formulary. Allergenic extracts (nonpollen) are listed under specific plans. In addition, allergists have access to grass pollen immunotherapy.
Saskatchewan	Restricted	No SLIT product listed on formulary. Allergenic extracts for SCIT are available to patients who require venom immunotherapy (via Social Services recommendation).
Manitoba	Restricted	Oralair recently listed on formulary (Spring 2015) SCIT is only covered for stinging insect immunotherapy
Ontario	Limited Use (SLIT products) Special Allergy Program (SCIT products)	Oralair and Ragwitek are listed in Ontario as Limited Use. SCIT products are available for ODB-eligible patients under the Special Allergy Program.
Nova Scotia	Restricted	Oralair available as a product requiring special authorization. Allergen immunotherapy (SCIT) available through special authorization. Note that all allergy serum extracts must be dispensed through a pharmacy
Prince Edward Island	Restricted	SLIT products are not covered SCIT products are covered for social service clients under Social Assistance program (i.e., not under drug program)
NIHB	Restricted	SLIT products are not covered. SCIT products are classified as Medical Supply and Equipment and are available as Full Benefit.
New Brunswick	Restricted	SLIT products are not covered SCIT products for social service clients (adults) are covered under Social Assistance program; for children, covered under Drug Program

Summary

- Most public drug programs (with the exception of Yukon Territories) provide coverage for allergen immunotherapy.
- SLIT products (Oralair, Ragwitek and/or Grastek) are listed on five public drug plans.
- Allergen extracts for SCIT administration are available in 11 (of 12) jurisdictions. In two provinces (New Brunswick and PEI), these products are covered under the Social Assistance program. Most allergen extracts are listed as a full benefit.
- Nova Scotia is the only jurisdiction that has developed clinical criteria for SCIT products, and include prior therapy with pharmacotherapy and allergen avoidance, history of insect sting allergy, rhinitis or allergic asthma AND continued for a maximum of five years.

Selected International Jurisdictions

United States

As a measure to control ever-increasing costs associated with healthcare, the use of a preferred drug list (“formulary”) has been implemented in some jurisdictions. For example a preferred drug list is a list of medications that the provider will cover the cost for without the need to request a prior authorization. The preferred drugs are usually medications that are available generically or are the result of price negotiations between the pharmaceutical company and the provider.

A tiered co-payment system is a combination of cost-sharing and a preferred drug list.¹² Three-tier structures commonly assign generic medications the lowest copay, formulary brand medications a somewhat higher copay, and non-formulary brand medications the highest copay. Three-tier copays provide consumers with more choice than in a closed formulary (where tier three drugs would not be covered at all) and attempt to reduce the number of prior authorizations that are needed for drug approval.¹³ In a five-tier system, tier 1 includes preferred generic drugs, tier 2 non-preferred generic drugs, tier 3 preferred brand drugs, tier 4 non-preferred brand drugs and tier 5 specialty drugs (e.g., injectables) (see Appendix F for examples of copayments with tiered formulary systems). (Exhibit 5)

Exhibit 5: Listing of allergen immunotherapy for select plans in the United States

Drug Plan	Oralair	Grastek	Ragwitek	Allergen Immunotherapy
AETNA Preferred List (www.aetna.com)	Tier 3	Tier 3	Not listed	Covered* (see Appendix G)
Amerigroup Medication Formulary (Medicaid markets in Florida, Louisiana, Maryland, Nevada, New Jersey and Washington) (www.Providers.amerigroup.com)	Non-preferred	Non-preferred	Non-preferred	Covered*
Blue Cross Blue Shield of South Carolina Preferred Drug List (www.southcarolinablues.com)	Non-preferred	Non-preferred	Non-preferred	Covered*
Blue Cross Blue Shield of Texas Standard Preferred Drug List (July 2015) (www.bcbstx.com)	Tier 4	Tier 4	Tier 4	Covered*
Connecticut Medicaid Preferred Drug List (www.ctdssmap.com)	Non-preferred	Non-preferred	Non-preferred	Covered*
Idaho Medicaid Preferred Drug List (www.healthandwelfare.idaho.gov)	Non-preferred	Non-preferred	Non-preferred	Covered*
Illinois Medicaid Preferred Drug List* http://www2.illinois.gov/hfs/sitecollectiondocuments/pdl.pdf	Tier 2	Not listed	Not listed	Covered*
Kaiser Permanente 2015 Medicare Part D Comprehensive Formulary (5-tier system) (www.healthy.kaiserpermanente.org)	Non-preferred	Tier 4	Tier 4	Covered*
Kentucky Preferred Drug List 2015 (www.15subsidiz.magellanmedicaid.com)	Prior authorization	Prior authorization	Prior authorization	Covered*
Texas Medicaid Preferred Drug List (http://www.txvendordrug.com/pdl/) (http://www.tmhp.com/News_Items/2013/03-Mar/03-15-13%20Benefit%20Criteria%20to%20Change%20for%20Allergen%20Immunotherapy%20for%20Texas%20Medicaid%20Effective%20May%201.pdf)	Not listed	Not listed	Not listed	Prior authorization
WellCare Comprehensive Formulary (Medicare Advantage Plans) (covers New York, Connecticut, Florida, Georgia, Hawaii and others) (5-tier system) (https://www.wellcare.com/medicare_formulary/new_york)	Step therapy (prior trial with nasal corticosteroid)	Step therapy (prior trial with nasal corticosteroid)	Step therapy (prior trial with nasal corticosteroid)	Covered*
Wellmark Prior authorization/Step therapy (http://www.wellmark.com/HealthAndWellness/DrugInformation/PharmacyHome.aspx)	Prior authorization	Prior authorization	Prior authorization	Covered*

*Covered under "Allergy Immunotherapy (Desensitization) Policy"

Other Countries

Australia: In Australia, the Pharmaceutical Benefits Scheme (PBS) only provides coverage for certain venom immunotherapy, namely paper wasp venom, bee venom and vespula spp. Venom.¹⁴ No coverage is available for sublingual immunotherapy (available in Australia as Oralair, Staloral liquid allergen extracts and ALK extracts).

*New Zealand*¹⁵: In New Zealand, the Pharmaceutical management Agency (PHARMAC) is the agency that decides which medicines, medical devices and related products are subsidized. Only venom immunotherapy (bee and wasp) is covered by PHARMAC. Initial approval is for 2 years and the patient requires a positive skin or RAST test and patient has a history of a severe generalized reaction to the sensitizing agent.

*Scotland*¹⁶: Grazax (timothy grass pollen allergen) is not recommended for use within NHS Scotland, as the manufacturer did not make a submission to Scottish Medicines Consortium (SMC) regarding this product.

Summary

- In the United States, most drug plans reviewed provide coverage for subcutaneous allergen immunotherapy for patients with specific conditions (e.g., allergic asthma, Hymenoptera sensitive individuals, perennial or seasonal allergic rhinitis). However, the SLIT products are generally considered “non-preferred” on most formularies.
- Australia and New Zealand provide coverage through the public plan programs only for subcutaneous venom immunotherapy.

Part B: Guidelines for the use of allergen immunotherapy

The objective of the allergen immunotherapy practice parameter is to establish safe and effective use of allergen immunotherapy while reducing unnecessary variation in immunotherapy practice.

American Academy of Allergy, Asthma and Immunology (AAAAI): Allergen immunotherapy practice

The AAAAI third update on allergen immunotherapy practice was published in 2011.¹⁷ In addition, a companion report addressed issues regarding allergen extract preparation, diluents, dosing and compatibility.¹⁸

Specific recommendations pertinent to this drug class review are as follows:

Multiallergen immunotherapy

- Summary Statement 72: There are few studies that have investigated the efficacy of multiallergen subcutaneous immunotherapy. These studies have produced conflicting results, with some demonstrating significant clinical improvement compared with placebo and others showing no benefit over optimal pharmacotherapy and environmental control measures. Thus it is important to treat the patients only with relevant allergens.
- Summary Statement 73: The selection of the components of an allergen immunotherapy extract should be based on a careful history in correlation with positive allergy skin test results or serum specific IgE antibodies. The allergen immunotherapy extract should contain only clinically relevant allergens. In choosing the components for a clinically relevant allergen immunotherapy extract, the physician should be familiar with local and regional aerobiology and indoor and outdoor allergens, paying special attention to potential allergens in the patient's own environment.

Allergen extract selection

- Summary statement 75: Nonstandardized extracts can vary widely in biologic activity and composition, regardless of a particular weight/volume or PNU potency, and should not be considered equipotent.
- Summary statement 76: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets.

Allergen extract preparation

- Summary statement 77: Allergen immunotherapy extract preparation should be performed by persons experienced and trained in handling allergenic products. A customized allergen immunotherapy extract should be prepared from a manufacturer's extract or extracts in accordance to the patient's clinical history and allergy test results and might contain single or multiple allergens (see allergen extract preparation section below for more detail).

Principles of mixing allergen immunotherapy

- Summary statement 78: Consideration of the following principles is necessary when mixing allergen extracts: 1) cross-reactivity of allergens, 2) optimization of the dose of each constituent and 3) enzymatic degradation of allergens.

Proteolytic enzymes and mixing

- Summary statement 82: Studies designed to investigate the effect of combining extracts with high proteolytic activity, such as cockroach and mold/fungi, with extracts such as pollen, dander and dust mite, have demonstrated a significant loss of potency with some of these extracts. Separation of extracts with high proteolytic enzyme activities from other extracts is recommended. It might be necessary to prepare 2 or more vials to provide allergen immunotherapy containing an optimal dose of each component while avoiding allergen extract combinations that might result in degradation of some or all of the components (see section below on compatibility of different antigens).

Allergen extract preparation

In Europe, no final allergen extract formulation is prepared by physicians and virtually all allergen immunotherapy is prepared by extract manufacturers, under national and international (European Medicines Agency) regulatory guidelines.¹⁹ In the United States, guidelines for allergen extract preparation have been established for products compounded by specially trained physicians and personnel under their direct supervision. The USP 797 guidelines (compounding standards for sterile preparations) distinguish allergen extract preparation from multidose medication vials and other compounded pharmacy-based sterile products, which require more stringent measures, such as laminar flow hoods, air sampling and sterility testing.²⁰ The American Academy of Allergy, Asthma and Immunology (AAAAI) have also developed guidelines for preparation of allergen extracts (see Appendix H).²¹ Both guidelines emphasize aseptic technique, handwashing, appropriate refrigerated storage, use of personal protective equipment, beyond-use dating and patient identification on labels. As well, the AAAAI guidelines specify that allergen extract dilutions must be bacteriostatic (phenol concentrations $\geq 0.25\%$ or if phenol $< 0.25\%$ then extract must have a glycerin concentration of at least 20%).

- The USP 797 and AAAAI/ACAAI/JCAAI Joint Task Force allergen extract preparation guidelines are designed to ensure safe sterile compounding.
- These guidelines emphasize handwashing, preservative use, appropriate labeling, and preparer qualifications that include media fill testing.
- Applicability of these guidelines depends on local regulatory requirements. One or a combination of both standards should be adopted by all entities preparing allergen extracts.
- Only a few studies to date have evaluated the safety of allergen extract preparation, and none have identified a significant contamination risk for patients.

Diluents

- As an extract stabilizer, normal saline is not as effective as glycerin or HSA.

- Human serum may protect against deleterious effects of phenol and adherence of dilute allergen extract on a glass vial wall.
- Glycerin preservative effect increases with concentration, but injection discomfort increases with total glycerin dose.
- Increasing glycerin concentrations do not appear to correlate with the incidence of SIT large or small local reactions.

Compatibility of different allergens

- Formulation of patient SIT mixtures requires knowledge about allergen compatibility and stability and the patient's sensitivity and responsiveness to specific allergens.
- Because fungal and insect allergen extracts contain proteolytic enzymes that can degrade pollen allergens, mixing them should be avoided.²²
- Venom immunotherapy should not be mixed together (unless commercially available as a mixed product).

Optimal dose for allergen extracts

- The safe and efficacious dosing of allergenic extracts relies on the standardization practices by extract manufacturers, including the relevant potency labeling of products and assurance of lot-to-lot consistency.
 - There are several standardized SCIT extracts available in Canada including venom, grass pollen, ragweed, cat dander and house dust mite.²³
- Estimates for probable effective dose ranges for nonstandardized extracts are difficult to estimate because validated potency assays are not available.

Canadian Society of Allergy and Clinical Immunology (CSACI): Consensus guidelines on practical issues of immunotherapy²⁴

The CSACI developed guidelines on practical issues of immunotherapy including skin testing, and prescription of specific immunotherapy. Some specific recommendations include:

- Successful treatment is normally carried on for 3 to 5 years; consideration is then given to stopping.
- Injections of a single allergen are preferred to the use of mixes (in mixes, cross-reactivity, the optimal dose of each allergen and enzymatic degradation have to be considered).
- Separation of aqueous extracts with high proteolytic enzyme activities (fungi, house dust mite, cockroach and insect venom) from other extracts is recommended.

British Society for Allergy and Clinical Immunology: Immunotherapy for allergic rhinitis²⁵

Guidelines for the management of allergic rhinitis in patients who failed to achieve adequate relief of symptoms despite treatment with intranasal corticosteroids and/or antihistamines were published in 2011. Some key points:

- Immunotherapy, both subcutaneous and sublingual, is an effective treatment for adults and children with severe allergic rhinitis that does not respond to conventional pharmacotherapy and allergen avoidance measures.
- The efficacy of immunotherapy depends on correct patient selection, the type of allergen and the product chosen for treatment. Each vaccine requires individual assessment before recommendation for routine use.
- In asthma, the risk benefit is less favourable than for rhinitis and therefore immunotherapy for asthma is not routinely recommended in the UK.
- Subcutaneous immunotherapy and sublingual immunotherapy have been shown to give long-lasting benefit for some years after stopping treatment.
- Single allergen vaccines are more effective than vaccines containing mixtures of allergens.
- Selection of patients for immunotherapy requires accurate identification of underlying allergic trigger through a combination of clinical history and skin and/or blood tests for allergen specific IgE.
- SCIT is safe when undertaken in selected individuals in a specialist allergy clinic by trained health professionals: in a setting with access to immediate treatment for anaphylaxis and resuscitation if required.
- The safety profile of SLIT appears to be superior to SCIT although there have been no head to head comparisons of efficacy.
- Cost effectiveness for immunotherapy has been shown but only in vaccines that provide long-term benefit.

S2k group (German, Austrian and Swiss professional associations): Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases²⁶

The guideline was developed to provide guidance on allergen-specific immunotherapy in IgE-mediated allergic diseases (e.g., asthma, rhinitis).

Some specific conclusions reached:

- Products for SCIT or SLIT cannot be compared at present due to their heterogeneous composition, nor can allergen concentrations given by different manufacturers be compared meaningfully due to the varying methods used to measure their active ingredients. Standardized allergen extracts should preferentially be used, as otherwise extracts vary significantly in their biological activity.
- Indications for allergen immunotherapy:
 - Verification of an IgE-mediated sensitization with a clear relationship to clinical symptoms
 - Availability of standardized or high-quality allergen extracts
 - Proof of efficacy of the planned allergen immunotherapy for the respective indication and age group
 - Allergen avoidance not possible or inadequate
 - Patient age 5 years or older

Summary

- There have been several guidelines that have published by various organizations on allergy immunotherapy.
- Guidelines include indications and selection of patients for immunotherapy, and efficacy and safety of the various products.
- In addition, there are recommendations for allergen extract preparation, diluents, dosing and compatibility for allergy immunotherapy.

Part C: Impact of different drug reimbursement schemes for allergen immunotherapy

Methods

A literature search was conducted in Pubmed using the terms: allergens or allergen immunotherapy or desensitization, immunologic AND (healthcare accessibility OR health policy OR reimbursement incentive OR national health programs OR cost sharing or deductibles and coinsurance or insurance coverage or insurance health). Bibliographies of identified articles were scanned for additional relevant articles.

Results

Only one study was identified through the literature search.²⁷ This study evaluated 155 patients with allergic rhinitis who prematurely discontinued subcutaneous allergen immunotherapy; the study was conducted in the US. Patients were contacted by telephone or mail in order to determine the reason they discontinued their allergy injections. A total of 62 patients (40%) discontinued immunotherapy prematurely for cost reasons (either they did not have medical insurance or the insurance that they had was inadequate). Other reasons cited for discontinuation included inconvenience (14%), concurrent health problems (8%), and ineffective therapy (7%).

An additional study that looked at adherence prior to and during a recent Spanish recession, showed a significant decrease in both SCIT and SLIT use during the recession (one year adherence pre-recession 78% vs. post-recession 67%; p=0.01) and more specifically, among those patients in whom SLIT was prescribed before vs. after the recession (91% vs 69%;p=0.003).²⁸

Summary

- There is a lack of published literature investigating various reimbursement schemes for allergen immunotherapy.

Part D: Rapid Review of Selected Topics

Duration of immunotherapy treatment

The optimal duration of immunotherapy is still unknown. Current guidelines recommend discontinuing immunotherapy on an individual basis, with the usual treatment durations ranging between 3 and 5 years, although it might be administered indefinitely for some patients with Hymenoptera venom allergy. The British guidelines suggest that immunotherapy is generally administered for 3 years, either continuously or pre-seasonally. Cessation of immunotherapy should be considered if clinical improvement is not apparent after 2 years of treatment.²⁵ Similarly, the AAAAI indicate that the decision to continue immunotherapy beyond 3 to 5 years should be based on individual patient factors such as the severity of the disease, benefits sustained from treatment, reaction history, patient preference and treatment convenience.²¹

There are only a few studies that have examined the long-term efficacy of SCIT with aeroallergens. One double-blind, placebo-controlled cessation study of grass pollen immunotherapy was published.²⁹ After 3-4 years of SCIT, immunotherapy was discontinued. Follow-up measures revealed no significant difference in symptom or medication scores in the subsequent three pollen seasons. Follow-up studies after discontinuation of SCIT in children have demonstrated a carry-over effect, which may last up to 12 years, although the studies evaluating the long-term effectiveness are neither randomized nor do they have a control group.³⁰⁻³² One randomized, prospective clinical trial evaluated a three-year or five-year course of specific immunotherapy for dust mite respiratory allergy.³³ Clinical improvement was obtained with three years of immunotherapy, especially for asthma symptoms. After 2 years of follow-up, 70% of asthma patients remained symptom free, and asthma score reductions remained unchanged. Importantly, there was no significant difference between patients who continued and those who discontinued immunotherapy. As well, there is some evidence to indicate that SCIT may help to relieve symptoms in the short-term and also act as a preventive strategy to reduce progression of rhinitis to asthma.⁶

The World Allergy Organization (WAO) 2013 update of their Sublingual Allergen position paper state that improvement in allergic rhinitis persists for one to two years after discontinuation of three years of SLIT with grass pollen extract.³⁴ In a five-year double-blind, placebo-controlled trial of grass SLIT therapy (Grazax, known as Grastek in Canada), 238 patients completed 3 years of active treatment and 2 years of followup.³⁵ The mean rhinoconjunctivitis daily symptom score was reduced by 25 to 36% ($p < 0.004$) in the grass allergy immunotherapy tablet group compared with the placebo group. The result was statistically significant for each of the 5 years including the 2 years off treatment.

Summary: Although the optimal duration of immunotherapy is unknown, three to five years duration for SCIT has been recommended. Patients receiving venom immunotherapy may require life-long administration. For SLIT, three years of therapy (pre- and co-seasonal) is recommended.

Venom Immunotherapy

Hymenoptera insects, primarily honeybee, wasp, yellowjacket, hornet and ant (e.g., fire ant in southeast US) can cause human stings and result in one of three types of reactions: a local reaction, a large local reaction and a systemic reaction. A local reaction presents with pain, swelling and erythema at the site of the sting whereas a large local reaction may have the symptoms expanding to a larger area of skin. A systemic allergic reaction can be life-threatening and often involves more than one organ system (e.g., skin, gastrointestinal, respiratory and/or cardiovascular systems). The prevalence of systemic allergic reactions following a sting is estimated between 0.15 to 0.8% in children and 0.3 to 8.9% in adults.³⁶ Diagnosis of Hymenoptera venom allergy is established by a history of anaphylactic sting reaction(s) and positive skin test responses and/or detection of specific immunoglobulin E (IgE) to a specific venom.³⁷

In addition to prescribing epinephrine for self-administration, patients with systemic reactions to Hymenoptera insect stings should be considered for venom immunotherapy. Venom immunotherapy has been shown to prevent systemic allergic reactions on re-sting in 75-95% of subjects (depending on the causative insect), compared to a 40-60% risk of a future systemic reaction in untreated subjects.³⁶ After at least 3 years of venom immunotherapy, studies have shown that patients may be protected for up to seven years after venom immunotherapy is discontinued. In patients with a severe reaction, venom immunotherapy is recommended to be continued for an extended (perhaps indefinite) period of time.³⁸ As well, patients with an elevated baseline serum tryptase (with or without mastocytosis) and/or increased basil sensitivity may be at an increased risk for severe or fatal reactions to stings if they discontinue venom immunotherapy.

Venom immunotherapy is associated with the potential for severe adverse reactions, especially in high-risk populations. Local reactions can occur in up to 50% of individuals; these can often be managed with premedication with antihistamines. Systemic reactions occurring during venom immunotherapy may be present in 6-25% of individuals (depending on type of Hymenoptera sting), although most reactions do not require the use of epinephrine.^{39,40}

Guidelines: The AAAAI in its practice guidelines for allergen immunotherapy suggests that immunotherapy should be considered if the patient has had a systemic reaction to a Hymenoptera sting, especially if such a reaction was associated with respiratory symptoms, cardiovascular symptoms, or both and if the patient has demonstrable evidence of specific IgE.²¹ As well, the guideline addresses discontinuation of venom immunotherapy. They note that a higher chance of relapse is possible following discontinuation of immunotherapy in patients with a history of a very severe reaction to a sting, an increased baseline serum tryptase level, a systemic reaction during venom immunotherapy, honeybee venom allergy and treatment duration less than 5 years.

The British Society for Allergy and Clinical Immunology (BSACI) guidelines indicate that venom immunotherapy is effective in 95% of patients allergic to wasp venom and about 80% of those allergic to bee venom.⁴¹ Venom immunotherapy is recommended for all patients with a severe systemic reaction after a sting and in many patients after a systemic reaction of moderate severity. Venom immunotherapy is not usually indicated for patients with less

severe sting-induced systemic reactions unless additional risk factors are present (e.g., raised baseline tryptase, a high likelihood of future stings, or effect on quality of life). The usual duration of venom immunotherapy is 3 years. Longer or even life-long treatment in patients with a raised baseline tryptase is not advocated in the United Kingdom because this is not evidence-based.

Systematic Reviews: A total of four systematic reviews and meta-analysis were identified since 2010 that evaluated the efficacy and/or safety of Hymenoptera venom immunotherapy.

The first study was a Cochrane meta-analysis (total number of participants: 392) that included 6 randomized controlled studies and one quasi-randomized controlled study and showed that venom immunotherapy (6 trials using SCIT and 1 trial using SLIT) was effective for preventing systemic allergic reactions to an insect sting.⁴² A total of 3/113 (2.7%) of participants treated with venom immunotherapy experienced a subsequent systemic allergic reaction to a sting compared with 37/93 (39.8%) untreated participants (risk ratio [RR] 0.10, 95% confidence interval [CI] 0.03 to 0.28). As well, venom immunotherapy was shown to be effective in preventing large local reactions to a sting (RR 0.41, 95% CI 0.24 to 0.69) and for improving quality of life (mean difference in favour of venom immunotherapy, 1.21 points on a 7-point scale, 95% CI 0.75 to 1.67). A significant risk of systemic adverse reaction was noted to venom immunotherapy treatment: 9.3% participants treated with venom immunotherapy and 0.7% participants treated with placebo or no treatment (RR 8.16, 95% CI 1.53 to 43.46). Review of the observational studies found that systemic adverse reactions occurred in 14.2% participants treated with bee venom immunotherapy and 2.87% treated with wasp venom immunotherapy.

A systematic review of venom immunotherapy (subcutaneous) was undertaken to assess the effects of this therapy among patients presenting with severe reactions after Hymenoptera stings.⁴³ Four RCTs were included in the review, although two of the studies were included in the meta-analysis and showed that there was a reduction in the risk of systemic reaction to insect stings (odds ratio 0.29, 95% CI 0.10 to 0.87).

A Health Technology Assessment of one manufacturer's venom immunotherapy products (Pharmalgen-Alk Abello) concluded that venom immunotherapy may only be cost effective for preventing systemic reactions in those at risk of >5 insect stings per year.⁴⁴ In this review, the clinical effectiveness and cost-effectiveness of Pharmalgen was reviewed for individuals with a history of an IgE-mediated systemic allergic reaction to bee or wasp venom. Four RCTs and five quasi-experimental studies were included in the systematic review. Eight studies reported resting data and the rate of systemic reactions ranged from 0 to 36.4%. Due to the heterogeneity between studies in the outcomes reports, it was not possible to conduct a meta-analysis or mixed-treatment comparison. Health related quality of life was not reported in any of the included studies. However, two other RCTs that used a combination of Pharmalgen and other venom immunotherapy indicate that the quality of life for people receiving venom immunotherapy improved more than the quality of life of those using an EpiPen.

A systematic review and meta-analysis was done evaluating the safety of bee venom immunotherapy.⁴⁵ A total of 145 studies were identified, including 20 RCTs, 79 audits and cohort studies, 33 single-case studies and 13 case series. Studies conducted using either bee

sting acupuncture or SCIT venom immunotherapy were included. The median frequency of patients who experienced adverse events related to venom immunotherapy was 28.9% in the audit series. Since a large proportion of studies included in the analysis utilized bee sting acupuncture, the results of this review are not applicable to the OPDP population (i.e., venom immunotherapy administered as subcutaneous injections).

Summary: Venom immunotherapy is an effective therapy for prevention of future allergic reactions to Hymenoptera stings, and also improves quality of life. However, venom immunotherapy is not without risk, and patients may develop local reactions or more rarely, systemic reactions.

Sublingual immunotherapy: focus on oral drop administration

Subcutaneous immunotherapy (SCIT) is effective in the management of patients with allergic rhinitis and asthma; however it requires regular injections in a physician's office, usually over 3 to 5 years and is associated with a risk of systemic reactions. Sublingual immunotherapy (SLIT) has been widely available in Europe, South America and Asia, but only recently has been introduced in North America. In Canada, there are three licensed sublingual immunotherapy products available: Grastek, Oralair and Ragwitek. In addition to these SLIT products, some practitioners have used commercially available extracts (primarily extracts available for SCIT) to compound products for SLIT administration, usually as SLIT drops; this is considered "off-label".⁴⁶ Most of the current literature on SLIT is focused on commercially available products, rather than off-label SLIT use of SCIT products.

Meta-analyses comparing SLIT tablets and SLIT drops: There have been several meta-analyses that have been published evaluating SLIT administered by either drops or tablets in patients with rhinitis.

The first study evaluated the efficacy and safety of sublingual immunotherapy for allergic rhinitis in adults and children.⁴⁷ This review included 49 RCTs that were suitable for pooling in the meta-analyses (2333 SLIT, 2256 placebo participants). Overall, a significant reduction in symptoms (standardized mean difference [SMD] -0.49; 95% CI -0.64 to -0.34, $p < 0.00001$) and medication requirements (SMD -0.32; 95% CI -0.43 to -0.21, $p < 0.00001$) in participants receiving sublingual immunotherapy compared to placebo. For the seasonal allergen group (namely grass pollen, Parietaria, ragweed, tree allergens), a total of 39 trials were included and showed significant reduction in symptoms (SMD -0.34; 95% CI -0.44 to -0.25, $p < 0.00001$). The perennial allergen studies (house dust mite) involved 10 trials (SMD -0.93; 95% CI -1.69 to -0.17; $p = 0.02$). The review looked at possible differences between different sublingual preparations (i.e., sublingual drops versus tablets). Although tablets were more effective than drops in terms of symptoms, overlapping confidence intervals and the substantial heterogeneity between studies made it difficult to draw any concrete conclusions. No severe systemic reactions or anaphylaxis were reported in any of the trials included in the review.

A network meta-analysis estimated the relative efficacy of SLIT tablets compared with SCIT and SLIT drops in commercially available products for grass pollens.⁴⁸ A total of 37 studies were included for symptoms scores and 31 studies for medication scores. SCIT and SLIT tablets (but not SLIT drops) were significantly different from placebo for symptom scores:

(SMD, -0.32, 95% CI -0.45 to 0.18) and (SMD -0.32, 95% CI -0.41 to -0.23), respectively. For medication scores, significant differences compared with placebo were observed for SCIT, SLIT tablets and SLIT drops. Network meta-analysis revealed no significant differences for symptoms scores or medication scores between SLIT tablets and SCIT or for symptom scores and medication scores between SLIT tablets and SLIT drops.

Another meta-analysis was completed to assess whether effectiveness was determined by the route of administration (SCIT, SLIT-tablet, SLIT-drops).⁴⁹ A total of 36 RCTs were included. Using an indirect meta-analysis based comparison, the overall effect size of SCIT for symptom score (SMD, -0.92; 95% CI, -1.26 to -0.58) was significantly higher than SLIT, both administered via drops (SMD, -0.25; 95% CI, -0.45 to -0.05) and tablets (SMD, -0.40; 95% CI -0.54 to -0.27). Similar results were reported for medication score. The authors conclude that SCIT is more effective than SLIT in controlling symptoms.

Multiallergen SLIT administration: SLIT has been shown to be effective in reducing symptom and medication scores. However, most of the studies have involved treatment with a single allergen or multi-allergen (5 grasses) administered as a tablet, but only limited trials evaluating SLIT drops (either as single antigen or multiallergen). A double-blind, placebo-controlled trial was done evaluating 54 patients who randomly received placebo, timothy grass extract or timothy grass extract plus 9 additional pollens; SLIT was administered as oral drops.⁵⁰ No significant differences were seen in medication or symptom scores in either treatment group compared with those receiving placebo. Only the timothy grass monotherapy differed significantly from placebo in improving nasal challenge results. In conclusion, multiallergen SLIT has not been well studied, and may not be as effective as single-allergen SLIT.

Doses: Effective doses have been defined for many pollen and indoor allergens for SCIT. However in a review of all randomized studies of SLIT, there was a very broad range of effective doses.⁵¹ SLIT efficacy is suggested to be dose-dependent.⁵² The commercialized products available in Europe vary from 5 to 45 times higher than the doses for SCIT products from the same manufacturers.³⁴ A daily SLIT dose is roughly equivalent to a monthly SCIT dose.⁵³

Summary: In meta-analyses that have compared SLIT tablets and drops, SLIT tablets are more effective than drops in terms of symptom improvement. The use of multiallergen SLIT administration (via drops) has not been well studied and may not be as effective as single-allergen SLIT.

Immunotherapy for food allergies

IgE-associated food allergies affect approximately 3% of the population. Milk, eggs, wheat, peanuts, nuts, sesame, fish, fruits and vegetables are common inducers of IgE-associated food allergy. Allergies to foods such as milk, egg, and wheat often are outgrown, whereas allergies to peanuts, tree nuts, and fish allergies persist over the patient's lifetime.⁵⁴

Management of food allergy relies primarily on allergen avoidance. Allergen-specific immunotherapy (administered subcutaneously or sublingually) has been used for the treatment of food allergies, as standardized vaccines are not available.⁵⁴ In the case of food

allergies, allergen-specific immunotherapy is most frequently conducted orally, by administration of the offending food instead of a vaccine. Once desensitization is complete, the treated patients manifest a decreased response to the ingested food allergens but must continue to take daily food doses to maintain the state of tolerance.⁵⁵ Oral immunotherapy has been studied in patients with peanut, milk, and egg allergies.⁵⁶ Sublingual administration has been utilized, but the evidence for SLIT is limited. For example, a RCT was conducted using peanut sublingual immunotherapy in 40 patients over a 3 year period. A total of 24 patients withdrew for various reasons (e.g., lost to follow-up, investigator decision, need for a prohibited medication, pregnancy). By the end of the study, 4 patients were fully desensitized (as defined to tolerance to an oral challenge).⁵⁷ Patients with allergies to other foods, such as kiwifruit, hazelnut, milk, and peach have also been desensitized using SLIT.⁵⁸ Subcutaneous allergen immunotherapy (SCIT) is considered impractical and unsafe for the treatment of food allergy due to an unacceptably high rate of anaphylactic reactions. An alternative to SCIT for food allergies is epicutaneous immunotherapy, although this route of administration is still considered experimental.⁵⁹

Summary: Use of subcutaneous allergen immunotherapy for food allergies is not recommended due to safety concerns. Although sublingual allergen immunotherapy has been studied for some food allergies, the evidence for its efficacy and safety is still limited and cannot be recommended for routine use at this time.

Health Canada Warnings

No Health Canada warnings have been issued for the allergen extracts.

Institute for Safe Medication Practices (ISMP) Canada recently issued a safety bulletin regarding missed doses of allergen extracts.⁶⁰ They describe a patient who missed several months of immunotherapy during the build-up phase. When he received full maintenance doses, he developed hives and felt unwell. Based on an in-depth review, ISMP provided several recommendations for allergy specialists and family practice/clinic practitioners.

Discussion

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability in Canada

- Allergen immunotherapy is available either for sublingual (SLIT) or subcutaneous (SCIT) administration in Canada.
- Four products are available as ready-to-use formulations: Pollinex R (available for SCIT administration), Oralair, Ragwitek and Grastek (the latter three are available for SLIT administration).
- Most subcutaneous products are formulated specifically for the allergic patient, based on the results of skin testing and clinical symptoms. The components of the patient-specific serum extract are available as Health Canada approved products with drug identification numbers (DINs).

Public Plan Listing in Ontario

- In Ontario, SLIT (namely Ragwitek and Oralair) are listed as Limited Use products on the ODB formulary.
- SCIT is available for ODB eligible patients under the special “Allergy Product” program.

Public Plan Listing in Canada

- Most public drug programs (with the exception of Yukon Territories) provide coverage for allergen immunotherapy.
- SLIT products (Oralair, Ragwitek and/or Grastek) are listed on five public drug plans.
- Allergen extracts for SCIT administration are available in 11 (or 12) jurisdictions. In two provinces (New Brunswick and PEI), these products are covered under the Social Assistance program. Most allergen extracts are listed as a full benefit.
- Nova Scotia is the only jurisdiction that has developed clinical criteria for SCIT products, and include prior therapy with pharmacotherapy and allergen avoidance, history of insect sting allergy, rhinitis or allergic asthma AND continued for a maximum of five years.

Selected International Jurisdictions

- In the United States, most drug plans reviewed provide coverage for subcutaneous allergen immunotherapy for patients with specific conditions (e.g., allergic asthma, Hymenoptera sensitive individuals, perennial or seasonal allergic rhinitis). However, the SLIT products are generally considered “non-preferred” on most formularies.
- Australia and New Zealand provide coverage through the public plan programs only for subcutaneous venom immunotherapy.

Part B: Guidelines for the use of allergen immunotherapy

- There have been several guidelines that have published by various organizations on allergy immunotherapy.
- Guidelines include indications and selection of patients for immunotherapy, and efficacy and safety of the various products.
- In addition, there are recommendations for allergen extract preparation, diluents, dosing and compatibility for allergy immunotherapy.

Part C: Impact of different drug reimbursement schemes for allergen immunotherapy

- There is a lack of published literature investigating various reimbursement schemes for allergen immunotherapy.

Part D: Rapid Reviews of Selected Topics

- *Venom immunotherapy*: Venom immunotherapy is an effective therapy for prevention of future allergic reactions to Hymenoptera stings, and also improves quality of life. However, venom immunotherapy is not without risk, and patients may develop local reactions or more rarely, systemic reactions.
- *Duration of therapy*: Although the optimal duration of immunotherapy is unknown, three to five years duration for SCIT has been recommended. Patients receiving venom

- immunotherapy may require life-long administration. For SLIT, three years of therapy (pre- and co-seasonal) is recommended.
- *Sublingual immunotherapy (drop formulation)*: In meta-analyses that have compared SLIT tablets and drops, SLIT tablets are more effective than drops in terms of symptom improvement. The use of multiallergen SLIT administration has not been well studied and may not be as effective as single-allergen SLIT
 - *Immunotherapy for food allergies*: Use of subcutaneous allergen immunotherapy for food allergies is not recommended due to safety concerns. Although sublingual allergen immunotherapy has been studied for some food allergies, the evidence for its efficacy and safety is still limited and cannot be recommended for routine use at this time.

Health Equity

In Ontario, allergen immunotherapy is available through the ODB formulary as Limited Use (for SLIT products) and through the special “Allergy Program”. No health equity issues were identified for Ontario.

Conclusion

Allergenic immunotherapy is available in Ontario as either Limited Use (SLIT products: Oralair and Ragwitek) or through the special “Allergy Program”. For prescriptions that are administered through the “Allergy Program”, a pharmacy is not required to process the prescriptions. Currently, there are no clinical criteria in Ontario for the use of the SCIT products. Most public drug plans in Canada provide funding for the SCIT allergenic products, and five jurisdictions list one or more of the commercially available SLIT products.

There are guidelines available that provide guidance to clinicians for allergen extract preparation, diluents, dosing and compatibility for allergy immunotherapy.

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Appendix A: Marketed products (DIN associated products) in Canada

Company	Product	Active ingredient(s)	Strength
Subcutaneous immunotherapy: pollen			
Alk-Abello	Allergenic extract - mixture of 4 standardized grass pollen	Standardized june grass pollen	25000 unit / ml
Alk-Abello	Allergenic extract - mixture of 5 standardized grass pollen	Standardized june grass pollen	20000 unit / ml
Alk-Abello	Allergenic extract - standardized june grass pollen	Standardized june grass pollen	100000 unit / ml
Alk-Abello	Allergenic extract - standardized meadow fescue grass pollen	Standardized meadow fescue grass pollen	100000 unit / ml
Alk-Abello	Allergenic extract - standardized orchard grass pollen	Standardized orchard grass pollen	100000 unit / ml
Alk-Abello	Allergenic extract - standardized perennial rye grass pollen	Standardized perennial rye grass pollen	100000 unit / ml
Alk-Abello	Allergenic extract - standardized redtop grass pollen	Standardized redtop grass pollen	100000 unit / ml
Alk-Abello	Allergenic extract - standardized sweet vernal grass pollen	Standardized sweet vernal grass pollen	100000 unit / ml
Alk-Abello	Allergenic extract - standardized timothy grass pollen	Standardized timothy grass pollen	100000 unit / ml
Alk-Abello	Allergenic extract pollens	Pollen	100000 unit / ml
Allergy therapeutics	Pollinex r	Modified ragweed tyrosine adsorbate	210 unit / ml
Greer laboratories	Allergenic extract - standardized grass pollen - bermuda	Bermuda grass	10000 unit / ml
Greer laboratories	Allergenic extract - standardized grass pollen - kentucky blue/june	Kentucky bluegrass	100000 unit / ml
Greer laboratories	Allergenic extract - standardized grass pollen - meadow fescue	Standardized meadow fescue grass pollen	100000 unit / ml
Greer laboratories	Allergenic extract - standardized grass pollen - orchard	Standardized orchard grass pollen	100000 unit / ml
Greer laboratories	Allergenic extract - standardized grass pollen - perennial rye	Standardized perennial rye grass pollen	100000 unit / ml
Greer laboratories	Allergenic extract - standardized grass pollen - red top	Standardized redtop grass pollen	100000 unit / ml
Greer laboratories	Allergenic extract - standardized grass pollen - sweet vernal	Sweet vernal grass	100000 unit / ml
Greer laboratories	Allergenic extract - standardized grass pollen - timothy	Standardized timothy grass pollen	100000 unit / ml
Greer laboratories	Allergenic extracts - 7 grass mix	Standardized june grass pollen	10000 unit / ml
Greer laboratories	Allergenic extracts - 7 grass mix	Standardized june grass pollen	100000 unit / ml
Greer laboratories	Non standardized allergenic extracts - pollens	Pollen	40000 unit / ml
Jubilant hollisterstier llc	Allergenic extract - pollens	Pollen	40000 unit / ml
Jubilant hollisterstier llc	Standardized grass pollen - kentucky bluegrass (10000 bau/ml)	Kentucky bluegrass	10000 unit / ml 100000 unit / ml
Jubilant hollisterstier llc	Standardized grass pollen - meadow fescue (10000 bau/ml)	Standardized meadow fescue grass pollen	10000 unit / ml 100000 unit / ml
Jubilant hollisterstier llc	Standardized grass pollen - orchard grass (10000 bau/ml)	Standardized orchard grass pollen	10000 unit / ml 100000 unit / ml
Jubilant hollisterstier llc	Standardized grass pollen - perennial ryegrass (10000 bau/ml)	Standardized perennial rye grass pollen	10000 unit / ml 100000 unit / ml

Jubilant hollisterstier llc	Standardized grass pollen - redtop (10,000 bau/ml)	Standardized redtop grass pollen	10000 unit / ml 100000 unit / ml
Jubilant hollisterstier llc	Standardized grass pollen - sweet vernal grass (10,000 bau/ml)	Sweet vernal grass	10000 unit / ml 100000 unit / ml
Jubilant hollisterstier llc	Standardized grass pollen - timothy (10000 bau/ml)	Standardized timothy grass pollen	10000 unit / ml 100000 unit / ml
Omega laboratories ltd	Omega allergenic extracts - pollens (aqueous)	Allergenic extracts pollens	40000 unit / ml
Omega laboratories ltd	Omega allergenic extracts - pollens (glycerinated)	Allergenic extracts pollens	40000 unit / ml
Omega laboratories ltd	Omega allergenic extracts - pollens (suspal)	Allergenic extracts pollens	40000 unit / ml
Subcutaneous immunotherapy: non-pollen			
Alk-Abello	Allergenic extract non pollens	Non pollen	100000 unit / ml
Alk-Abello	Allergenic extract, standardized mite, d. Farinae	Dermatophagoides farinae	10000 unit / ml
Alk-Abello	Allergenic extract, standardized cat pelt	Standardized cat pelt	10000 unit / ml
Alk-Abello	Allergenic extract, standardized mite mixed	Dermatophagoides farinae	5000 unit / ml
Alk-Abello	Allergenic extract, standardized mite, d. pteronyssinus	Dermatophagoides pteronyssinus	10000 unit / ml
Greer laboratories	Allergenic extract - standardized mite dermatophagoides farinae	Dermatophagoides farinae	10000 unit / ml
Greer laboratories	Allergenic extract - standardized mite dermatophagoides pteronyssinus	Dermatophagoides pteronyssinus	10000 unit / ml
Greer laboratories	Allergenic extract - standardized mite mix	Dermatophagoides farinae	5000 unit / ml
Greer laboratories	Allergenic extract-standardized cat hair	Cat (felis domesticus) pelt and cat dander	10000 unit / ml
Greer laboratories	Non standardized allergenic extracts - non pollens	Non pollen	40000 unit / ml
Jubilant hollisterstier llc	Allergenic extract - non-pollens	Non pollen	500 unit / ml
Jubilant hollisterstier llc	Allergenic extract mixture of standardized mites (15,000 au/ml)	Dermatophagoides farinae	5000 unit / ml 15000 unit / ml
Jubilant hollisterstier llc	Allergenic extract standardized mite df (10,000 au/ml)	Dermatophagoides farinae	10000 unit / ml 30000 unit / ml
Jubilant hollisterstier llc	Allergenic extract standardized mite dp (10,000 au/ml)	Dermatophagoides pteronyssinus	10000 unit / ml 30000 unit / ml
Jubilant hollisterstier llc	Standardized cat hair ap	Standardized cat hair acetone precipitated	10000 unit / ml
Jubilant hollisterstier llc	Standardized cat pelt ap	Standardized cat pelt acetone precipitated	10000 unit / ml
Medic savoure ltd.	Allergenic extracts inj	Non pollen	0 nil / nil
Omega laboratories ltd	Omega allergenic extracts - non-pollens (aqueous)	Allergenic extract non-pollen	40000 unit / ml
Omega laboratories ltd	Omega allergenic extracts - non-pollens (glycerinated)	Allergenic extract non-pollen	40000 unit / ml
Omega laboratories ltd	Omega allergenic extracts - non-pollens (suspal)	Allergenic extract non-pollen	40000 unit / ml
Subcutaneous immunotherapy: venom			
Alk Abello	Pharmalgen honey bee venom	Apis mellifera venom protein extract	120 µg / vial 1.1 mg / vial
Alk Abello	Pharmalgen mixed vespid venom protein	White faced hornet venom protein	120 µg / vial 1.1 mg / vial
Alk Abello	Pharmalgen wasp venom protein	Polistes spp venom protein extract	120 µg / vial 1.1 mg / vial
Alk Abello	Pharmalgen white faced hornet venom protein	Dolichovespula maculata venom protein extract	120 µg / vial 1.1 mg / vial
Alk Abello	Pharmalgen yellow hornet venom protein	Dolichovespula arenaria venom protein extract	120 µg / vial 1.1 mg / vial
Alk Abello	Pharmalgen yellow jacket venom protein	Vespula spp venom protein extract	120 µg / vial 1.1 mg / vial
Jubilant hollisterstier llc	Honey bee venom multidose 13.0 ml (1300mcg)	Apis mellifera venom protein extract	1300 µg / vial

Jubilant hollisterstier llc	Hymenoptera venom product - honey bee venom (550 mcg)	Honey bee venom protein	550 µg / vial
Jubilant hollisterstier llc	Hymenoptera venom product - yellow jacket venom protein (550 mcg)	Yellow jacket venom protein	550 µg / vial
Jubilant hollisterstier llc	Hymenoptera venom product-mixed vespid venom protein (1650 mcg)	White faced hornet venom protein	550 µg / vial
Jubilant hollisterstier llc	Hymenoptera venom product-wasp venom protein (550 mcg)	Wasp venom protein	550 µg / vial
Jubilant hollisterstier llc	Hymenoptera venom product-white-faced hornet venom protein (550 mcg)	White faced hornet venom protein	550 µg / vial
Jubilant hollisterstier llc	Hymenoptera venom products-yellow hornet venom protein (550 mcg)	Yellow hornet venom protein	550 µg / vial
Jubilant hollisterstier llc	Mixed vespid venom protein multidose 13.0 ml (3900 mcg)	White faced hornet venom protein	1300 µg / vial
Jubilant hollisterstier llc	Venomil honey bee venom (120 mcg)	Honey bee venom protein	120 µg / vial
Jubilant hollisterstier llc	Venomil mixed vespid venom protein (360mcg)	White faced hornet venom protein	120 µg / vial
Jubilant hollisterstier llc	Venomil wasp venom protein (120mcg)	Wasp venom protein	120 µg / vial
Jubilant hollisterstier llc	Venomil white-faced hornet venom protein (120mcg)	White faced hornet venom protein	120 µg / vial
Jubilant hollisterstier llc	Venomil yellow hornet venom protein (120mcg)	Yellow hornet venom protein	120 µg / vial
Jubilant hollisterstier llc	Venomil yellow jacket venom protein (120mcg)	Yellow jacket venom protein	120 µg / vial
Jubilant hollisterstier llc	Wasp venom protein multidose 13.0 ml (1300 mcg)	Polistes spp venom protein extract	1300 µg / vial
Jubilant hollisterstier llc	Yellow jacket venom protein multidose 13.0 ml (1300 mcg)	Vespula spp venom protein extract	1300 µg / vial
Subcutaneous immunotherapy: pollen and non-pollen			
Alk-Abello	Center-al	Pollen and non-pollen	20000 unit / ml
Allergy Canada	Allergy Canada allergen extract	Allergenic extracts	0 unit / ml
Allergy Canada	Allergy Canada allergen extract - alum precipitated	Allergen extract - alum precipitated	100 unit / ml 1000 unit / ml 10000 unit / ml
Sublingual immunotherapy			
Stallergenes Canada	Oralair	Grass pollen allergen extract	100 unit 300 unit
Merck Canada	Grastek	Standardized timothy grass pollen	2800 unit
Merck Canada	Ragwitek	Standardized short ragweed pollen allergenic extract	12 unit

Appendix B: Special Authorization Form (Allergen)

	<p>Ministry of Health and Long-Term Care Ministère de la Santé et des Soins de longue durée</p>	<p><i>Send to:</i> Claims Services Branch PO Box 2300, Stn "A", LCD1 Hamilton ON L8N 4A2</p>	<p><i>Envoyez au :</i> Direction des services pour les demandes de règlement CP 2300, Succ "A", LCD1 Hamilton ON L8N 4A2</p>
Prescriber name and address/Nom et adresse du médecin		Microfilm no./N° du microfilm Special Authorization (Allergen) Autorisation spéciale (allergène) SAA-	
Section A – to be completed by Prescriber / Partie A – à remplir par le médecin			
<p>Dear Doctor: Authorization of allergen extract / epinephrine products as a benefit for the patient named is granted on behalf of the Minister of Health and Long-Term Care, provided that your patient has a Health Card or a Drug Benefit Eligibility Card valid for the month in which service is rendered. This Special Authorization (Allergen) is valid for use once only for allergen extract products.</p> <p>Please ensure that section A is completed before forwarding this authorization form to the allergen extract supplier or pharmacy (if applicable).</p>		<p>Docteur, L'autorisation de prescrire l'extrait allergénique / produit d'épinéphrine dans le cadre des prestations du Programme de médicaments de l'Ontario vous est accordée au nom du ministre de la Santé et des Soins de longue durée, à condition, toutefois, que la patiente ou le patient nommé soit titulaire d'une carte Santé ou d'une carte d'admissibilité au Programme de médicaments de l'Ontario valide pour le mois au cours duquel ce service est fourni. Cette autorisation spéciale (allergène) ne peut servir qu'une seule fois pour extrait allergénique.</p> <p>Veillez vérifier que la partie A est dûment remplie avant d'envoyer cette formule d'autorisation au fournisseur / à la fournisseuse de l'extrait allergénique ou à la pharmacie (si applicable).</p>	
CPSO/Prescriber number N° d'inscription à l'OMCC ou n° du médecin	Specialty code Code de spécialité	Patient date of birth Date de naissance du patient/de la patiente	Contents and concentration of allergen extract / Ingrédients et concentration de l'extrait allergénique
Patient surname/Nom de famille du patient/de la patiente	Init.		
Patient address/Adresse du patient/de la patiente		Prescriber signature/Signature du médecin	
		Date	
Health/Eligibility number (include any plan code prefix) N° de carte Santé/admissibilité au PMO (spécifiez le code de régime qui précède le numéro, le cas échéant)		Version	Note / Nota : After section A is completed send this form to Allergen Extract Supplier or pharmacy (if applicable). Une fois la partie A remplie, veuillez envoyer la formule au fournisseur/à la fournisseuse de l'extrait allergénique ou à la pharmacie (si applicable).
Section B – to be completed by Supplier / Partie B – à remplir par le fournisseur/la fournisseuse			
<p>Please ensure that the form contains all required information and signatures. Valid for one supply only for allergen extracts. Veuillez vous assurer que la formule porte tous les renseignements et signature nécessaires. Valide seulement pour un approvisionnement pour les extraits allergéniques.</p>			Supplier name and address/Nom et adresse du fournisseur/de la fournisseuse
ODP Supplier number / N° du (de la) fournisseur(se) du PMO	Date of service Date de prestation du service	DIN/FIN	
Long Term Care Facility (if applicable) Établissement de soins de longue durée (le cas échéant)	Quantity / Quantité	Days supply Approvisionnement (en jours)	
Drug/Extract cost / Coût du médicament / de l'extrait	Mark up / Majoration	Fee / Honoraires	Total claimed / Total demandé
<p>The information collected on this form, including those on paper and electronic media, is collected under the authority of S.13 of the Ontario Drug Benefit Act for the purpose of claims payment and drug utilization review. For information contact: Director, Drug Programs Branch, 3rd Floor, 5700 Yonge Street, Toronto, ON M3M 4K5 or call 416-327-8100. Les renseignements demandés dans les demandes de règlement du Programme de médicaments de l'Ontario, notamment celles présentées sur papier et sur supports électroniques, sont réunis aux fins de paiement et d'étude de la consommation de médicaments en vertu de l'article 13 de la Loi sur le régime de médicaments de l'Ontario. Pour obtenir de plus amples renseignements, veuillez vous adresser au directeur ou à la directrice des programmes de médicaments, 5700, rue Yonge, 3^e étage, Toronto, ON M3M 4K5, ou composer le 416-327-8100.</p>			I hereby certify that the Allergen Extract / epinephrine injectable product charged for herein has been provided on the date indicated in Section B to the person identified above and that the transportation and handling charges are not included. J'atteste que l'extrait allergénique / produit d'épinéphrine injectable facturé ci-dessus a été fourni à la date indiquée à la partie B à la personne identifiée ci-dessus et que le montant indiqué ne comprend pas les frais de transport et de manutention.
Authorized signature/Signature de la personne autorisée			Date
2772-87 (2014/11)			7530-4711

Appendix C: Webpages for Provincial Drug Formularies

Province	Webpage for Drug Formulary
British Columbia	http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp
Alberta	https://idbl.ab.bluecross.ca/
Saskatchewan	http://formulary.drugplan.health.gov.sk.ca/
Manitoba	http://web6.gov.mb.ca/eFormulary/
Ontario	https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
Quebec	http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx
New Brunswick	http://www.gnb.ca/0212/nbpdpformulary-e.asp
Nova Scotia	http://novascotia.ca/dhw/pharmacare/formulary.asp
Prince Edward Island	http://healthpei.ca/formulary
Newfoundland	http://www.health.gov.nl.ca/health/nlpdf/fmlsearch.asp
Yukon Territories	https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961::::
NIHB (Non-insured Health Benefits) Program	http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fourmir/pharma-prod/med-list/index-eng.php

Appendix D: Restriction Criteria for Allergen Immunotherapy

Jurisdiction	Allergen extract	Criteria
Nova Scotia	Allergy serum, Pollinex-R injection	<p>for immunotherapy with specific, standardized allergenic material, administered in high-dose schedules for carefully selected patients with a diagnosis of:</p> <ol style="list-style-type: none"> 1. IgE mediated anaphylactic reactions to insect stings or 2. severe, seasonal (lasting two or more years) or perennial IgE dependent allergic rhinoconjunctivitis when optimal drug therapy and allergen avoidance have not been sufficiently effective in controlling symptoms or 3. IgE mediated allergic asthma, specifically where there is a clear temporal association between exposure and signs and symptoms of asthma and when optimal drug therapy and avoidance measures have not been sufficiently effective in controlling symptoms <p>Note: The allergy serum must be dispensed from a pharmacy on prescription from a prescriber. Initial authorization is for two years, and can be continued for up to five years if improvement is noted.</p>
	Oralair	<p>For the seasonal treatment of grass pollen allergic rhinitis in patients that have not adequately responded to , or tolerated conventional pharmacotherapy</p> <p>NOTE: Treatment with Oralair must be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic disease. Treatment should be initiated four months before onset of pollen season and should only be continued until the end of the season. Treatment should not be taken for more than 3 consecutive years.</p>

Appendix E: Interview Questions

How long have you listed allergen immunotherapy on your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list these agents this way?
What was the basis for this listing (e.g., quantity limits, general listing)?
Do you have any studies comparing usage/costs before and after implementation of this listing?
Why are certain allergen immunotherapies NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?
Do you have any special restrictions regarding the use of allergen immunotherapy?

Appendix F: Tiered cost-sharing options

Prescription Drug Plan	Tier 1 (generic)	Tier 2 (preferred brand)	Tier 3 (non-preferred brand)	Tier 4 (specialty)
Plan A	\$5	\$28	\$55	25%
Plan B	\$2	\$20	\$40	N/A
Plan C	\$10	\$25	50%	25%
Plan D	\$4	\$17	75%	25%

Adapted from:

<http://www.cancer.org/treatment/findingandpayingfortreatment/managinginsuranceissues/medicare/medicarepartd/medicare-part-d-formularies-and-drug-coverage>

Appendix G: Select Allergen Immunotherapy Policies from Third-party Payers in the US

Aetna (http://www.aetna.com/cpb/medical/data/1_99/0038.html):

Aetna considers allergy immunotherapy administered in a medical facility medically necessary for the treatment of the following IgE-mediated allergies:

- Allergic (extrinsic) asthma
- Dust mite atopic dermatitis
- Hymenoptera (bees, hornets, wasps, fire ants) sensitive individuals
- Mold-induced allergic rhinitis
- Perennial rhinitis
- Seasonal allergic rhinitis or conjunctivitis

When *all* of the following conditions are met:

- Member has symptoms of allergic rhinitis and/or asthma after natural exposure to the allergen; *or*
- Member has a life-threatening allergy to insect stings (bees, hornets, wasps, and fire ants), *and*
- Member has skin test and/or serologic evidence of IgE-mediated antibody to a potent extract of the allergen, *and*
- Avoidance or pharmacologic therapy cannot control allergic symptoms or member has unacceptable side effects with pharmacologic therapy.

Aetna considers home administration of allergy immunotherapy experimental and investigational because its safety and effectiveness has not been established.

Aetna considers allergy immunotherapy experimental and investigational for all other indications, including the following because its effectiveness for these indications has not been established:

- Angioedema
- Atopic dermatitis (cover for dust mite atopic dermatitis)
- Chronic urticaria
- Food allergy
- Intrinsic (non-allergic) asthma
- Migraine headaches
- Non-allergic vasomotor rhinitis

Appendix H: Allergen Immunotherapy Extract Preparation Guidelines

Table 1: AAAAI Guidelines for Allergen Immunotherapy Extract Preparation

1. Qualifications of Extract Preparation Personnel:

- Compounding personnel must pass a written test on aseptic technique and extract preparation.
- Compounding personnel must be trained in preparation of allergenic products.
- Compounding personnel must annually pass a media fill test, as described in Addendum A.
- Compounding personnel who fail written or media fill test would be reinstructed and reevaluated.
- Compounding personnel must be able to demonstrate understanding of antiseptic hand cleaning and disinfection of mixing surfaces.
- Compounding personnel must be able to correctly identify, measure, and mix ingredients.
- Compounding personnel should be appropriately trained health professionals, including, but not limited to, registered nurses, licensed practical nurses, medical technicians, medical assistants, physician assistants, advanced practice nurses, and physicians.

2. Physician Responsibility:

A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in preparation of immunotherapy using aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files. The physician is responsible for providing general oversight and supervision of compounding.

3. Bacteriostasis:

Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25% or, if phenol concentration is less than 0.25%, the extract must have a glycerin concentration of at least 20%.

4. Dilutions prepared in accordance with manufacturer's instructions:

Allergen extracts must be diluted in accordance with antigen manufacturer's instructions.

5. Potency:

The manufacturer's expiration dates must be followed. Beyond-use dates for allergy extract dilutions should be based on best available clinical data.

6. Mixing of extracts with high and low proteolytic enzymes.

Separation of aqueous extracts with high proteolytic enzyme activities from other extracts is recommended.

7. Storage:

Extracts should be stored at 4°C to reduce the rate of potency loss or according to manufacturer's directions. Extracts beyond expiration date of the manufacturer are to be discarded. Storage must be in a designated refrigerator for medications, not used for food or

specimens.

8. Subcutaneous Injection:

Allergen extracts may only be administered intradermally or through subcutaneous injection unless US Food and Drug Administration–approved package insert or accepted standards of clinical practice permit another route of administration.

9. Aseptic Technique:

Preparation of allergy immunotherapy must follow aseptic manipulations defined as follows:

- The physician must designate a specific site, such as a countertop, in an area of the practice facility where personnel traffic is restricted and activities that may contribute to microbial contamination (eg, eating, food preparation, placement of used diagnostic devices and materials and soiled linens) are prohibited.
- The extract preparation area must be sanitized with 70% isopropanol that does not contain added ingredients, such as dyes and glycerin.
- Extract preparation personnel must thoroughly wash hands to wrists with detergent or soap and potable water. Substitution of hand washing by treatment with sanitizing agents containing alcohol and/or 70% isopropanol is acceptable.
- Necks of ampules to be opened and stoppers of vials to be needle-punctured must be sanitized with isopropanol.
- Direct contact contamination of sterile needles, syringes, and other drug administration devices and sites on containers of manufactured sterile drug products from which drugs are administered must be avoided. Sources of direct contact contamination include, but are not limited to, touch by personnel and nonsterile objects, human secretions, blood, and exposure to other nonsterile materials.
- After mixing is complete, visual inspection to be performed for physical integrity of vial.

10. Labeling:

Immunotherapy vials are to be clearly labeled with patient's name and beyond-use date of the vial.

11. Mixing log:

A mixing log is to be kept with information on the patient's name, extract used for mixing, mixing date, and expiration date and lot numbers.

12. Policy and Procedure Manual:

Practices preparing allergy extracts must maintain a policy and procedure manual for the procedures to be followed in mixing, diluting, or reconstituting of sterile products and for the training of personnel in the standards described above.

Table 2: US Pharmacopeia (USP) Chapter 797: Sterile Compounding Standards for Allergy Vaccine Preparation

Allergen extracts as compounding sterile preparations (CSPs) are single-dose and multiple-dose intradermal or subcutaneous injections that are prepared by specially trained physicians and personnel under their direct supervision. Allergen extracts as CSPs are not subject to the personnel, environmental, and storage requirements for all CSP microbial contamination risk levels in this chapter only when all of the following criteria are met:

1. Before beginning compounding activities, personnel perform a thorough hand-cleansing procedure by removing debris from under fingernails (using a nail cleaner under running warm water), followed by vigorous hand and arm washing to the elbows for at least 30 seconds with either nonantimicrobial or antimicrobial soap and water.
2. Compounding personnel wear hair covers, facial hair covers, gowns, and face masks.
3. Compounding personnel perform antiseptic hand cleansing with an alcohol-based surgical hand scrub with persistent activity.
4. Compounding personnel wear powder-free sterile gloves that are compatible with sterile 70% isopropyl alcohol (IPA) before beginning compounding manipulations.
5. Compounding personnel disinfect their gloves intermittently with sterile 70% IPA when preparing multiple allergenic extract as CSPs.
6. Ampule necks and vial stoppers on packages of manufactured sterile ingredients are disinfected by careful wiping with sterile 70% IPA swabs to ensure that the critical sites are wet for at least 10 seconds and allowed to dry before they are used to compound allergen extract as CSPs.
7. The label of each multidose vial of allergen extract as CSPs lists the name of 1 specific patient, a beyond-use date, and storage temperature range that is assigned based on manufacturer's recommendations or peer review publications.
8. Single-dose allergen extract as CSPs shall not be stored for subsequent additional use.