Summary of Basis of Approval

Reference Number: 86-0482, 88-0172, 95-1301, 95-1302, 95-1303 and 95-1305

Licensed Name: Allergenic Extract /Standardized Kentucky (June) Bluegrass (86 0482,*Poa pratensis*), Timothy Grass (88-0172, *Phleum pratense*), Meadow Fescue (95-1301, *Festuca elatior*), Sweet Vernal (95-1302,*Anthoxanthum odoratum*), Orchard Grass (95-1303,*Dactylis glomerata*),and Redtop Grass (95-1305, *Agrostis alba*)

Manufacturer: Allergy Laboratories, Inc., License No. 103

Introduction:

Allergy Laboratories, Inc., has submitted Supplements to their product license application for Allergenic Extracts to include the manufacture of Standardized Kentucky (June) Bluegrass (*Poa pratensis*), Timothy Grass (*Phleum pratense*), Meadow Fescue (*Festuca elatior*), Sweet Vernal (*Anthoxanthum odoratum*), Orchard Grass (*Dactylis glomerata*),and Redtop Grass (*Agrostis alba*) Pollen Extract in 50% glycerol (v/v). These extracts will be marketed as standardized extract labeled in Bioequivalent Allergy Units (BAU/ml).

I. Indications and Usage: Standardized Grass Pollen Extracts are used for the diagnosis and treatment of allergic disease to grass pollen. Diagnosis of allergic disease to these grasses is made through a combined medical history sufficiently complete to identify allergic symptoms to grass pollen and identification of grass allergy diagnostic skin testing. It is recommended that diagnostic skin testing (scratch or puncture) be performed with 10,000 BAU/ml grass pollen extracts. Grass pollen immunotherapy is intended for patients whose grass allergic symptoms cannot be satisfactory controlled by avoidance of the offending allergen or by the use of symptomatic medications.

II. Dosage Form, Route of Administration and Recommended Dosage:

Standardized Grass Pollen Extracts are supplied with potencies of 100,000 and 10,000 BAU/ml in 50% glycerol (v/v) in 10, 30 and 50 ml vials. For scratch testing, Standardized Grass Pollen Extracts are

supplied at 10,000 and 100,000 BAU/ml in 2 ml vials. For intradermal testing, Standardized Grass Pollen Extracts are supplied at 100 BAU/ml in 5 ml vials. The recommended dosage for puncture testing is 10,000 BAU/ml. The recommended dosage for intracutaneous testing and immunotherapy depends on the sensitivity of the patient (see package insert).

III. Manufacturing and Controls:

A. Manufacturing and Controls: The pollen source material is obtained from [redacted] The identity and purity of the source material is established by microscopic identification and by isoelectric focusing (IEF) gel electrophoresis. The pollen source material is extracted with 50% glycerinated extracting solution, concentrated, sterile filtered and filled into bulk and final containers as necessary. Tests were performed on each lot of the bulk Standardized Grass Pollen Extract and on each lot of the final container of Standardized Grass Pollen extract based on CBER's lot release protocol.

The relative potency of each lot is analyzed by a competitive ELISA assay against a CBER Reference Extract for each grass and a reference serum pool collected from grass allergic patients. Standardized Grass Pollen Extract will be labeled at 100,000 BAU/ml when it is shown to be equipotent to the 100,000 BAU/ml CBER Reference and will be labeled at 10,000 BAU/ml when it is shown to be equipotent to the 10,000 BAU/ml CBER Reference. The lots submitted in support of these Supplements were determined to contain 100,000 and 10,000 BAU/ml. The potency for 100 BAU/ml Standardized Grass Pollen Extract was assigned by dilution based on 10,000 BAU/ml extract.

B. Dating Period and Stability Studies: The interim dating period for these Standardized Grass Pollen Extract with potencies of 100,000 BAU/ml and 10,000 BAU/ml containing 50% glycerol (v/v) shall not exceed 36 months from the date of manufacture when stored at 2 - 8°C. The date of manufacture is defined as the date of the initiation of extraction of the source pollen material. The provisional dating period for 100 BAU/ml extract, containing less than 50% glycerin, shall be 12 months from the date of manufacture when stored at 2-8°C.

The expiration date of the 100 BAU/ml product shall not exceed the final expiration date of the 10,000 BAU/ml concentrate.

This 36 months of interim dating is supported by a minimum of 12 months of real time stability data submitted and the 36 months dating (manufacturer's storage) allowed for glycerinated unstandardized grass pollen extracts (21 CFR 610.53). The manufacturer will continue the stability study for up to 72 months based on the approved stability protocol. If at any time during the stability study, the extract fails to meet the limits set by the protocol, the manufacturer will inform CBER immediately and the lots could be resulted in a recall.

C. Validation: Two lots of each of the Standardized Grass Pollen Extracts have been evaluated at CBER for sterility, general safety, IEF, relative potency, total protein and glycerol content and were found to be satisfactory.

An official release must be obtained by the licensed manufacturer for each lot of these Standardized Grass Pollen Extracts manufactured. The release criteria are as follows:

1. A sufficient number of vials of each lot must be submitted to permit repetition of all required tests.

2. A written protocol giving the results of all required test for each lot will be submitted. The protocol will include the lot number of reference reagents used for ELISA and IEF tests. In addition, the pollen source material supplier and pollen source material lot numbers are to be specified.

D. Labeling: The labeling, including package insert, package label and container label have been reviewed for compliance with 21 CFR 610.60, 610.61, 610.62, 201.56 and 201.57, and found to be satisfactory. All labeling will contain the following caution: "Not interchangeable with non-standardized grass pollen extracts or grass pollen extracts labeled in AU/ml".

E. Establishment Inspection: The facilities for manufacturing these Standardized Grass Pollen Extracts were inspected in September 1995. The inspection findings showed compliance with Good Manufacturing Practices.

F. Environmental Assessment Report: The applicant has filed an Environmental Assessment Report (EA) for these Standardized Grass Pollen Extracts. The applicant has concluded that there will be no measurable impact on the environment. Following review of the EA, CBER has determined that this licensing action does not adversely affect the environment and that the manufacturer is in compliance with all applicable Federal, State and local environmental regulations.

IV. Pharmacology:

The diagnostic use of allergenic extracts for scratch, puncture, prick or intradermal testing produces a characteristic wheal and flare response at the skin test site. This skin test response is the result of mediators released from mast cells or basophils which possess IgE directed against component(s) of the allergenic extract on their membranes. The cross-linking of at least two of these IgE molecules by the appropriate allergen causes degranulation of the sensitized cell and release of its mediators. The mechanism by which immunotherapy achieves hyposensitization is not completely understood. There is an increase in "blocking antibody" (IgG) titer and in some patients a decrease in specific IgE, a decrease in histamine release to specific allergen, and an increase in allergen specific suppressor cell populations.

V. Medical:

There is substantial general clinical experience with non-standardized Grass Pollen Extract in the US and in Europe. The manufacturer provided data comparing two previous non-standardized lots for each grass (only one lot for orchard, manufactured in 1993 and 1995) to CBER Reference extract, (100,000 BAU/ml). Most of the lots were found to be equal or slightly more potent than the Reference by ELISA competition assay. There are no substantial changes between the manufacture of non-standardized and standardized extracts. In 1994, the Allergenic Products Advisory Committee recommended the licensing of standardized grass extracts for diagnosis and immunotherapy. As a reference for the skin test dose and size of skin test reactions, skin test data were obtained with the CBER Grass Reference extracts.

The use of these Grass Pollen Extracts for diagnostic purposes is intended as an adjunct to a carefully taken allergic history and complete physical examination. Skin testing by scratch, puncture, prick and intradermal methods using allergenic extracts has been shown to be of value both in defining the atopic status of the individual and in demonstrating the presence of skin-sensitizing IgE antibody against the suspected allergens. The sensitivity of patients to an allergenic extract will vary widely. Scratch, puncture and prick tests will usually be positive in highly sensitive patients and are usually much safer than intradermal tests; however, they may fail to produce positive reaction in patients having a moderate or low degree of clinical sensitivity in which case intradermal testing may be necessary. These Grass Pollen Extracts are also intended for immunotherapy following the clinician's assessment regarding whether the offending allergens are present in the area where the patient lives and whether exposure is correlated with positive skin test results and clinical symptoms.

A. Skin testing: The instructions for diagnostic use of these products specify dose and route of administration, use of positive and negative controls, and criteria for interpretation of positive tests. Individuals with histories compatible with Grass pollen allergy were skin tested with the CBER Grass Reference extracts by puncture and intradermal methods. There were no serious adverse events observed.

The results shown in Table 1 were observed with 10,000 BAU/ml CBER extracts administered to 15 highly sensitive grass allergic persons by the puncture method. The intradermal doses of grass pollen extracts (CBER reference) required to elicit the 50 mm sum of erythema are shown in Table 2.

Table 1. Puncture data with 10,000 BAU/ml grass pollen extracts

Reference pollen	FDA Lot	N	PΣE *(mm) Mean	PΣE *(mm) Range	PΣW **(mm) Mean	PΣW **(mm) Range
June	E3-Jkb	15	77.3	47 - 107	15.9	6 - 28
Timothy	E6-Ti	15	88.3	51 - 109	16.9	8 - 40
Meadow Fescue	E4-MF	15	81.1	57 - 115	11.9	7 - 22
Orchard	E4-Or	15	84.3	57 - 111	14.1	9 - 19
Redtop	E4-Rt	15	77.1	42 - 98	14.1	8 - 19
Sweet Vernal	E4-SV	15	81.2	28 - 123	15.7	8 - 30

* PΣEz: Sum of erythema of the longest and orthogonal diameters.

** PΣW: Sum of edema (wheal) of the longest and orthogonal diameters.

Table 2. Calculated interdermal dose of CBER reference grass pollen extracts to elicit 50 mm sum of erythema.*

Reference pollen	FDA lot	Mean** (BAU/ml)	Range (BAU/ml)
June	E3 -Jkb	0.02	0.1 - 0.004
Timothy	E6 -Ti	0.02	0.6 - 0.002
Meadow Fescue	E4 - MF	0.02	0.9 - 0.002
Orchard	E4 - Or	0.02	1.9 - 0.002
Redtop	E4 - Rt	0.02	0.8 - 0.004
Sweet Vernal	E4 - SV	0.02	1.0 - 0.002

* Sum of the longest and orthogonal diameters.
**0.02 BAU/ml = 1:500,000 v/v dilution of 10,000 BAU/ml extract and 1:5,000,000 v/v dilution of 100,000 BAU/ml extract.

B. Immunotherapy: The instructions for therapeutic use of the product specify the initial dosages, dosage increments, and maximum dosages. The optimal treatment dose must be based on the clinical response of each patient.

C. Adverse Reactions: Anticipated adverse local and systemic reactions are described in the labeling. Since there is no change in the manufacturing process from non-standardized to standardized extract and the fact that the potency of standardized procuct is within the range of potencies for non-standardized products, it is expected that the risk of adverse reaction will be equal or less than the previously distributed non-standardized extracts. Allergenic extracts are the only products in which patient hypersensitivity to the product is one essential indication for its use, therefors, life-threatening and/or fatal allergic reaction can occur. To inform physicians of the risk of life-threatening reactions from use of these products, a prominent warning box is placed on the label.

VI. Phase 4 study

A Phase 4 study to evaluate the products' risks, benefits and optimal use will be initiated after the approval of these Standardized Grass Pollen Extracts. A minimum of — volunteer allergic patients will be selected for the study based on a protocol submitted by Allergy Laboratories. The

study will be performed at the , and
is anticipated to be completed in 7 to 18 months.

Yuan Lin

Yuan Lin, Ph.D. Chair

Martha F. Monser

Martha Monser, Committee Member