

**DRAFT GUIDELINE FOR THE DESIGN OF CLINICAL TRIALS
FOR EVALUATION OF SAFETY AND EFFICACY
OF ALLERGENIC PRODUCTS FOR THERAPEUTIC USES**

November, 1988

(Revised)

For further information regarding the guideline, please contact:

Paul, C. Turkeltaub, M.D.
Laboratory of Allergenic Products (HFB-620)
Center for Biologics Evaluation and Research,
Food and Drug Administration
8800 Rockville Pike
Bethesda, MD 20892
(301) 496-4204

Comments regarding this guideline should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. Comments should be identified with docket number 85D0480.

Draft Guideline for the Design of Clinical Trials for Evaluation
of Safety and Efficacy of Allergenic Products for Therapeutic Uses
Center for Biologics Evaluation and Research (CBER)

TABLE OF CONTENTS

I. General Methodology	3
A. Selection of subjects	3
1) Clinical Histories	4
2) Medication requirements	4
3) Assessing severity	4
4) Selection criteria	4
5) History of prior immunotherapy	4
6) Ages of patients.....	5
7) Patient disease entities	5
8) Skin sensitivity.....	5
9) Skin sensitivity cut-off.....	5
10) Exposure estimate	5
11) Records of patients not included.....	6
12) The method of acquisition	6
B. Number of Patients	6
C. Randomization of Patients	6
D. Study Control.....	7
E. Blinding.....	7
F. Dosage considerations.....	7
G. Mverse Reactions.....	8
1. Reporting by patients:	8
2. Systematic reporting by physicians:.....	8
H. Patient Compliance:.....	9
I. Assessment of Benefit:.....	9
J. Natural Exposure to Allergen:	10
K. Monitoring:	10
L. Data Collection and Recording:.....	11
M. Data Presentation:	11
N. Statistical Analyses.....	12
O. Absorption, Distribution, Metabolism, and Excretion:	12
P. Tests for Safety:.....	12
II. Phases of Clinical Allergen Evaluation:.....	13
A. Phase I.....	13
B. Phase II.....	13
C. Phase III.....	13
D. Phase IV.....	13
III. Subject and Setting A.....	14
A. Phase I studies.....	14
B. Phase II and III studies.....	14

Revised 7/11/86, 5/28/87, and 11/3/87 following discussion at the Allergenic Products Advisory Committee meeting 6 26 86 and after review of submitted comments. The original version was announced on October , 22, 1985 in the FEDERAL REGISTER with the comment period extended in the 2/7/86 FEDERAL REGISTER.

INTRODUCTION: This document is concerned with clinical methodologies which are intended to demonstrate that an allergenic product is safe and effective for treatment of allergic disorders. The document provides suggestions by the Center for Biologics Evaluation and Research (CBER) for allergenic product manufacturers and other Irk, sponsors for designing clinical studies to assess the safety and efficacy of allergenic products for therapeutic uses. It is anticipated that these guidelines will be used during product development to assist in establishing the safety and efficacy of new allergenic products or standardized extracts for which claims of safety and efficacy for immunotherapy are to be made in the labeling. This document does not address guidelines for clinical trials designed to determine the efficacy of allergenic products for diagnostic uses.

Since this Draft Guideline is not all-inclusive, and some parts may not be applicable to all situations, the CBER will review the adequacy of specific clinical trial designs on a case-by-case basis. The general characteristics for adequate and well-controlled studies are outlined in 21 CFR 314.126.

BACKGROUND: Issues related to the manufacture and control testing of the product and appropriate in vitro and preclinical studies of safety are not discussed in detail in this document. They should be reviewed on an individual basis with CBER for inclusion in specific Ila) and product license applications. The following discussions presuppose that the product has been characterized, standardized, assigned potency units, tested for stability, and has met all the requirements of CBER evaluation of toxicity prior to its introduction into humans. It also presupposes that the IND sponsor or licensee is familiar with the principles concerning the conduct of clinical studies, institutional review, and informed consent. Methods acceptable to CBER for standardizing allergenic extracts and assigning units to reference preparations are detailed in the "Methods of the Laboratory of Allergenic Products" manual available from the Center for Biologics Evaluation and Research, Laboratory of Allergenic Products. A "Protocol for Real Time Stability Studies of Allergenic Extracts," Feb.1987, is also available from the Laboratory for guidance in standardizing allergenic extracts.

I. General Methodology

A. Selection of subjects.

Selection of subjects for study should be viewed in the total context of the study. "hose subjects studied should be representative of well-defined segments of the allergic population in whom it is anticipated this product will be used therapeutically. In each instance the populations used for study should depend on the nature of the questions asked.

Therapeutic studies presuppose that adequate diagnostic criteria have been established. In view of the paucity of data relevant to diagnostic efficacy for many FDA standardized allergens, the CBER should be consulted before initiating any study in order to prevent the use of resources and volunteers on an activity that may later be determined to be unacceptable. Because the patient history is critical to selection of a well-defined patient population and patients must be able to understand and complete a variety of patient data self-reporting forms, it is important to obtain evidence directly from the patients that they understand what is expected and are able to express themselves adequately in writing. This can be ascertained by having patients complete forms regarding their clinical history which can to independently evaluated by the investigator for patient suitability.

For therapeutic studies it is preferable that patients be selected as follows:

1) Clinical Histories

Patients should have clinical histories of allergic disease following exposure to the allergen of interest of more than 2 years duration. The pattern of symptom severity, (for example, 0=absent, 1=mild, 2=moderate, 3=severe, interferes with sleep and/or routine activity) should be estimated by the patient for each month or each season of the prior year and related to natural allergen exposure in that area. Severity of the patient's disease should be estimated by a variety of methods, including patient recollection, patient records if available, independent evaluation by the investigator, or determined by prospective use of symptom diaries. The method for scoring symptom severity should be well-defined to reduce interpatient and investigator variability in interpretation. When feasible, the symptom scoring method used to assess severity of past history should be similar to the method used for scoring of prospective symptoms. Where the allergen of interest is an identifiable source, e.g., animal allergy, the frequency and duration of exposure as well as severity of symptoms following exposure should be documented in addition to any seasonal symptoms. As a minimum, the patient's history of disease severity obtained by patient self-reporting should be a part of the patient record.

2) Medication requirements

Medication requirements (e.g. average number of tablets and sprays per day) should be estimated for each month or each season in the previous year for control of allergic disease and should be reported based on patient recollection, patient records if available, or prospective evaluation. The patient should comment on the degree of symptomatic relief obtained. The need for use of medication following exposure to a well-defined allergen source, e.g., animal allergy, should also be specified if applicable. As a minimum, the patient's history of medication usage and relief, obtained by patient self-reporting should be a part of the patient record.

3) Assessing severity

Similar approaches to the estimation of the severity and requirement for and adequacy of medication for treatment of a coexistent allergic disease such as asthma should also be obtained as above.

4) Selection criteria

Selection criteria for patient inclusion/exclusion in the study should specify a cut-off based on the severity of symptoms, medication requirements, and whether the patient symptoms are adequately controlled by ancillary medication.

5) History of prior immunotherapy

History of prior immunotherapy should be obtained including the allergens used, the duration of treatment, date of last treatment, and response to treatment (beneficial as well as adverse effects). Previously immunized patients may be included in therapeutic studies as a separate subgroup.

6) *Ages of patients*

New allergenic products should be studied in patients above the age of legal consent and followed with studies in children if indicated.

7) *Patient disease entities*

Patients with identified disease entities - defined by specifying an etiology and syndrome, (e.g., ragweed hay fever, grass hay fever, cat asthma, etc.) are suitable for study. Because it may not be possible to find a sufficient number of patients with single disease entities, patients with other allergic diseases (e.g. hay fever plus asthma) may be studied as a subgroup. Because exposure to the etiologic allergen may not be able to be restricted to a single source, such as cat, a group of allergens producing symptoms at the same time, e.g., grasses, may be studied. However, in this circumstance, the degree of sensitivity to the mixed extract should be determined as well as for each component. Patients who require medications that may suppress allergic symptoms or modulate immunological responses for indications other than the index disease under study should be considered a special population and studied as a separate subgroup. Patients with other disorders which may exacerbate or contribute to symptoms of the disease under study should be identified and studied as separate subgroups. Statistical analyses of these subgroups may subsequently permit pooling of the data.

8) *Skin sensitivity*

Skin sensitivity to the therapeutic and diagnostic allergenic extracts should be determined for each patient by a method with defined accuracy and reproducibility that is acceptable to the CBER. A procedure for evaluating skin sensitivity to allergens is detailed in the "Methods of the Allergenic Products Branch" which can be obtained from the Laboratory of Allergenic Products, CBER.

9) *Skin sensitivity cut-off*

Selection criteria for patient inclusion/exclusion should specify a cut-off based on skin sensitivity to the diagnostic reagent. Guides for establishing these cut-off values should be based where possible on studies of the diagnostic efficacy of skin tests in which skin sensitivity of a certain degree is predictive of the allergic disease under study and/or the risk of adverse reactions and/or benefit during immunotherapy.

10) *Exposure estimate*

Because the severity of allergic disease is related to the duration and intensity of exposure to the allergen of interest, it would be helpful for each patient who is accepted into the study to provide an estimate of the time of exposure (hours per day or per week) to the allergen of interest during the previous year. This can be estimated by patient recollection (e.g., the

amount of time spent in unfiltered air for outdoor allergens, frequency and duration of exposure to identifiable allergens, e.g., animals). It would be important to know whether the patient anticipates a change in their exposure (e.g. change in occupation -such as outdoor occupation to white collar worker; change in indoor environment such as the addition of pets, air conditioning, etc.) during the time of the study.

11) Records of patients not included

A record of each patient screened but not included in the study should be maintained with an explanation of his/her ineligibility.

12) The method of acquisition

The method of obtaining prospective patients for interview should be specified.

B. Number of Patients

The overriding consideration should be that the planned studies provide sufficient data while keeping to a minimum the number of subjects at risk. This often requires the contribution of a biostatistician to perform proper sample size calculations. Considerations in sample size estimates should include: 1) the magnitude, duration (e.g. whole pollen season), and variability of the difference in response between the groups to be detected; 2) the desired assurance against a false positive finding (alpha-level); 3) the acceptable risk of failure to demonstrate the response when it is present in the population, a false negative finding (beta-level); 4) the type of study design. The elements used to determine the sample size estimate should be specified in the protocol. If the study is to be used to demonstrate efficacy in support of a product license the adequacy of the number and type of patients to be studied as well as the number of studies required to conclusively demonstrate efficacy should be discussed with CBER to insure that CBER and the product sponsor are in agreement. In general, a sufficient number of adequate and well-controlled studies in different centers should be planned to conclusively demonstrate reproducibility of efficacy and safety. This may be modified on a case-by-case basis. Guidance in setting the magnitude of the difference in response between the treatment and placebo groups to be detected and the number of patients studied should be obtained from the published literature where available and from studies of dose-dependent, adverse, and beneficial effects with the proposed product (see F. Dosage considerations). If a one-sided hypothesis is considered, reducing alpha to 0.025 is suggested to provide the same degree of clinical evidence to declare a treatment effective, regardless of whether a one-sided or two-sided hypothesis is used.

C. Randomization of Patients

The method of randomization and the analysis performed to verify how well the randomization procedure worked should be specified. Randomization based on random number generation is often a satisfactory method of assigning patients to various treatment groups. At times it may be preferable to stratify patients into blocks prior to their randomization to treatment groups. Such block randomization will facilitate statistical comparisons within strata by ensuring comparable sample sizes in each treatment group. Stratifying variables may include the following: age, sex, severity of prior disease (including requirement for medication), skin sensitivity, history of prior immunotherapy, and anticipated degree of allergen exposure. The allocation of patients to treatment groups should be carried out by an individual who is not aware of the personal identity, clinical

history, skin sensitivity, or identity of the therapeutic agent to which the patient is allocated. Because patients in natural exposure studies cannot be matched for all relevant variables influencing disease (e.g., duration and degree of allergen exposure), an unpaired analysis of the treatment groups is appropriate.

D. Study Control

The objective in general of initial human trials with a new product is to assess safety and determine the doses at which various biological and clinical effects are observed. These early studies in certain circumstances may often best be done on an open (nonblind) basis. Placebo groups, however, should be included in such trials if the evaluation of adverse and beneficial effects rely on subjective assessments by either patient or investigator. The most important requirement for early phase clinical trials is that patients be under careful observation. In some instances where appropriate, to minimize the number of subjects exposed to the risks inherent in any study, preliminary efficacy evaluation may be accomplished by open studies compared against a historic baseline.

During all phases of clinical investigation the objective in using a placebo is to control the study adequately. In some studies, for example, when comparative claims of safety and efficacy are to be established, the use of an appropriately standardized, unmodified active control allergen in addition to a placebo is necessary. These studies can be designed to ascertain the degree of safety and effectiveness of the investigational allergens compared to one or more standardized allergens labeled for the same indication. Due to the complexity of these studies, especially in determining bioequivalent allergenic doses of each standardized product in each patient, the CBER should be consulted before initiating any study in order to prevent the expenditure of resources for a clinical trial that may later be determined to be unacceptable.

In certain diseases or conditions where the natural course of the disease or the condition is predictable, and is not likely to vary, and in which objective measurements of therapeutic or prophylactic response can be made, carefully executed open studies may be compared to the historical data to provide preliminary evidence of efficacy. With the majority of investigational allergens, however, pivotal studies providing conclusive evidence of efficacy will require placebo-controlled trials.

E. Blinding

Regardless of the use of placebo or active controls, study groups and investigators should not know which patient is receiving which product or control (double-blinding). In certain instances where safety and efficacy data are obtained from patient diaries, blinding of the data monitor who is scoring and/or interpreting the patient diaries, is also advisable. The adequacy of blinding should be assessed prior to and following the study to ensure that the blinding procedures are effective. This will require documentation that the "placebo" and allergen under study appear identical prior to injection. In circumstances where the "placebo" has skin test reactivity, data should be provided which documents that the dose of placebo and the active agent to be administered elicit similarly intense skin reactions.

F. Dosage considerations

It is desirable to ascertain a range of effectiveness so that the lowest effective dose and the highest safe and effective dose are determined. Products that are normally administered prior to

allergen exposure should be administered so that sufficient time is allotted to permit completion of the dose regimen prior to allergen exposure. This will avoid confounding the effects of environmental allergen exposure with the effects of treatment.

The dose regimen should be based on potency units mutually agreed to by the sponsor and the CBER. The interval between injections, dose increments, initial peak doses, and maintenance doses should be specified. The clinical criteria for dose escalation, reduction, and repetition should be clearly stated. These criteria may be related to factors such as size, duration and/or severity of local reactions, and/or systemic reactions, and/or clinical state of patient at time of dosage administration and/or missed doses and/or intercurrent illness. The time allocated for dose administration should take into account the effect the above factors may have in prolonging the regimen.

G. Averse Reactions

Adverse reactions should be systematically recorded to permit an accurate assessment of safety (See P., Tests for Safety). Adverse reactions should be obtained by a variety of reporting methods so as to include spontaneous reporting by the patient at and between visits, as well as systematic adverse reaction ascertainment at each visit by the investigator.

1. Reporting by patients:

Patients should be provided a self-reporting form (and ruler if applicable) to measure and record the size of local reactions (wheal, erythema) as well as the severity, duration, and requirement for treatment of pain, itching, heat, swelling, and erythema. Written self-reports should be made at specified time intervals following allergen administration, e.g. 6, 12, 24, 48, and 72 hours post dosage. All subjective symptoms experienced should be recorded by the patient with an assessment of onset, duration, severity, description, requirement for treatment and probability of relationship to treatment. All intercurrent illnesses, including treatment, severity, duration, and relation to the product administered, should be recorded.

If adverse reactions are not observed, a statement that no reaction occurred should be solicited from patients to verify the absence of adverse reactions.

2. Systematic reporting by physicians:

Prior to each treatment (including the first) an adverse effect reporting form evaluating a number of relevant symptoms and systems should be completed by the physician. A similar report should be completed prior to and following administration of the allergen for each dose. All intercurrent illnesses should be recorded by the physician and described as to onset, duration, severity, requirement for treatment and attribution to the product administered.

Local reactions should be quantified at a specified time interval following dose administration (e.g. 15 minutes) as to size of wheal and erythema and characterized as to severity of heat, pain, itch, and requirement for treatment.

A scoring system to quantify severity of each symptom reported, such as 0=absent, 1=mild, 2=moderate, 3=severe, 4=interferes with sleep and/or routine activity, should be well-defined to reduce interpatient and interinvestigator variability in interpretation and should be assigned to each symptom reported in G1 and 2.

H. Patient Compliance:

Protocols should state clearly how patient compliance is to be monitored and the degree of compliance acceptable for continuation in the study or for analysis of data. If it is apparent at follow-up visits that patients are not complying, the reasons for their noncompliance should be recorded. Efforts to maintain these patients' participation in the study should be as conscientious as those for patients who are complying. All patients initially included in studies should be reported regardless of degree of compliance. Rules for excluding data based on lack of compliance should be specified in the protocol. All patients who drop out should be contacted to determine the reason for dropping out. When it is not possible to contact the patient, the sponsor should document the efforts made to contact dropouts. A list of reasons for patient drop out should be provided by the investigator. These reasons may include but are not limited to 1) ineffective treatment, 2) effective treatment, 3) adverse reactions, 4) personal reasons, 5) failure to comply, 6) other. Patient dropouts should be contacted to determine the reason for dropping out prior to breaking the code.

I. Assessment of Benefit:

Quantitative measures of each relevant symptom severity and duration should be recorded by patients on at least a daily basis along with use of all medications. Each daily report should include an estimation of the amount of time spent exposed to the allergen (for example, time outdoors or in unfiltered air for outdoor aeroallergens) as well as an indication of exposure to a novel environment or development of an intercurrent illness which may interfere with assessment of symptoms

The severity of disease for each day using a well-defined scoring system to reduce interpatient and inter investigator variability in interpreting the scores should be estimated by a total score including use of medications as well as severity and duration of symptoms. Rules for excluding data due to changes in environment (e.g. vacations, trips out of the area, exposure to other allergens, etc.) or to intercurrent illness or lack of compliance should be specified prior to breaking the code by the individual reviewing the patient diaries.

Because symptom diaries are completed by the patient, detailed instruction in completing the diaries and interpreting the scoring system should be provided to the patients so that an accurate and unambiguous assessment of symptoms can be made. A completely filled in diary should be provided as an illustrative example to the patient along with instructions for use. Symptom diaries should be collected on a regular basis, e.g., weekly. Following completion of each diary, the patient should sign the form attesting that all symptoms and medication use have been recorded on the form and all blank spaces have been filled in. Patient compliance with the record keeping should be regularly assessed (e.g. weekly). When data are received by the investigator, they should be audited for completeness, accuracy, and consistency. Any changes or additions made to the raw data sheets have to be documented by whom made, when, initialed by all involved and submitted with the data.

Medications provided to patients for control of symptoms should be administered in a systematic manner beginning with least potent and progressing to the most potent depending on patient response. Each medication used for control of symptoms may be assigned a weighted score reflecting its relative potency. Because of the importance of medication score in assessing efficacy, special attention needs to be paid to accurately recording medication use and reliance of each study patient prior to entry in the study (e.g. type of drug used, dose, route, frequency, duration, adverse and beneficial effects) to insure that each study group is well-matched at baseline in their use and reliance on medications (see "C Randomization of Patients"). The protocol should specify the severity of the clinical conditions required to prompt administration of antiallergic medication during the study and specify the conditions for replacing a less potent antiallergic medication with a more potent medication. The administration of all medication during the study will require contact with the investigator and a consistent method which is applied to all study participants for eliciting information which will be used to assess the need for institution and replacement of medication. This method should be specified in the protocol, in detail, along with the appropriate forms where this information is to be systematically collected and documented for each participant.

When assessment of benefit is based on objective test procedures, the statistical reproducibility and accuracy of the test measures should be known.

At the end of the study, it would be helpful to assess patient acceptance of the treatment by requesting information such as whether the patient would undergo this treatment in the future or whether the patient's assessment of the benefit of treatment outweighed the time and discomfort required for treatment. For allergenic products or dosage forms different from conventional, standardized extracts, inclusion of an unmodified, appropriately standardized extract using allergenically equipotent doses in comparison to the proposed product and the placebo is invaluable in establishing any comparative claims for the benefit and risk of the new product.

J. Natural Exposure to Allergen:

It is assumed that in addition to any challenge studies (where dose and duration of allergen exposure is controlled) which are performed to evaluate efficacy, therapeutic efficacy trials will be designed to assess the clinical effects of the investigational product on a patient during natural exposure to the allergen of interest. Natural exposure trials should quantitatively estimate allergen exposure both in terms of units of allergen per volume of air in the atmosphere to which the patient is exposed at a specified time interval and the length of time the patient was exposed to the allergen during that time interval. The estimated time of exposure to the allergen of interest can be recorded by the patient based on the time spent in specific environments (e.g., outdoor or indoor air (not filtered)) and can be included on the symptom diary form. The estimated quantity of airborne allergen (e.g. pollen, mold counts) should be obtained by the investigator to determine the relationship between allergen intensity, exposure, duration, and symptom severity. Because the patient's environment is critical in producing disease, specific rules for excluding data due to changes in the patient's environment (e.g., vacations, trips out of the area, etc.) need to be specified. In circumstances where a natural allergen challenge is to be conducted under controlled conditions, consideration should be given to blinding the subject to the challenge allergen to avoid conditioned responses confounding allergic responses.

K. Monitoring:

The sponsor is responsible for the proper monitoring of all studies performed on an investigational new allergenic product. Close contact between IND sponsors and clinical investigators should be maintained to assure that studies are well-planned, realistic and executed properly. The monitor serves a unique role in assessing adequacy of blinding procedures, as well as observing and documenting how closely the protocol is being followed. The monitor can also assure that the potential benefits of the product continue to outweigh any risk during the study to determine whether the study should continue. In addition, there should be continuing contact between the sponsor (monitor) and the FDA to assure that studies will provide meaningful information at each stage of product development.

L. Data Collection and Recording:

Complete and accurate recording of the data derived from clinical trials is needed in order to reach valid conclusions regarding safety and efficacy. In general, the record should contain: 1) the lot numbers, characterization, and potency of the allergenic extracts studied for diagnosis and therapy, 2) patient entry and exclusion criteria, 3) the diagnostic and therapeutic procedures followed during the trial, 4) the "case history" of each patient, 5) the criteria for evaluating the allergic disease, laboratory, physical examinations, and side effects, and 6) other variables which may have an influence on the results of the trial. To the extent that previously standardized and validated forms and methods are available and appropriate to assess the populations and allergens being evaluated, these are preferred since results are then more easily interpreted. The emphasis or extent of documentation for measures of safety versus efficacy or degree of specificity regarding efficacy will vary with the phase of the study.

M. Data Presentation:

Once the data have been accurately collected during the clinical trial (documentation), the data should be organized in a form which allows the results to be analyzed in the most meaningful fashion. For a single clinical trial or study done by one investigator, this may be done by: 1) preparing an individual case record for each patient, 2) summarizing the data according to the treatment groups (or other meaningful groupings) in tabular and graphic form (essentially showing frequencies), and 3) performing appropriate statistical inference tests to indicate whether observed results are likely or unlikely to have occurred by chance. The ways in which the data may be presented will vary with study design but should be appropriate to the measures employed and the design of the trial. The use of well-validated and documented statistical procedures enhances the interpretation of results but novel approaches which are well-documented and enhance the understanding of the results of a trial are encouraged. It should be possible in a well-documented and well-presented study to trace an individual patient's raw data through to its contribution in arriving at a probability statement.

While the previous paragraph dealt with data presentation from single clinical trials, it is usual that evidence considered sufficient to establish safety and efficacy is derived from multiple studies carried out over time and at different locations by many investigators. To meaningfully interpret these studies requires that they be considered together. This may be done by comparing the results of one study to another, or where appropriate by combining or pooling the data from several studies into a larger analysis. Where efforts of this type are undertaken, the rationale for pooling and the procedures employed should be clearly given.

N. Statistical Analyses.

The experimental design should include the statements of the null and alternative hypotheses, as well as the alpha-level at which the null hypothesis will be tested.

A preferred corresponding statistical analysis is inherent in certain designs and should be stated. The assumptions underlying the analyses need to be tested and the effects of any violations have to be assessed. When alternate analyses are used (e.g. parametric vs. nonparametric) the underlying reasoning should be presented for the choice made. The extent and limitations of the statistical inferences which can be drawn from the study should be discussed. The robustness of the statistical analysis should be demonstrated by analyzing all patient data and comparing these analyses with subsets of data which have been adjusted by patient exclusion for confounding variables (e.g., incomplete data, intercurrent illness, trips out of the area, etc.) and patient subgroups. When multiple comparisons are anticipated, consideration to apportioning alpha should be addressed. In general, pooling of data from different sources is not acceptable. However, studies undertaken as multi-center trials may employ data from all centers in a single (stratified) analysis. The appropriateness of doing so depends on the relative contribution (sample size) of each center and the reproducibility of results from center to center. The latter should be addressed statistically. The proposed analysis should anticipate dropouts and address how the analysis is to be carried out for different levels of dropouts.

O. Absorption, Distribution, Metabolism, and Excretion:

Because of the nature of allergenic products, each investigational product should be evaluated individually to determine how much of an assessment is meaningful at each stage of the investigation. Studies in humans may confirm whether the absorption, distribution, metabolism, and excretion is similar to that observed in any preclinical immunological, toxicology, and metabolic studies. The need for a complete study of the absorption, distribution, metabolism, and excretion of an allergenic product is contingent on the specific product in question, its potential usefulness and stage of development.

Because the type and extent of these studies is contingent on the product and the state of scientific knowledge and capability, the sponsor should propose evaluations which are meaningful at each stage of product development. Studies designed to address whether the product is rapidly absorbed following injection and whether the product is biodegraded and eliminated should be considered. The staff of CBER will be available to advise the sponsor regarding the adequacy of the sponsor's proposals.

P. Tests for Safety:

The type and frequency of laboratory parameters and other tests appropriate for the determination of clinical safety will depend upon the composition of the product being investigated. The Center for Biologics Evaluation and Research is prepared to work with the developers of allergenic products to facilitate the implementation of appropriate laboratory tests.

Generally, baseline and post-treatment studies of hematologic and renal effects, as well as blood chemistries, are considered important. If the product is intended for repetitive administration, data with regard to any long-term, cumulative effects, including immunologic sequelae, are considered relevant.

Preclinical tests of product safety do not obviate the need for careful clinical monitoring of safety parameters. Laboratory or animal tests of product safety are of value only to the extent that they can predict clinical safety. In immunotherapy studies of allergic disease, clinical observations are often an earlier and more dependable index of an adverse allergic effect than a laboratory test. For example, clinical manifestations of local and systemic allergic adverse reactions are reliable manifestations of allergic side effects often occurring in the absence of any abnormality in routine laboratory tests. Since overdose effects are related in part to the skin sensitivity of the patient to the treatment allergen, inclusion of patients most highly sensitive to the therapeutic agent at the earliest trials will facilitate development of safe dose regimens as well as generate safety data on the population at highest risk from use of the product. The adequacy of the studies of safety and the numbers and types of patients to be studied to establish safety in a product license should be discussed with CBER.

II. Phases of Clinical Allergen Evaluation:

A. Phase I.

This, in general, constitutes the initial human experience with the product. Such studies may be conducted in subjects with the appropriate allergic sensitivity and uncomplicated allergic disease and are intended to determine the immunologic actions and metabolism of the product, the side effects associated with varying doses and, if possible, to gain early information of dose-dependence for effectiveness. Absorption, distribution, metabolism, and excretion studies of allergenic products, where indicated, are considered to be Phase I clinical studies.

Phase I studies may not be necessary for: 1) A product which has been extensively studied abroad. 2) A product that has been studied previously for other indications. 3) Marketed drugs which are being investigated by other manufacturers.

In the above cases, it is usually feasible to bypass Phase I after consultation with the CBER and proceed directly to Phase II.

B. Phase II.

These studies are designed to provide preliminary evidence of clinical efficacy and may progress from carefully conducted open or single-blind studies in appropriate patient groups toward controlled studies designed to establish efficacy in well-defined patient populations. Normally these are performed on closely monitored patients of limited number.

C. Phase III.

During this phase, clinical trials are expanded with studies designed to extend and confirm findings from Phase II studies. These studies are performed after some evidence of effectiveness is available and are intended to gather additional evidence of safety and effectiveness to support labeling for specific indications and treatment regimens.

D. Phase IV.

Post-Marketing studies may be undertaken to support additional indications or to further assess adverse reaction information.

III. Subject and Setting A.

A. Phase I studies.

The studies will ordinarily be performed in adult patients with defined sensitivity to the allergen of interest and uncomplicated allergic disease, but who are normal in all other respects. Normality in this context is freedom from abnormalities which would complicate the interpretation of the trial results.

B. Phase II and III studies

Patients selected for early Phase II studies should be free of hematologic, hepatic, renal, cardiac or other serious diseases, to avoid possible interference with evaluation of safety. The criteria for selection should be similar to patients studied in Phase I.

Patients who have concomitant diseases and special populations, i.e. children, may be included in later Phase II and Phase III studies, since they would be expected to be representative of certain segments of the population who will be receiving the product following approval for use.