# Allergic Rhinitis: Developing Drug Products for Treatment

## Guidance for Industry

***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Sofia Chaudhry at 301-796-4157.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**February 2016**
**Clinical/Medical**
**Revision 1**

# Allergic Rhinitis: Developing Drug Products for Treatment

## Guidance for Industry

*Additional copies are available from:*

*Office of Communications, Division of Drug Information*
*Center for Drug Evaluation and Research*
*Food and Drug Administration*
*10001 New Hampshire Ave., Hillandale Bldg., 4th Floor*
*Silver Spring, MD 20993-0002*
*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov*
*http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**February 2016**
**Clinical/Medical**
**Revision 1**

## TABLE OF CONTENTS

# Allergic Rhinitis: Developing Drug Products for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

## I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the development of drug products for the treatment of allergic rhinitis in children and adults.[2] The guidance addresses issues of trial design, effectiveness, and safety for new products being developed for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).

The recommendations in this guidance are based on an assessment of important issues raised in the review of both adult and pediatric allergic rhinitis clinical trials and the Agency's current understanding of the mechanism of the two related disorders of SAR and PAR. The pathophysiology of SAR and PAR are similar in terms of the chemical mediators produced and end-organ manifestations, with differences between the two entities primarily based on the causes and duration of disease. The trial design issues pertaining to SAR and PAR trials are also similar. Thus, these two categories are treated collectively in this guidance as *allergic rhinitis*, with differences in recommendations for the design of SAR and PAR trials indicated. Sponsors are encouraged to discuss details of trial design and specific issues relating to individual products with division review staff before conducting clinical trials.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

[1] This guidance has been prepared by the Division of Pulmonary, Allergy, and Rheumatology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *drug product* is inclusive of the small or large molecule active moiety or moieties in the formulation, along with the delivery device, if applicable.

*Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[3]

This guidance revises the draft guidance for industry *Allergic Rhinitis: Clinical Development Programs for Drug Products* issued April 2000. All of the public comments we received for the draft guidance have been considered and the guidance has been revised as appropriate.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## II. BACKGROUND

Information about the pathophysiology and treatment of allergic rhinitis and its subtypes, SAR and PAR, has grown markedly in the past decade. Patients with allergic rhinitis may have both nasal and non-nasal symptoms. The main nasal symptoms of allergic rhinitis are nasal itching (i.e., nasal pruritus), sneezing, rhinorrhea, and nasal congestion. Nasal pruritus and sneezing are induced by sensory nerve stimulation, whereas congestion results from vasodilation with resultant engorgement of cavernous sinusoids. Rhinorrhea can be induced by increased vascular permeability as well as direct glandular secretion. Important non-nasal symptoms commonly associated with allergic rhinitis include eye itching, tearing, eye redness, and itching of ears and/or palate.

A growing number of chemical mediators are believed to contribute to allergic rhinitis. Despite different causes and temporal patterns of disease, the same groups of chemical mediators appear to be regulators of the responses in SAR and PAR. It is for this reason that distinctions between SAR and PAR in terms of clinical trial design are made only in clinically relevant areas.

## III. OVERALL CONSIDERATIONS — ADULT PROGRAM

### A. Number of Trials

For approval of a new molecular entity in adults, the Agency recommends at least two adequate and well-controlled phase 3 clinical trials to support either the SAR or PAR indication. Alternatively, a sponsor can submit one SAR and one PAR trial in support of both indications, if both are adequate and well-controlled phase 3 trials and both demonstrate the safety and effectiveness of the drug for the indications. If a drug is approved for one of these two related indications, a single trial may support approval for the other indication. For example, a single PAR trial may support approval for a PAR indication if the drug is already approved for SAR.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

### B. Dose

The dose-response relationship for an investigational product should be evaluated in these trials or in dedicated dose-ranging trial(s). The goal of dose exploration is to identify the optimal dose and dosing frequency, balancing benefit with risk. Ideally, dose exploration should be conducted in a real-world setting, because other exposure models, such as park or inhalation chamber trials, may not be predictive of real-world clinical responses. Likewise, dose selection should be based on clinically meaningful endpoints, because pharmacodynamic (PD) markers may not be predictive.

### C. Safety Monitoring

Clinical efficacy trials must also address safety concerns, such as monitoring for adverse events, performing routine laboratory tests (i.e., blood chemistry, liver function tests, complete blood count with differential), urinalyses, and electrocardiograms, as appropriate (21 CFR 312.23(a)(6)). For SAR and PAR phase 3 trials, routine laboratory tests are recommended in trial patients at least at the initial screening and at the last visit.

For products with systemic bioavailability, the Agency recommends that the safety program include a thorough cardiac safety evaluation. In general, a risk of clinically significant QT prolongation would render the risk-benefit unfavorable for an allergic rhinitis product intended for symptomatic benefit. Clinical electrocardiographic evaluation should be performed early in clinical development. Clinical trials to assess the potential of a product to delay cardiac repolarization are described in detail in the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*. Sponsors are encouraged to contact the review division regarding appropriate cardiac safety monitoring for their respective development programs.

For some classes of products, sponsors may wish to provide some assessment of the degree of sedation compared to the placebo in the safety database. Adequate assessments of sedation are primarily based on individual patient adverse event reports of sedation and/or drowsiness (or similar terminology, as defined by the sponsor's adverse event dictionary). The need for additional evaluation, such as driving simulation trials, depends on the characteristics and intended use of the individual product.

Long-term safety data should include at least 300 patients evaluated for 6 months and 100 patients evaluated for 1 year, with the overall patient database including at least 1,500 patients. We recommend that a sufficient number of patients receive the highest dose proposed for marketing. (See the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended For Long-Term Treatment of Non-Life-Threatening Conditions*.) Measurements of efficacy endpoints are recommended in long-term safety trials as secondary assessments.

### D. Corticosteroid-Specific Issues

Important safety issues for intranasal corticosteroids that ordinarily should be addressed in the adult clinical program include:

- Assessment of adrenal function using either 24-hour urinary-free cortisol levels or 24-hour plasma cortisol area under the curve levels measured pretreatment and after at least 6 weeks of treatment with the investigational product. A placebo and an active control are recommended in these trials.

- Evaluation for possible cataract formation in long-term trials by slit lamp examination, pre- and post-treatment.

- Evaluation for glaucoma in long-term trials, using intra-ocular pressures monitored pre- and post-treatment.

### E. Issues Specific to Topical Products

Given the risk for local toxicity, safety monitoring should include baseline and serial nasal examinations. Prespecified grading criteria to assess for the presence of nasal irritation (e.g., mucosal edema, erythema, epistaxis), ulceration, and septal perforation can be useful for documenting any changes over the course of the treatment period.

The whole product, including the dedicated delivery system, is considered a drug-device combination product as defined in 21 CFR 3.2(e). Changes in the formulation, excipients, formulation flow path within the device, or device components (e.g., dimensions, materials of construction, coatings) can alter the delivery characteristics and affect the clinical performance and user interface of the product. Therefore, we recommend that all key trials in the development program, including dose-ranging trials and confirmatory efficacy and safety trials, be conducted with the to-be-marketed product. Furthermore, data should be provided on the performance and reliability of the new delivery system over the period of intended use.

In vitro and clinical bridging data may be needed to support any changes in the formulation and delivery system. Depending on the nature and extent of the changes, the altered product may be viewed as a new product, necessitating a separate development program with efficacy and safety trials. We recommend that sponsors discuss any planned changes to a topical product with the review division.

Bridging studies of nasal products for local action, particularly products that are in a suspension state, can be a substantial undertaking. Principles that may apply to such a bridging program are outlined in the draft guidance for industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.[4]

[4] When final, this guidance will represent the FDA's current thinking on this topic.

# IV. OVERALL CONSIDERATIONS — PEDIATRIC PROGRAM

The pediatric age ranges proposed for a product, particularly for young patients, should be justified by the sponsor based on the prevalence of disease and the need for treatment in that age group. Products indicated for the treatment of SAR generally should be evaluated in children down to the age of 2 years, while products indicated for the treatment of PAR should be evaluated in children down to the age of 6 months. For topical products, the appropriateness of the delivery system for the proposed age range is an additional consideration. Sponsors are encouraged to discuss the specifics of pediatric programs with the division on a case-by-case basis and to begin discussions about their pediatric formulation and clinical development plan as early as feasible because sponsors are required to submit pediatric study plans under the Pediatric Research Equity Act no later than 60 days after an end-of-phase 2 meeting. We recommend sponsors refer to the Pediatric Research Equity Act as amended by the Food and Drug Administration Safety and Innovation Act.[5]

## A. Pediatric Dose Selection

For products already approved and/or adequately studied in adults but not yet studied in children, an appropriate pediatric dose should be determined. In addition, adequate short- and long-term safety information for the proposed pediatric age group should be provided. For oral formulations where a reasonable pharmacokinetic (PK)/PD link for efficacy has been established, PK data from children can be used to determine comparable exposure to adult patients, and therefore the appropriate pediatric dose.

For intranasal formulations, efficacy trials in pediatric patients are recommended, because plasma drug levels are not consistently detectable or reliable as measures of local bioavailability and topical efficacy.

## B. Safety Data

Typically, 3 months of additional specific pediatric safety data for intranasal products and 1 month of additional specific pediatric safety data for oral products are recommended. We suggest that these data be collected in controlled trials. However, the duration and number of pediatric patients exposed to the investigational product for safety monitoring should be determined on an individual basis for each product, based on anticipated side effects, pediatric PK data, and safety concerns.

## C. Corticosteroid-Specific Issues

For intranasal corticosteroids, we recommend a 6-week hypothalamic-pituitary-adrenal (HPA) axis trial, with a placebo and an active control. Such a trial is intended to evaluate influences of the product on the HPA axis that are not limited to HPA axis suppression alone. Because of

[5] See section 505B(e) of the Federal Food, Drug, and Cosmetic Act, as amended by section 506 of the Food and Drug Administration Safety and Innovation Act, and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

ethical concerns about the use of oral prednisone as an active control in adrenal response trials in children, alternative approaches may be more appropriate. Such approaches can include use of an approved intranasal corticosteroid that is sufficient to cause an HPA axis effect.

Based on information indicating that intranasal corticosteroids have the potential to decrease growth velocity in children, a growth trial is recommended for prepubertal children. If the trials are to be conducted postapproval, it may be useful for a sponsor to include a knemometry trial in the new drug application to provide PD growth data for consideration during the initial review. Recommendations regarding the design and conduct of a growth trial are outlined in the guidance for industry *Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children*. Sponsors are encouraged to discuss the details of their pediatric growth trial design with the review division.

## V. PROTOCOL ISSUES AND ELEMENTS

### A. Trial Design

The following are general recommendations on trial design for phase 3 allergic rhinitis (SAR and PAR) trials.

- Double-blind, placebo-controlled, and parallel group trials are recommended, preferably with a placebo run-in period. The placebo run-in period can be used to assess for a minimum level of compliance and symptom severity before the double-blind treatment period.

- The suggested duration of the double-blind treatment period is at least 2 weeks for SAR trials and 4 weeks for PAR trials.

- For SAR trials, the Agency recommends that the protocol include plans for measuring pollen counts at the different trial centers. The final report can then document the exposure of patients to the relevant allergens during the trial period. It may also be helpful to collect data on the number of rainy days during the trial and the extent of patient exposure to outdoor air.

- For SAR trials, we encourage randomization of patients within each center into the double-blind portion over a short time period, because this generally reduces variability in allergen exposure. The time period for randomization should be the shortest period that is feasible, given the size of the trial and variability in weather.

- Many patients with PAR may have concomitant SAR. Therefore, it is helpful if PAR efficacy trials are conducted during a time when relevant seasonal allergens are less abundant and therefore less likely to influence trial results.

### B. Inclusion Criteria

The following are general recommendations on the inclusion criteria for phase 3 allergic rhinitis trials.

- For SAR trials in older children, adolescents, and adults, it is recommended that patients have a history of SAR for a minimum of 2 years before trial entry. The Agency recommends documentation of sensitivity by positive skin testing (by prick or intradermal methods) or by adequately validated in vitro tests for specific Immunoglobulin E (IgE) (e.g., radioallergosorbent test (RAST), paper radioimmunosorbent test (PRIST)) to the relevant seasonal allergen for the geographic area of the trial within 12 months before enrollment. In general a positive skin test is defined as a wheal greater than or equal to 3 millimeters (mm) larger than the diluent control with erythema for prick testing or greater than or equal to 7 mm larger than the diluent control with erythema for intradermal testing. Positive in vitro tests are determined by the standards of the individual reference laboratory. Positive skin tests or in vitro tests for specific IgE should correlate to the allergy history before the results are accepted as meeting inclusion criteria.

- For PAR trials, allergy to perennial allergens (e.g., dust mites, cockroaches, cats, dogs, molds) can be demonstrated in trial patients by prick or intradermal skin testing (using the criteria for positivity above) or by adequately validated in vitro tests for specific IgE (e.g., RAST, PRIST). We suggest that these tests be performed during the 12 months before enrollment. The patient should have a relevant allergy history to the tested allergen.

- The Agency recommends that patients not start immunotherapy or have a change in dose for approximately 1 month preceding enrollment in the trial. Ideally, patients should maintain the same dose throughout the trial.

- Patients should be experiencing symptoms meeting or exceeding an appropriate minimum level at the time of trial enrollment. This can be ensured by assessing the severity of the symptoms for the primary endpoint and requiring at least moderate severity for all or the majority of individual symptoms, as defined by the trial's symptom scoring scale.

### C. Exclusion Criteria

The following are general recommendations on the exclusion criteria for phase 3 allergic rhinitis trials:

- Asthma, with the exception of mild intermittent asthma,[6] to lessen confounding by asthma medications, some of which may modify allergic rhinitis.

[6] See the National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma" at http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/index.htm.

- Chronic or intermittent use of inhaled, oral, intramuscular, intravenous, and/or potent topical corticosteroids.

- Use of leukotriene modifiers.

- Use of long-acting antihistamines.

- Prohibited medications or inadequate washout periods (for certain drug classes). The following washout periods are generally sufficient:

  - Intranasal or systemic corticosteroids (1 month)
  - Leukotriene modifiers (1 month)
  - Intranasal cromolyn (2 weeks)
  - Intranasal or systemic decongestants (3 days)
  - Cetirizine, fexofenadine, loratadine, desloratadine, hydroxyzine (5 to 10 days)
  - Intranasal antihistamines (3 days)
  - Other systemic antihistamines (3 days)

- Documented evidence of acute or significant chronic sinusitis, as determined by the individual investigator.

- Chronic use of concomitant medications (e.g., tricyclic antidepressants) that would affect assessment of the effectiveness of the investigational product.

- A history of hypersensitivity to the product or its excipients.

- Presence of rhinitis secondary to other causes.

- Presence of ocular herpes simplex or cataracts (for intranasal corticosteroid trials), or a history of glaucoma (for intranasal corticosteroid or anticholinergic trials).

- Planned travel outside the trial area for a substantial portion of the trial period.

### D. Blinding

Because allergic rhinitis trials are based on subjective endpoints, blinding is a critical consideration. The process of ensuring blinding to the investigational product should be described in the protocol. If double-blinding is not possible, a rationale should be provided, along with a discussion of the means for reducing or eliminating bias. For topical nasal formulations, a description of the differences in appearance between active and placebo treatments in the protocol (e.g., differences in the device or in the odor or characteristic of the formulation) can help determine the adequacy of the trial blind.

## E. Formulations and Dosage Regimens

Sponsors are encouraged to provide information in the protocol on the specific formulations used for both the to-be marketed product and the placebo, along with a description of the dosing regimen. We recommend that dose-ranging and confirmatory trials use the to-be-marketed product. If not, the sponsor should address how the safety and effectiveness of the studied formulation will be bridged to the to-be-marketed formulation. If bridging of one formulation to another is proposed, information about the formulation composition and trial lots should be included in the final reports for the respective products.

## F. Evaluation

The following are general recommendations on trial assessments in phase 3 allergic rhinitis trials.

### *1. Assessment of Patient Compliance*

The protocol or final report should provide information about how compliance with the investigational product use will be determined and documented throughout the trial and how noncompliance and/or missing data will be dealt with, either in the form of patient exclusion or exclusion of data points (e.g., use of last visit data carried forward).

### *2. Assessment of Rescue Medication Use*

If rescue medications are allowed during the trial, the protocol should document how rescue medication use will be analyzed in the different treatment groups. We recommend inclusion of a section in the clinical trial report that presents rescue medication use in the different treatment groups.

### *3. Rating System*

The preferred measures of efficacy in allergic rhinitis trials are patient self-rated *instantaneous* and *reflective* total nasal symptom scores. These summed scores generally include the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing rated on a 0 to 3 scale of severity. Addition or deletion of symptoms to or from the total score can be appropriate, based on the mechanism of action. Such changes should be discussed with the review division. Patient-rated scores are preferred as the primary measure of effectiveness.

A common allergic rhinitis rating system that has been used in clinical trials is the following 0 to 3 scale:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom present, but minimal awareness; easily tolerated)

- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)

- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Regardless of the scoring system chosen, a detailed description of the symptom rating scale should be provided to patients. This should include instructions on proper completion of the symptom diary and definitions of the different categories in the scale.[7]

*4. Recording Scores*

The Agency recommends that patients be instructed to record their symptom scores in a diary at least as often as the daily dosing interval. Collection of both reflective symptom scores (i.e., an evaluation of symptom severity after a predefined time period such as 12 hours) and instantaneous symptom scores (i.e., an evaluation of symptom severity immediately before the next dose) is recommended. Reflective symptom scores assess the overall degree of effectiveness over a prespecified time interval, whereas instantaneous scores assess effectiveness at the end-of-dosing interval and can be used to assess onset of action.

*5. Adverse Event Recording*

We recommend that adverse events be recorded in a daily patient diary record, in addition to being elicited by trial staff at clinic visits.

## VI. DATA ANALYSIS ISSUES

### A. Symptom Scores

Symptom scores should be collected at baseline and daily over the course of the trial. Collection of baseline symptom scores over several days immediately preceding patient randomization will permit the evaluation of baseline comparability of the various treatment arms, as well as the determination of treatment effects over time.

An appropriate primary efficacy endpoint is the change from baseline in the reflective total nasal symptom score (TNSS) for the *entire* double-blind treatment period (2 weeks for SAR and 4 weeks for PAR). Depending on the drug class being evaluated, the TNSS is defined as a total score composed of at least three of the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing. Inclusion of nasal congestion in the TNSS may be appropriate for an intranasal corticosteroid or a decongestant, but may not be appropriate for an antihistamine, anticholinergic, or cromolyn-like agent.

[7] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

An appropriate key secondary endpoint is the change from baseline in the instantaneous TNSS for the double-blind treatment period to assess the appropriateness of the dosing interval. The development program should demonstrate a significant difference between the product and placebo at the end of the dosing interval.

When designing allergic rhinitis protocols, sponsors are encouraged to numerically define a clinically meaningful change in the primary efficacy endpoint, and provide the rationale for this selection. The statistical section of the protocol should include a power calculation using this value and should prospectively discuss how missing data will be handled in the analysis plan.

In addition to evaluating the effectiveness of the product over the entire double-blind period, additional data presentations can be helpful in evaluating effectiveness. These include:

- Presenting the morning and evening symptom scores separately for both the reflective and instantaneous symptom assessments.

- Presenting the efficacy data for the first few days of the trial separately for both the reflective and instantaneous symptom assessments. This data presentation also can separate the morning and evening scores. This allows some assessment of the onset of action.

- Presenting the efficacy data for each week individually for both the reflective and instantaneous symptom assessments. This allows determination of both the onset of action and the durability of the response over the course of the clinical trial.

- Presenting the efficacy data for the individual component symptom scores that comprise the total symptom complex.

Other patient-rated and physician-rated measures can be included as secondary efficacy endpoints. For example, assessment of ocular symptoms associated with allergic rhinitis may be applicable for certain products. Patient-rated, reflective, and instantaneous total ocular symptom scores, similar to the symptom scoring system used for nasal symptoms, can be used to support inclusion of relevant information in labeling. Information from disease-specific quality-of-life measures also can be considered for inclusion in labeling. We anticipate replicate data from at least two trials to support inclusion of such measures in labeling.

### B. Onset of Action

The definition of the onset of action of an allergic rhinitis product is the point at which patients might reasonably expect to see a meaningful decrease in their allergic rhinitis symptoms. For the purposes of allergic rhinitis, it is the first time point after initiation of treatment when the product demonstrates a greater change from baseline in the primary efficacy endpoint compared to the placebo treatment that proves durable from this point until the end of the proposed dosing interval.

Because onset of action information may be included in labeling, at least two trials are recommended to support a particular onset of action claim. It is useful to assess onset of action during development, regardless of any proposed claims. The two trials do not have to be identical in design, nor do they have to evaluate both SAR and PAR. Because onset of action is largely a PD issue, a number of different trial designs can be used. Following are three types that have been used:

1. Standard phase 3 allergic rhinitis efficacy trials in which symptom scoring data are collected frequently for the first few days

2. A single-dose, parallel group, placebo-controlled trial of patients in a *park setting* in which patients are exposed to relevant outdoor seasonal allergens and, following dosing, have nasal symptoms evaluated on an hourly basis

3. An inhalation chamber trial (also known as environmental exposure unit (EEU)) in which previously asymptomatic patients are exposed to a relevant allergen (generally a seasonal allergen, such as ragweed) in a controlled indoor setting and, following dosing, have their nasal symptoms evaluated on an hourly basis

Onset of action data can come from any of these three designs. However, if EEU and/or park trials are used to support an onset of action claim shorter than the onset of action seen in the phase 3 trials, the Agency recommends that the results be replicated to be considered independently informative. This is due to the shorter duration of these trials and the restricted setting and manner in which they are conducted. In any case, information about onset of action derived from the phase 3 trials used to support approval also can be included in the proposed package insert along with any data from park or chamber trials, to reflect the real world setting of the treatment trials.

## VII. FIXED-DOSE COMBINATION PRODUCTS

In addition to the general principles outlined in 21 CFR 300.50 regarding the development of fixed-dose combination products, other considerations for allergic rhinitis combination products include the following:

- The contribution of each monotherapy component should be supported by replicate, appropriately designed and conducted trials where the combination product is compared to each component. The treatment difference between each component and the combination product should be clinically meaningful and statistically significant.

- The efficacy and safety of the dose and dosing regimen for each individual component should be established (i.e., the monotherapy components should be tested at an effective dose and dosing regimen).

- For locally acting topical products, pharmaceutical differences between the combination product and each component may obscure the comparison of the combination product to

each of its components used in a clinical trial. As a result, commercially available comparators may not be appropriate for the purposes of factorial comparison. Sponsors will likely need to develop monotherapy comparator products specifically for the purposes of the combination product development program.

- Patients who have already failed one component of the combination product should be excluded, unless there is scientific justification to an exception.

Given the complexity of development programs for fixed-dose, locally acting combination products, sponsors are encouraged to discuss the details of the monotherapy components and trial design with the review division early in the development program.