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## Medical Devices

### Important Issues for Allergen-Specific IgE Testing

Immunoglobulin E is a distinct class of serum antibody which mediates Type 1 hypersensitivity reactions, also known as atopic allergy. In sensitized individuals suffering from this immediate (atopic or anaphylactic) type of allergy, IgE molecules act as point of contact between the allergen and mast cells or basophilic leukocytes that release histamine and other agents upon exposure. This initiates the events recognized as allergic reactions, the most common clinical manifestations being sinusitis, asthma, dermatitis, hives and, in rare cases, anaphylactic shock. Assessing the level of allergen-specific IgE in a patient's serum in conjunction with a clinical evaluation based on patient history and other testing can help a physician confirm a diagnosis of atopy allergy and assist in the treatment of the patient.

#### Limitations of the Testing:

Clinicians and laboratorians should be aware of inherent problems with currently available allergen-specific IgE tests. Following pre-market review, FDA allows these tests on the market but suggests that manufacturers and distributors include limitations in the labeling (package insert) that accompanies each test kit to the clinical laboratories/physicians.

- A definite clinical diagnosis should not be made solely on the basis of an *in vitro* allergen-specific IgE result. Diagnosis should be made by the physician only after all clinical and laboratory findings have been evaluated.
- The results of an allergen-specific IgE antibody test should not be used as a definitive guide to select an initial dose for immunotherapy. Prior to implementing such therapy, a skin test with the planned initial dilution of the immunotherapy solution should be performed to prove that the patient tolerates *in vivo* administration of this allergenic extract.
- Very low levels of allergen-specific IgE antibodies should be evaluated with caution when total IgE values are above 1000 kU/L.
- In food allergies, circulating IgE antibodies may remain undetectable despite a convincing clinical history because these antibodies may be directed toward allergens that are revealed or altered during industrial processing, cooking or digestion and therefore do not exist in the original food for which the patient is tested.
- False positive test results in persons who are tested for food allergies may lead to inappropriate dietary restrictions while false negative results in food sensitive persons may result in anaphylactic reactions of varying severity.
- A positive result may be due to cross-reactivity with other similar allergens and not to the specific allergen tested. The user should be aware of the possibility of clinical cross-reactivity within an allergen family.
- Latex specific IgE antibodies may show cross-reactivity with ragweed and certain food allergens such as banana, avocado, kiwi and chestnut. Since a latex assay measures allergen-specific IgE, type IV delayed reaction or irritation from latex will not be detected.
- Results below the limit of quantitation obtained for a drug-specific IgE determination indicate the absence or undetectable levels of specific IgE antibodies to the drug, as is found in nonsensitized individuals. However, negative specific IgE results can also be found in patients who are nevertheless hypersensitive to drugs, for example when:
  - The symptoms are mediated without IgE involvement.
  - The blood sample was collected a long time after the latest adverse reaction to a therapeutic treatment procedure. The concentration of IgE antibodies can decrease over time after the allergic reaction.
  - The blood sample was collected very soon after the allergic reaction. An interval between the time of the allergic reaction and the appearance of measurable specific IgE antibodies can occur and can lead to "false" negative results for drug-specific IgE determinations. Such results can be checked by collecting a new blood sample and repeating the test two weeks after the allergic reaction.
- Allergen-specific IgE antibody results below the limit of quantitation for venom-specific IgE indicate absent or undetectable levels. Such results do not preclude existence of current or future clinical hypersensitivity to insect sting.
- Identical results for different allergens may not be associated with clinically equivalent manifestations, due to differences in patient sensitivities and IgE binding capacities.

#### Allergens as Analyte Specific Reagents (ASRs): Frequently Asked Questions

**What is the definition of an ASR?** ASRs may be thought of as the "active ingredients" of tests that are used to identify one

specific disease or condition. They are defined as "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands nucleic acid sequences, and similar reagents which, through specific binding or chemical reactions with substances in a specimen are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens" (21 CFR 864.4020). ASRs are components of *in vitro* diagnostic devices that are regulated by FDA.

ASRs may be purchased by a clinical laboratory to develop in-house tests used exclusively by that laboratory. In this case, the laboratory would perform all necessary verification and validation of the assays. Laboratories using ASRs should be regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity testing or they should be clinical laboratories regulated under VHA Directive 1106.

FDA views an ASR as having the following characteristics:

- used to detect a single ligand or target (e.g. protein, single nucleotide change, epitope);
- not labeled with instructions for use or performance claims; and
- not promoted for use on specific designated instruments or in specific tests.

For additional information on ASRs, please refer to [Guidance for Industry and FDA Staff - Commercially Distributed Analyte Specific Reagents \(ASRs\): Frequently Asked Questions](#)<sup>1</sup>

**Are allergens considered ASRs?** Allergens would not be considered ASRs: if more than one allergen is combined together by the manufacturer, e.g. AgA + AgB in the same vial; if more than one ASR is bundled together in a single pre-configured or optimized mixture so that they must be used together in the resulting laboratory developed test; if the product marketed includes some or all of the products needed to conduct a particular test; if they are designed or formatted to be used only on a specific instrument; if they are promoted for use with specific named reagents e.g. buffers, diluents or controls used with that instrument; or if they are marketed with analytical or clinical performance claims.

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