Allergenic Source Materials

Considerations and challenges for biopharmaceutical product or assay development

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With over 50 million Americans suffering from allergies, the diagnosis, treatment and prevention of allergic reactions has grown into a $5.3 billion industry. Until recently, most allergy treatments were designed to treat common symptoms of allergic reactions, not the actual cause of the disease itself. Today, pharmaceutical and biotechnology companies are working on the next generation of therapeutic products, many of which are aimed at altering the specific immunological mechanisms responsible for allergic diseases.

R&D teams are striving to create new formulations and delivery methods for allergy immunotherapy treatments. Detection methods and immunoassay platforms are also evolving as reference laboratories and hospital or clinical practices continue to drive changes in the *in vitro* allergy diagnostic market. The demands and competition for clinically-relevant allergy detection and treatment methods that are convenient, easy-to-use and cost effective present a formidable challenge to corporate scientists, clinical investigators and regulatory professionals.

As the development of new types of allergy treatments grows, the need for diverse and well-characterized allergenic source materials grows as well. In today's highly regulated biopharmaceutical environment, companies sourcing these materials are challenged to demonstrate that their products contain appropriate allergenic components that meet stringent quality standards from collection to product development and manufacturing. Establishing a collaborative partnership with an allergen source material provider capable of offering a variety of sourcing, production, analytical and technical services has become an essential step in the feasibility and development processes for many companies entering the allergy marketplace, and has remained a pivotal activity for nearly all firms with existing products or assay technologies.

Not just your ordinary range of molds and pollens

For more than 100 years, Greer has provided allergenic source materials to biopharmaceutical companies, clinics and research institutions. These materials elicit immediate-type hypersensitivity reactions in humans and animals. The most common allergen sources are pollens, dust mites, molds and animal danders. Today, allergy companies source an expanding spectrum of allergens including rare or exotic foods, environmental or occupational materials and biting or stinging insects. Food allergies remain a critically important disease that is difficult to diagnose accurately and is usually not treated due to the risks of severe or fatal adverse reactions. New approaches are being developed to provide safe and effective treatments for individuals with life-threatening allergic reactions to foods such as peanut.

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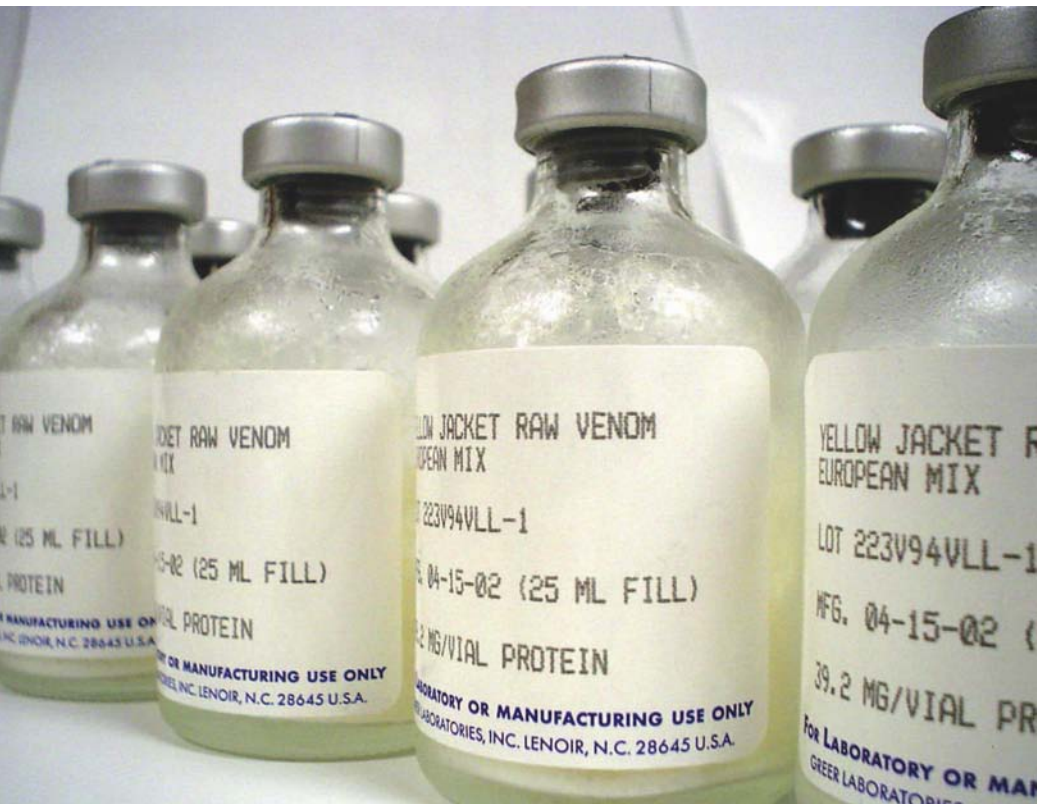
Raw yellow jacket venom



The discovery of new allergens, and the identification of materials that cause or exacerbate allergic reactions, has increased in parallel with scientific and technological developments such as the design and expression of recombinant proteins and monoclonal antibodies, and the detection and quantization of local (cytokines) and systemic (allergen-specific IgE) immunologic markers of immediate-type allergic responses. Allergy researchers continue to identify and understand even the rarest of allergies that, even just a few years ago, were not recognized or were misdiagnosed. Not long ago, there were less than 100

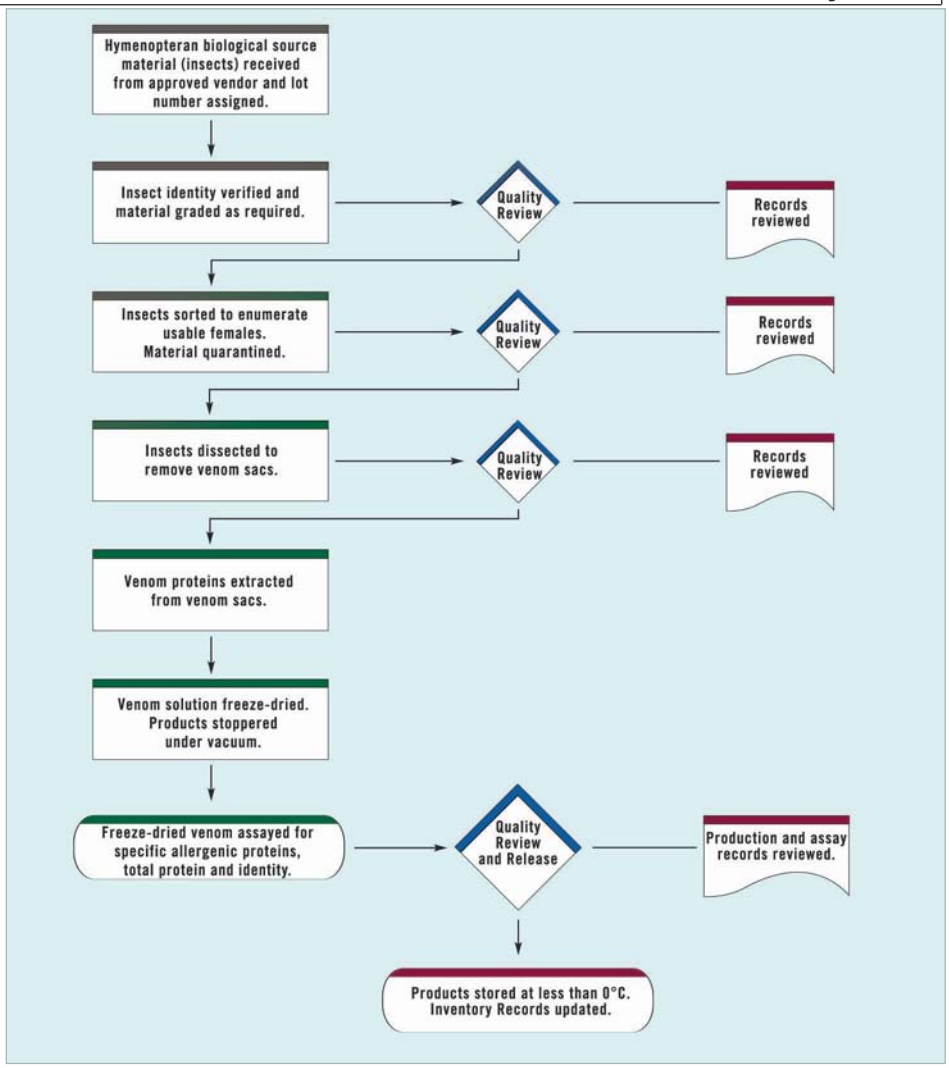
known allergenic materials. Today, the number has reached 500 and is still climbing. In addition, we now know that even within a single allergen source, significant variations in climate, geography or environmental conditions can produce materials with different levels or types of specific allergens. These differences may be critical to the ultimate performance characteristics of a new product and often reflect nuances of allergic patient reactions not yet understood or reported within the allergy community.

Source materials collection

Most allergenic source materials are obtained from their natural environments. Ragweed and other pollens are collected from fields and processed to produce source material lots with high purity and confirmed identity. Animal danders and epithelia can be sourced from multiple types or individual breeds. Foods are available in a number of forms, types, variants or cultivars and can often be processed using common preparative steps to facilitate side-by-side investigations. Allergen manufacturers such as Greer employ a world-wide network of source material collectors. Quality assurance begins with these collectors, as they identify the materials and their harvest locations. It is critically important for both suppliers and end users to document collection data (plant, source material, purity, location, preparative method) prior to downstream processing. Subsequent steps (extraction, isolation and presentation of allergens) are no less important in determining the allergenicity, consistency and stability of final products, but the selection and qualification of a particular material source can be just as fundamental to successful product development.

Other allergenic materials, such as fungi, dust mites and some insects, cannot be collected easily from their natural habitats, and must be produced from laboratory cultures using specific and highly-controlled growth and workup conditions. Molds present a unique challenge because allergenically-important fungal species can exist naturally in a variety of biochemically-distinct strains. They have an ability to mutate based on adaptation to their living (parasitic) or non-living (saprophytic) food sources.

Once an allergenic source material arrives at the manufacturer, or has completed production at the same facility, it is typically identified under the microscope or by definitive chemical or biochemical procedures. Purity is also confirmed at this stage. Pollens may contain no more than a one percent impurity (ex. plant parts) to satisfy current FDA regulations for human use products. I*n vitro* products may possess higher levels of impurities but are usually processed to meet the same purity standards as human use materials. Source materials are usually defatted with acetone or ether to remove non-allergenic lipids, fats and oils that complicate extraction and filtration procedures. Non-defatted materials can also be provided if desired. Materials are often dried and milled to improve extraction efficiencies. After extraction and clarification, extracts can be manufactured in liquid concentrate, freeze-dried intermediate and target final product formulations based on end-user preferences.



Allergenic source materials process, quality and document review process.

Regulatory hurdles and responsibility

When purchasing allergenic materials for new product or diagnostic development, it is important for the end user to understand the current regulations associated with these products. While the FDA regulates manufacturers of allergenic extract and serum antibody detection platforms for human use applications, source materials supplied to pharmaceutical or biotechnology firms are not regulated by FDA or USDA, and no standards or approvals are required. At Greer, both extract production and source material facilities are inspected by FDA and USDA and are GMP-compliant. In many cases, the same source materials used to manufacture the licensed allergenic extracts provided to allergy specialists for allergy immunotherapy injections are available to biopharmaceutical companies. Allergen manufacturers that do not prepare extracts on site may not be subjected to similar inspections or regulatory scrutiny.

In spite of the minimal regulatory requirements for source materials, it is important that pharmaceutical com-

Top left: Some allergenic materials cannot be collected easily from their natural habitats, and must be produced from lab cultures using highly-controlled growth and workup conditions. Bottom left: Once the source material arrives at the manufacturer, it is typically identified under the microscope or by definitive chemical or biochemical procedures.

panies request thorough documentation from allergen manufacturers. In addition to the source-specific information described previously, other types of information may be required. For example, pollens cannot be collected from plants that have been exposed to herbicides or pesticides or grown near highways or industrial plants. Due to concerns over blood-borne illnesses, cultured insects are not given blood meals. In addition, animal products are derived from animals assessed to be free of blood borne illnesses. Manufacturers should provide a certificate of analysis which includes how the materials were collected, when it was collected and the 'use by' date. Documentation should also include results of random sampling for purity as well as how the materials were processed. If this documentation is not in order when the FDA requests it, months of work and thousands of dollars may be wasted.

Advice to companies sourcing allergenic materials

For companies in search of allergenic source materials, the process does not have to be exhaustive, but it should be comprehensive. Ideally, the process should begin while the product is still in the feasibility phase. When contacting suppliers, it is best to start by discussing the end use of the product and work backwards. Is it a new composition of the source material or mode of delivery? Due to the nature of the product, you may not be able to divulge proprietary information, but any details you can provide are helpful to your allergen manufacturer.

Timing is another element to consider early in the process since forecasting and planning are crucial to any R&D project involving source materials. For example, collectors can only harvest ragweed pollen during certain times of the year. After the pollen collection window closes, it will be another 12 months before these suppliers will replenish their supply. Sourcing the same materials from different vendors or geographic locations may introduce subtle or more significant variations in content that may influence downstream processes or results. Working with an experienced team of source material procurement and scientific specialists at the allergen manufacturer is important to determine which sources may pose a risk to development timelines and which ones are essentially equivalent or qualified for use in the final products.

Documentation of source material collection, processing procedures and collaborative scientific investigations should be provided by allergen manufacturers in a format suitable for a biopharmaceutical company. This helps to ensure the quality of the materials and services provided, as well as satisfying pertinent FDA regulations for active ingredients or final products. Ask for explanations and examples of these documentation procedures to address any quality concerns with potential vendors.

It is also important to ask what types of services the vendor provides. This conversation will usually reveal the true capabilities of a particular vendor and their commitment to a time-sensitive collaborative partnership. During this process, basic questions or concerns such as the specific materials needed, the available and potential forms of these products, and the process of evaluation and qualification are often resolved. Allergen manufacturers should be available and able to assist you throughout the development process.

Product quantity and quality must also meet clearly defined requirements. Manufacturers must be capable of providing materials in the quantities and time periods desired to meet product development timelines. Product and source material consistency must remain high throughout the feasibility, research, development and validation stages of each project. It is appropriate to ask specific questions regarding collectors and collection or cultivation procedures. Although some information may be proprietary, manufacturers will share as much information as possible with their customers, but will retain any company-specific interactions and investigations as confidential.

Moving forward

The development of allergy products and treatments has never been more specialized and diversified as it is today. New treatments and modes of delivery are under development for patients suffering from well-known and easy-to-diagnose allergens to more esoteric and rare diseases that may have been undetected for years. The role that allergen manufacturers play in this environment is changing daily, and partnerships with allergenic source material or extract providers require significant resources and capabilities tailored to the needs and demands of today's pharmaceutical and biotechnology companies. When considering an allergen manufacturer or selecting one for a long-term relationship, it is appropriate to view the allergen provider as an extension of your own company. A manufacturer that is structured and ready to meet these challenges is an invaluable asset to any product development process, and can provide unique products and services to help differentiate new products and improve existing ones. ■