

Recombinant allergens in the US^{☆,☆☆}

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Abstract

Recombinant allergens may increase the safety and efficacy of allergen immunodiagnostics and immunotherapy, and may prove to be excellent tools for the standardization of existing, natural allergens. However, there are several biological and regulatory issues that need to be addressed as these products are moved from bench to bedside. This article discusses some of these issues.

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Recombinant protein technology has been applied to numerous biological products. Although many investigators have generated recombinant allergens for basic and clinical study, none has been approved for human use. In this paper, I will discuss some of the ethical and scientific issues that will need to be addressed for these products to be licensed in the US.

Currently licensed allergenic extracts are derived from naturally occurring plant and animal materials, and are minimally processed to assure that they contain allergenic biomolecules in their native form for diagnostic or immunomodulatory indications. This remarkable group of products has broad diagnostic use and has been shown to be efficacious in the treatment of allergic disease due to mite, cat, grass pollen, ragweed pollen, and hymenoptera venom exposure.

In the US, standardized extracts bear units that are based on biological potency and are controlled for potency and stability. Unitage is determined by comparing the potency of the extract to that of a reference standard maintained at FDA/CBER, using a validated assay. The majority of allergenic extracts are not standardized. These extracts are labeled only with a designation of extraction ratio (w/v) or with a protein unit designation,

which is determined using the Kjeldahl method (protein nitrogen units/ml). Unfortunately, there appears to be little correlation between these two designations and biological measures of allergen potency [1,2].

For standardized cat, dust mite, and grass pollen allergen vaccines, the basis for biological standardization is the ID₅₀EAL skin testing protocol [3]. Thus, the unitage assigned to these standardized products is based upon the correlation between the biological activity and safety of the product and its skin test reactivity [4].

Another feature of all currently available allergen vaccines is that they have been used for both immunotherapy and immunodiagnosis. Each of the standardized allergen vaccines has been approved for such use. Although many non-standardized allergen vaccines are approved only for immunodiagnosis, all natural vaccines—in concept—should be efficacious for immunotherapy as well.

The problems associated with natural allergen vaccines are well known. These include adverse allergic reactions (local and systemic), diverse and obscure unitage, inconsistent potency and composition, spontaneous precipitation, empiric expiry dating, and production shortfalls due to shortages of source materials. Many, but not all, of these problems have been reduced or eliminated with the advent of standardized allergen vaccines. However, the US market still has hundreds of non-standardized products and standardization of the remaining products is proceeding slowly [3].

Recombinant protein technology has been applied to numerous approved biologics. At present, recombinant

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allergens are potent research tools that have been used to dissect and modify immune responses, elucidate allergen structure, determine structure–function relationships, and generate products with novel immunologic or immunochemical properties. Several authors have recognized the therapeutic potential for recombinant allergen vaccines [5–7]. Foremost among these potential advantages is the unique opportunity to separate the immunogenicity of the product from its allergenicity, thus enhancing the therapeutic index of recombinant allergens substantially over their natural counterparts. In addition, with proper engineering and quality control, recombinant allergens can be expected to be more pure, more consistent, and more stable than natural allergens. With theoretically unlimited supplies of consistent product, recombinant allergens should be an ideal standardization tool. Finally, we can expect recombinant allergens that are engineered to improve bioavailability and delivery in ways not possible with natural products.

With these potential advantages there are some concerns. Since allergenicity will not necessarily correlate with immunogenicity in these new products, recombinant allergens pose a challenge to the standardization model that has been so successfully implemented in the US market over the past 20 years. Different products may require unique standardization approaches; it is unlikely that a single approach will be appropriate for more than a few of these novel products. In addition, the indications for the recombinant proteins will likely be very different from their native counterparts. Diagnostic and therapeutic uses will need to be redefined, as will the target populations on which these products will be studied and used. An extensive period of careful investigation and education lies before all of us—scientists, regulators, and health care providers.

So how will these products, currently in various stages of investigation, progress from the laboratory to the physician's office?

Ultimately, to bring a product from bench to bedside, one has to make a product that fulfills a real clinical need, is safe and effective, and can be manufactured consistently using established current Good Manufacturing Practices (21 CFR 211 and current related guidance documents). Then, one must perform the necessary studies to demonstrate the product's safety and efficacy, and to establish the indications and appropriate uses of the product. The first such studies are performed in animals and are needed to establish the biological activity of the product and its potential toxicity. After the animal studies have been completed, the investigator must apply to the FDA for permission to use the product in an ethical, scientifically sound, three-phased human investigation. This application is called an Investigational New Drug (IND) application, and only investigational products that are under an approved IND may be administered to humans in the US.

Most INDs are submitted for products intended for licensure; as such, the IND investigation must be designed to support the product's intended clinical use. All INDs must ultimately show that the product, as used, is safe and effective, and must indicate how and when the product should be used to maximal patient benefit. The FDA's objectives in reviewing IND applications are to assure the safety and rights of study subjects, and to assure that the scientific quality of the study is adequate to permit an evaluation of the drug's safety and efficacy. Implicit in the process is that a poorly designed study is not only a waste of time and money, but is an unethical abuse of the trust that study subjects place in medical research.

To maximize the safety of the study subjects, all IND trials are divided into three phases. Phase 1 is the initial introduction of the investigational substance into humans and represents a closely monitored safety and dose-ranging study in a small group of volunteers. Phase 2 trials are the initial effort to gauge drug efficacy, using the dose ranges and safety precautions established in the Phase 1 experience. The number of study subjects is still relatively small, usually in the hundreds. The Phase 3 trial is the so-called pivotal trial, with hundreds to thousands of study subjects enrolled to definitively establish the efficacy of the new product prior to licensure.

The FDA may put an IND on clinical hold—effectively stopping the study—for the reasons summarized in Table 1. Since the placement of a study on clinical hold nearly always results in study revisions to address these issues, these hold criteria highlight the advantages of the IND process. First, it protects the safety and rights of human research subjects. Second, it improves the scientific validity of the investigation by assuring the rigor of the study design and the integrity of data collection and analysis. Finally, since the IND process gives FDA personnel the opportunity to review and comment on study design in all phases, it facilitates the licensure of a product at the end of a successful trial.

In order for recombinant allergens to be approved, there will be a series of hurdles that will need to be overcome. Some of these would need to be addressed for any new allergenic products, whether natural or recombinant; others are of concern specifically for recombinant products. All are surmountable and each

Table 1
Reasons for the placement of an IND on clinical hold (21 CFR 312.42)

Phase 1, 2 or 3

- Unreasonable and significant risk of illness or injury
- Clinical investigator is not qualified
- Investigator's Brochure is misleading, erroneous or materially incomplete
- Insufficient information to assess risk

Phase 2 or 3 only

- Protocol or plan is deficient in design to meet its stated objectives

Table 2
Some hurdles in the study and approval of new recombinant allergens

<i>For new allergens (whether recombinant or natural)</i>
Biological justification
Manufacturing practices
Lot to lot consistency
Good potency assay
Study power
<i>For new recombinant allergens</i>
Character and stability of gene construct
If cell line is used, the cell line needs to be extensively tested for absence of adventitious agents (such as retroviruses, EBV, and SV40)
Fermentation/growth media/growth conditions
Purification
Characterization/proof of structure

of them is important in assuring that the new product is safe and effective. They are listed in Table 2.

Two additional specific issues will need to be addressed in the course of successful investigations and licensure applications for recombinant allergens. The first is that the study design must target the appropriate patient population, which may or may not be the same population for which the recombinant allergen's natural counterpart is used. Thus, while we would expect a recombinant Fel d 1 product to be curative in the immunotherapy of most cat allergic individuals, a recombinant Der p 1 allergen vaccine would not likely be effective treatment for most dust allergic individuals. The purpose of a well-designed IND trial would be to define the target population for the investigational product with enough precision that the licensed product could be used to greatest therapeutic effect.

Another specific issue is the unitage of the product. With the exception of the hymenoptera venoms, all standardized allergenic products are labeled in biological units. While the labeling of the new recombinant products in mass unitage is attractive—both from manufacturing and clinical standpoints—CBER is unlikely to approve such units for these products unless the following can be shown during the IND investigations:

1. the purity of the product is consistent and assured;
2. the correlation between biological activity and mass units is defined and constant; and
3. the product—and thus the specific activity—is stable under the conditions under which the product will be shipped, stored, and used.

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