

Future Aspects of Regulation

Jay E. Slater

The views expressed in this article are the personal opinions of the author and are not the official opinion of the U.S. Food and Drug Administration or the Department of Health and Human Services.

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 presentation, 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 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 used for both immunizations and vaccines has been the use of adjuvants. Vaccines are approved only if they should be efficacious.

The problems associated with these products include adverse reactions, inconsistent potency, and product quality. Some of these problems are the result of allergen vaccine products, and some are the result of the manufacturing process.

Recombinant protein technology. At present, recombinant protein technology is used to produce and modify proteins. The function relationship between the chemical properties of the recombinant allergen and the unique opportunity it provides, thus enhancing their natural characteristics. Recombinant allergens are more stable than natural allergens. In fact, recombinant allergens are expected to be more effective in ways not yet known.

With these products, it is not necessarily correct to say that allergens pose a challenge. The challenge is to develop a unique standard for these products. The standard is appropriate for more products. Recombinant protein technology. Diagnostic and therapeutic applications on which the investigation and development of providers.

So how will the industry move from the laboratory to the clinic?

** In the US, the implementation of the Federal Food, Drug, and Cosmetic Act of 1944. While the act provides for safety and efficacy, it also provides for flexibility in the use of new biologics. The act is consistent with the FDA's Guidance for Industry on the use of biologics and the FDA's Guidance for Industry on the use of biologics in detail and flexibility.*

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 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 immunological 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 a 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 twenty 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 re-defined, 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*?

* In the US, the investigation and approval of biologics for human use is governed by the Food, Drug and Cosmetics Act of 1938 (last revised in the FDA modernization Act of 1997) and the Public Health Service Act of 1944. While these laws established the role of the US Food and Drug Administration in assuring the safety and efficacy of these products, the Code of Federal Regulations provides a greater level of detail and flexibility than do the laws regarding the requirements and processes necessary for human investigation with new biologics and their ultimate approval. The International Conference on Harmonisation of technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (<http://www.ich.org/ich5.html>), and the FDA's Guidance documents (<http://www.fda.gov/cber/guidelines.htm>), provide an even greater level of detail and flexibility. Relevant Guidances and ICH documents appear in Table 1.

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 2. 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.

The last new allergenic products licensed in the US were the standardized grass pollen extracts, licensed in 1997. 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 of them is important in assuring that the new product is safe and effective. They are listed in Table 3.

Two additional investigations and study design must be conducted in the same population. Thus, while we have immunotherapy of allergic disease would not likely be the result of a well-designed clinical trial of a new product with the best therapeutic effect.

Another specific example is the use of *Hymenoptera* venom. While the use of venom units. While the use of venom – both from many different units for these purposes:

1. the purity of the venom
2. the correlation of venom units to a constant; and
3. the product's stability under which

Table 1. Guidance on

For allergenic products

Guidance for Industry: Clinical Controls Informing the Use of Extract or Allergen

Guidance for Industry: Clinical Controls Informing the Use of Pollen Extracts

Guidance for Industry: Clinical Controls Informing the Use of Vaccines: A Review

For recombinant products

(ICH) Quality of Clinical Controls Informing the Use of Recombinant

(FDA/CBER) Clinical Controls Informing the Use of Monoclonal Antibodies

(ICH) Viral Safety of Clinical Controls Informing the Use of Human or Animal

(FDA/CBER) Clinical Controls Informing the Use of Related Products

make a product that
 manufactured consistently
 R 211 and current
 studies to demon-
 strate and appropriate
 and are needed to
 safety. After the ani-
 the FDA for permis-
 sed human investi-
 D application, and
 be administered to

as such, the IND
 nical use. All INDs
 and must indicate
 benefit. The FDA's
 and rights of study
 quate to permit an
 ss is that a poorly
 ethical abuse of the

divided into three
 nce into humans,
 n a small group of
 y, using the dose
 e. The number of
 Phase 3 trial is the
 ntrolled to defini-

the study – for the
 nical hold nearly
 terna highlight the
 of human research
 n by assuring the
 ysis. Finally, since
 and comment on
 the end of a suc-

standardized grass
 s to be approved,
 ne of these would
 al or recombinant;
 urmountable, and
 nd effective. They

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.

Table 1. *Guidance documents.*

For allergenic products (all FDA/CBER)

Guidance for Industry On the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test (1999)

Guidance for Industry: Testing Limits in Stability Protocols for Standardized Grass Pollen Extracts (2000)

Guidance for Reviewers: Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol (2000)

For recombinant products

(ICH) Quality of Biotechnology Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products (1995)

(FDA/CBER) Guidance for Industry: Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for *In-Vivo* Use (1996)

(ICH) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (1997)

(FDA/CBER) Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (1999)

The development and licensure of new recombinant allergens in the US is a deliberate process, intended to assure that safe and effective products come to market at the end of a well-designed and ethical series of human investigations. While the process may be expensive and lengthy, it is important to recall that many successful recombinant products have been approved by CBER over the past years, and the sponsors of investigations with recombinant allergens may be able to benefit from the experiences of the sponsors of successful prior applications. Resources are available, both at CBER and elsewhere, to assist in this process*.

Table 2. 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 3. Some hurdles in the study and approval of new recombinant allergens.

For new allergens (whether recombinant or natural)

Biological justification

Manufacturing practices – Lot to lot consistency

Good potency assay

Study power

For new recombinant allergens

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, SV40)

Fermentation/growth media/growth conditions

Purification

Characterization/proof of structure

* IND applications and instructions may be found at <http://www.fda.gov/cber/ind/ind.htm>. The American Academy of Allergy, Asthma and Immunology (AAAAI) has established a Future Immunomodulation Initiative to assist developers of new immunomodulatory products. The AAAAI may be reached at Phone No. 414-272-6071.

References

1. Baer H, Maloney J. Commercially prepared allergens.
2. Baer H, Godfrey J. Commercially prepared allergens.
3. Morrow KS, Slater J. 2001; 21: 141-152.
4. Turkeltaub PC, A. In: Allergens and Allergy. Dekker Inc, pp. 1-10.
5. Chapman MD. S. diagnosis and therapy.
6. Valenta R. The future of allergen immunotherapy. 453.
7. Løwenstein H. J. Rep 2001; 1: 474.

Discussion

Lehrer: Dr. Slater, allergen products in various allergen food allergens. T requests from ph to companies abo they would alway approved and tha gens and went thr ved for other pro comes to mind ag industry in the U bottom line. I am allergens, which n which will certain nion on that, do y about it? I know

Slater: There are tal investment in that this is consid have been throug that can be done applying for IND regulate certain i cedures using lice people who do n actually involved was going to put Individuals have

in the US is a deliberate
 to market at the
 While the process
 successful recombi-
 and the sponsors of
 from the experiences
 able, both at CBER

References

1. Baer H, Maloney CJ, Norman PS, Marsh DG. The potency and Group I antigen content of six commercially prepared grass pollen extracts. *J Allergy Clin Immunol* 1974; 54: 157-164.
2. Baer H, Godfrey H, Maloney CJ, Norman PS, Lichtenstein LM. The potency and antigen E content of commercially prepared ragweed extracts. *J Allergy* 1970; 45: 347-354.
3. Morrow KS, Slater JE. Regulatory aspects of allergen vaccines in the US. *Clin Rev Allergy Immunol* 2001; 21: 141-152.
4. Turkeltaub PC. Allergen Vaccine Unitage Based on Biological Standardization: Clinical Significance. In: *Allergens and Allergen Immunotherapy*, Lockey R, Bukantz SC (Eds), 1999, New York, Marcel Dekker Inc, pp. 321-340.
5. Chapman MD, Smith AM, Vailes LD, Arruda LK, Dhanaraj V, Pomes A. Recombinant allergens for diagnosis and therapy of allergic disease. *J Allergy Clin Immunol* 2000; 106: 409-418.
6. Valenta R. The future of antigen-specific immunotherapy of allergy. *Nat Rev Immunol* 2002; 2: 446-453.
7. Løwenstein H, Larsen JN. Recombinant allergens/allergen standardization. *Curr Allergy Asthma Rep* 2001; 1: 474-479.

Discussion

Lehrer: Dr. Slater, my question would be related to the development of recombinant allergen products and other allergen products. Over the years we have been interested in various allergens that are not available commercially such as some of the fungi and food allergens. There seems to be a real need for them, since I frequently receive requests from physicians to obtain allergen samples to test patients. Yet, when I spoke to companies about why they do not consider producing these allergens commercially, they would always say that it is a very difficult process to get an allergenic product approved and that it just is not worth it. I know that when you cited recombinant allergens and went through the process, you also stated that recombinants have been approved for other products but they are not currently available for allergenic products. It comes to mind again that one of the issues, as some claim, with the allergenic products' industry in the United States is that they always have, as any industry, to consider the bottom line. I am convinced that these currently unavailable allergens and recombinant allergens, which may not have the profit margin to bring them to market, are products which will certainly improve the diagnosis and treatment of allergy. What is your opinion on that, do you think that there may be some truth in this and what can be done about it? I know it is a tough question but I think it is an important issue.

Slater: There are a couple of different issues here. One is simply the expense and capital investment in bringing a product through the licensing process. There is no doubt that this is considerable. I think that now, after there are dozens of such products that have been through the process, this is a process that is navigable, it is something and that can be done. You are probably well aware that we have had many new people applying for INDs because of recent events in the United States that have led us to regulate certain investigational procedures. For instance, bronchoalveolar lavage procedures using licensed products now require an IND. So we have had a number of new people who do not have any products that they try to bring to market who are now actually involved in applying for INDs. After an initial period of great concern that this was going to put an end to these investigations, quite the opposite has been the case. Individuals have applied and have been approved and safe procedures have been insti-

te of adventitious