



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

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Re: Docket Number 97P-0281/CP 1

Dear Mr. Korwek:

This responds to the petition you filed on behalf of the Allergen Product Manufacturers Association ("APMA"), requesting that the Food and Drug Administration withdraw certain requirements pertaining to the standardization of eight grass pollen extracts. Specifically, you have requested that FDA not impose the following requirements:

1. Measurement and labeling of the potency of these products in bioequivalent allergy units ("BAUs"), as defined by the intradermal erythema skin testing method described by the Center for Biologics Evaluation and Research ("CBER"), or an alternative method approved by FDA;
2. Deletion from product labeling of other systems of units describing the allergen content, such as the ratio of weight to volume ("W/V") and/or the protein nitrogen units ("PNUs");
3. Mandatory FDA lot release testing by CBER for each commercially available product strength;
4. Stability testing for each product formulation and each marketed strength;
5. Issuance of letters from manufacturers to physicians explaining the transition to bioequivalent allergy units; and
6. Phase IV testing of the new, standardized extracts.

(Emphasis supplied.) FDA notified grass pollen extract manufacturers of these requirements, imposed pursuant to 21 C.F.R. §§ 610.10 and 680.3(e), in a letter dated April 8, 1994. FDA extended the date for compliance with these provisions several times. By July 8, 1998, all grass pollen extract manufacturers appeared to be in compliance with items one through five of these requirements, with Phase IV testing underway.

97P-0281

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You have based your petition on arguments that FDA should have required the use of standardization technology only through notice and comment rulemaking, and that FDA has acted arbitrarily and capriciously. After careful review of your petition, the Agency denies the petition for the reasons that follow.

## **I. Background**

Allergenic products "are products that are administered to man for the diagnosis, prevention or treatment of allergies." 21 C.F.R. § 680.1(a). They are regulated as biological products under the Public Health Service Act, see 42 U.S.C. § 262(i), which requires a showing that each product is "safe, pure, and potent." 42 U.S.C. § 262(a)(2)(B)(i). Allergenic products are also "drugs" within the meaning of the Food, Drug, and Cosmetic Act, since they are "intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease" and "intended to affect the structure or any function of the body." 21 U.S.C. § 321(g)(1)(B), (C). At this time, FDA regulates over 1000 allergenic products, including the eight grass pollen extracts at issue here.

### **A. Allergies and the Uses of Allergenic Products**

An allergy is an illness due to an immune response following exposure to a foreign substance. Scientists first recognized illnesses associated with exposure to foreign organic substances in the early part of the nineteenth century. Since that time, a number of conditions such as dermatitis, conjunctivitis, rhinitis, asthma, urticaria, vomiting, diarrhea, and anaphylactic shock have been shown to follow exposure of a susceptible individual through contact, injection, inhalation, or ingestion of a particular allergen.

Clinicians typically diagnose patients as sensitive to a particular allergen on the basis of the patient's reaction to a challenge, almost always in the form of a skin test, with an allergenic product containing that allergen. Skin testing with allergenic products allows the production of a local allergic response under limited and controlled conditions. Carefully performed skin tests are currently regarded as reasonably reliable and sensitive, and as the most practical method for confirming the presence of a specific sensitivity.

Nevertheless, several variables affect every skin test: the environmental conditions (for example, the presence of allergens in the air), the immunological response of the patient, and the allergenic product used as a test material. If not performed with due care, skin testing could cause a dangerous systemic reaction, e.g., tachycardia, hypotension, and death. There have even been incidents of death following diagnostic skin testing.<sup>1</sup>

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<sup>1</sup> See, for example, Report of Panel on Review of Allergenic Extracts ("Panel Report") 50 Fed. Reg. 3082, 3095 (Jan. 23, 1985); Reid, M., Lockey, R.F., Turkeltaub, P.C., Platts-Mills, T.A.E., Survey of Fatalities from Skin Testing and Immunotherapy, 1985-1989, J.Allergy Clinical Immunology, 92:6-15 (1993); Lockey, R.F., Benedict, L.M., Turkeltaub, P.C., Bukantz, S.C., Fatalities from Immunotherapy and Skin Testing, J.Allergy Clinical Immunology 79:660 (1987); Death Associated with Allergenic Extracts, FDA Medical Bulletin, 24:7 (1994); Deaths

After detection of a sensitivity to a particular allergen, a clinician may diagnose the patient as having an allergic disease and may treat the patient by allergen immunotherapy, which involves a series of injections of an allergenic product containing the allergen to which the patient is sensitive. Each injection is an allergen challenge. The clinician begins treatment with small doses. The more sensitive the patient, the smaller the dose tolerated, particularly at the initiation of treatment. As the patient develops a tolerance to a dose (as most patients do), the clinician progressively increases the dose. Treatment may last three to five years, or longer.

Once again, the success of the treatment is subject to several variables, including environmental conditions, the immunological response of the patient, and the allergenic product administered. Dangerous systemic reactions occur with varying frequency following injection treatments. There have been incidents of death following injection treatment.<sup>2</sup>

### **B. Potency of Allergenic Products; the Need for Standardized Products**

As noted above, there are several variables inherent in the use of allergenic products for diagnosis or treatment of allergies: environmental conditions, the immunological response of the patient, and the allergenic product administered.

Environmental conditions may increase the unpredictability of patient response to administration of the allergenic product. Unanticipated variations in the patient's immunological response may increase the risk that a patient will suffer a systemic reaction during diagnosis or treatment. A patient's allergic condition might become more severe, or another illness might exacerbate that condition. An unstandardized allergenic product may vary greatly from manufacturer to manufacturer, or even from lot to lot. Significant variations might increase the risk that a patient will suffer a systemic reaction during diagnosis or treatment. Since individual immunological and allergenic responses are unpredictable, scientists and clinicians have focused their efforts to reduce risk to the patient by decreasing the level of variability in the allergenic product.

You suggest that standardized allergenic products are deficient because they can not control the variability of a patient's allergic response.<sup>3</sup> You appear to argue that, since manufacturers and clinicians can not control every variable affecting patient response, they should attempt to control no variable. FDA has rejected this approach. The unpredictable nature of an individual's allergic response is exacerbated by the use of unpredictable allergenic products. By using properly labeled, standardized allergenic products, and thereby limiting the unpredictability of the allergenic product, a physician will reduce risk to the patient.

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Associated with Allergenic Extracts, JAMA 272:1488 (1994).

<sup>2</sup> See, for example, Panel Report, 50 Fed. Reg. at 3095; Reid, M., et al., Survey of Fatalities; Lockey, R.F., et al., Fatalities from Immunotherapy; Fatalities with Allergenic Extracts, FDA Medical Bulletin; Deaths Associated with Allergenic Extracts.

<sup>3</sup> See Citizen Petition at 16 ("The standardization system may even mislead physicians into believing that the BAU units accurately predict clinical effect, which could prove detrimental to patient safety.")

One way to decrease the level of variability in allergenic products is through standardization; that is, a demonstration that the quality of a particular allergenic product is comparable to that of a reference standard.<sup>4</sup> Standardization of allergenic products presents a challenge, since most allergenic products are heterogeneous mixtures of which the active allergens are only a small portion of the total mixture. The remainder of the allergenic product is typically composed of a variety of characterized and uncharacterized substances.<sup>5</sup>

Physicians noted the need for standardization of allergenic products, both before,<sup>6</sup> and after,<sup>7</sup> CBER began to implement the standardization regulations. Since the safety and effectiveness of allergenic products are a function of specific allergen content, allergists have embraced the use of standardized extracts. Standardization allows them to administer doses with far greater confidence than they had before.

Until relatively recently, standardization efforts were stymied by the lack of potency tests capable of measuring the allergenic activity of allergenic products. In the absence of such tests, manufacturers attempted to describe the potency of an allergenic product by using one of two designations: 1) the ratio of the weight of the allergen source material to the volume of extracting fluid ("W/V"); or 2) protein nitrogen units per milliliter ("PNU/mL") present. Neither designation is a reliable measure of biological or allergenic activity, since they do not accurately measure the presence of allergenically active antigens in an allergenic product.<sup>8</sup>

As discussed in Section I.D.3, below, biological potency is accurately defined by BAU (Bioequivalent Allergy Units)/mL as determined by skin testing on allergic patients and by laboratory testing using the Enzyme-Linked Immuno-Sorbent Assay ("ELISA"). Table I lists the ranges of relative potency over all manufacturers for each grass pollen extract, as compared to a 100,000 BAU/mL reference. The ranges for aqueous 1:10 W/V extracts are typically a factor of 9-10, and in one case a factor of 83; ranges for the glycerinated 1:20 W/V extracts are somewhat smaller, but do vary by as much as a factor of 17,<sup>9</sup> compared to a 100,000 BAU/mL reference.

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<sup>4</sup> See Panel Report, 50 Fed. Reg. at 3108.

<sup>5</sup> Id.

<sup>6</sup> See Creticos, P.S. and Norman, P.S., Why Standardized Extracts are Necessary, *Clinical Rev. Allergy* 4:355-361 (1986). Moreover, as you note, the American Academy of Allergy and Immunology issued a position statement in 1980 supporting the need for standardization. Citizen Petition at 8, n. 29 (citing AAAI Position Statement on Allergen Standardization (No. 6), *J. Allergy Clinical Immunology* 66:431 (1980)).

<sup>7</sup> See Committee on Allergen Standardization, The Use of Standardized Allergen Extracts, *J. Allergy Clinical Immunology* 99:583-86 (1997).

<sup>8</sup> See Panel Report, 50 Fed. Reg. at 3108-09.

<sup>9</sup> The potency range for the glycerinated extracts is narrower than the range for the aqueous extracts because the addition of glycerin to an allergen extract dramatically increases the stability of allergen solution. Anderson, M.C., and Baer, H., Antigenic and Allergenic Changes During Storage of a Pollen Extract, *J. Allergy*

Nor does the PNU/mL designation correlate to biological potency. In one study,<sup>10</sup> FDA scientists plotted protein content for 171 lots of standardized grass pollen extracts, all with a potency of 100,000 BAU/mL. The protein content of those extracts varied from 0.73 to 11.53 mg/mL.<sup>11</sup> Thus, dilution of the extracts to a constant value of PNU/mL would result in final products that varied in allergenic activity by a factor of 16.

Conversely, potency may vary significantly for extracts whose protein content is very similar. For example, the package insert used for one standardized grass pollen extract reports data for seven lots of unstandardized Orchard grass pollen extract. The protein content of those lots varied from 116,000 to 159,000 PNU/mL (a factor of 1.4) while the potency ranged from 24,000 to 225,000 BAU (a factor of 9.4).<sup>12</sup>

You recognize the variability of unstandardized allergenic products, "The ratio of allergenic components may vary among products and, thus, also may significantly alter allergenic response."<sup>13</sup> As discussed above, unstandardized extracts are highly variable in their biological activity. Many of the ranges of relative potency set out in Table I are well outside the range of variability that has been identified as clinically safe. This range of clinically safe variability is approximately a factor of four.<sup>14</sup> A patient who received one dose of Orchard grass pollen extract, with a relative potency of .24, followed by another dose with a relative potency of 2.42, would be in danger of a serious allergic reaction. On the other hand, if, during a course of immunotherapy, a weak extract followed an extract that was ten times stronger, the weak extract could threaten the success of the therapy. The effectiveness of immunotherapy depends in large measure on the maximum dose and the cumulative dose injected.<sup>15</sup>

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Clinical Immunology, 69:3-10 (1982). As a result, all standardized allergen extracts are glycerinated. Prior to CBER's allergen standardization program, only a minority of allergen extracts was sold in glycerin solutions. In fact, aqueous (non-glycerinated) extracts remain the norm among currently marketed non-standardized extracts, in spite of clear evidence of improved stability associated with the addition of glycerin.

<sup>10</sup> Slater, J.E., Gam, A.A., Solanki, M.D., Burk, S.H. May, F.M., Pastor, R.W., Statistical Considerations in the Establishment of Release Criteria for Allergen Vaccines, Arb. Paul Ehrlich Inst. Bundesamt Sera Impfstoffe Frankf. A.M. (in press).

<sup>11</sup> Id., Figure 1 .

<sup>12</sup> See Center Laboratories package insert.

<sup>13</sup> Citizen Petition at 6.

<sup>14</sup> Slater, Jay E. and Pastor, Richard W., The Determination of Equivalent Doses of Standardized Allergen Vaccines, J. Allergy Clinical Immunology (in press). The range of potencies for standardized extracts is less than a factor of three.

<sup>15</sup> Creticos, P.S., "Chapter Five: Efficacy Parameters," Immunotherapy, A Practical Guide to Current Procedure, American Academy of Allergy and Immunology, Milwaukee, WI (1994).

Thus the variability of unstandardized product directly impacts our ability to evaluate the safety and effectiveness of an allergenic product for a particular indication. As the expert Panel on Review of Allergenic Extracts ("Allergenic Extracts Panel") noted:

Extensive clinical trials cannot be performed each time a new lot of a given allergenic extract is prepared. If results of clinical trials of individual lots are to be extrapolated to subsequent lots of the same product, there is an implicit assumption that the biological characteristics (in particular, potency and stability of the product) can be adequately specified and controlled by the manufacturer. This Panel has noted that this prerequisite has not yet been adequately fulfilled by many of the products under review and wishes to emphasize its importance . . . it is imperative that, before a clinical study is initiated, an acceptably standardized reference preparation be established for use in the clinical trial to allow for subsequent comparison.<sup>16</sup>

According to the Allergenic Extracts Panel, this variable state of affairs was unacceptable:

The increasing ability to define complex biological materials has made it apparent that these techniques [measuring potency of allergenic products by reference to W/V or PNU] provide inadequate information about composition or potency of allergenic extracts. Proof should be expected that the biologically active ingredients claimed to be in a biological product are in fact present. Active ingredients of allergenic extracts should be identified as precisely as is consistent with current knowledge and a quantitative estimate of their concentration should be provided.<sup>17</sup>

By 1985, "the means of standardizing most allergenic extracts [we]re well within [existing] technical capabilities."<sup>18</sup> The Allergenic Extracts Panel recommended that: (1) FDA should develop and maintain allergenic extract samples to serve as reference standards, and make those reference standards available to manufacturers of allergenic extracts and to individuals and groups engaged in research; and (2) the biological or immunological activity associated with a reference standard should be estimated by suitable in vitro [laboratory] or in vivo [involving clinical study in patients] methods.<sup>19</sup>

### **C. FDA's Rule on Standardized Potency Designations**

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<sup>16</sup> Panel Report, 50 Fed. Reg. at 3119

<sup>17</sup> Id. at 3108.

<sup>18</sup> Id. at 3112 (citing Lichtenstein, L.M., Editorial: Standardization and Efficacy of Allergen Extracts, *New Eng. J. Med.*, 295: 1195-96 (1976)).

<sup>19</sup> Id.

In 1985, FDA published a proposed rule relating to standardized potency testing of allergenic products.<sup>20</sup> Afterward, FDA continued to work with the Allergenic Products Advisory Committee and industry members to address the need for standardization. On June 26 and 27, 1986, the Allergenic Products Advisory Committee met to consider standardization of mite extracts. Industry representatives, including APMA members, were also in attendance. FDA representatives, industry representatives, and other internationally recognized allergy experts described laboratory standardization techniques, parallel line skin-test methodology for evaluation of relative potency, and correlation of parallel line testing with laboratory techniques.<sup>21</sup> On March 12 and 13, 1987, the Allergenic Products Advisory Committee met again, and again industry representatives, including an APMA representative, were in attendance. FDA presented data on the development of standardization methods and skin test methods for standardization using ID<sub>50</sub>EAL methodology.<sup>22</sup>

On October 8, 1987, FDA promulgated the following rule:

The potency of each lot of each Allergenic Product shall be determined as prescribed in § 610.10 of this chapter. Except as provided in this section, the potency test methods shall measure the allergenic activity of the product. Until manufacturers are notified by the Director, Office of Biologics Research and Review, of the existence of a potency test that measure the allergenic activity of an allergenic product, manufacturers may continue to use unstandardized potency designations.<sup>23</sup>

At that time, as now, Section 610.10 provided:

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in 600.3(s) of this chapter.<sup>24</sup>

With respect to these provisions:

The word *potency* is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data

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<sup>20</sup> 50 Fed. Reg. 30211 (July 24, 1985).

<sup>21</sup> Transcript of Proceedings, Allergenic Products Advisory Committee Meeting, June 26-27, 1986, at 5-186.

<sup>22</sup> Transcript of Proceedings, Allergenic Products Advisory Committee Meeting, March 12-13, 1987, at 131-54.

<sup>23</sup> 21 C.F.R. § 680.3(e); 52 Fed. Reg. 37605 (October 8, 1987).

<sup>24</sup> 21 C.F.R. § 610.10.

obtained through the administration of the product in the manner intended, to effect a given result.<sup>25</sup>

Thus, the 1987 rule made explicit the obligation of manufacturers of allergenic products to change their practices to meet technological and manufacturing advances in the area of allergenic product standardization. To assure that allergenic product manufacturers would not remain ignorant of such advances, FDA undertook to advise manufacturers when potency tests measuring the allergenic activity of an allergenic product were developed. As the Preamble to the Final Rule stated:

FDA will recommend potency test methods to manufacturers when FDA believes that the method results in a reliable measure of biologic or allergenic activity. . . FDA will recommend a specific potency test method only after the method has been shown to be effective and has been discussed or demonstrated in one or more public workshops, has appeared in scientific publications, or has been discussed with individual manufacturers.<sup>26</sup>

FDA recognized that scientists might develop more than one such method of measurement, or that one method might be replaced by another:

more than one appropriate measurement of allergenic activity may exist for a specific allergenic product, and this rule provides flexibility so that more than one method may be used provided any methods used results in reliable measurements of a product's potency.<sup>27</sup>

**D. Application of the Standardized Potency Rule, 21 C.F.R.680.3(e), to Manufacturers of Grass Pollen Extracts**

**1. Technological Developments and Communication with Industry Members**

After promulgating the 1987 rule, FDA continued to participate in discussions regarding standardization of allergenic products. At the May 24 and 25, 1988 Allergenic Products Advisory Committee Meeting, FDA discussed potency test methodologies, references and serum pools, and the ID<sub>50</sub>EAL skin test methodology.<sup>28</sup> The Committee approved FDA's proposal not to require skin testing from manufacturers, as long as other materials supporting the license

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<sup>25</sup> 21 C.F.R. § 600.3(s).

<sup>26</sup> 52 Fed. Reg. at 37605.

<sup>27</sup> *Id.* at 37606.

<sup>28</sup> Transcript of Proceedings, Allergenic Products Advisory Committee Meeting, May 24-25, 1988, at 2-48, 147-211.

application were complete.<sup>29</sup> An APMA representative actively participated in discussions with the advisory committee members.<sup>30</sup>

APMA representatives continued to work toward standardization of grass pollen extracts. In early September, 1990, at the Sixth International Paul Ehrlich Seminar,<sup>31</sup> Greer Laboratories, an APMA member, presented data utilizing an ELISA test for grass allergenic products.<sup>32</sup> Recognizing the importance of this technological advance, the firm's promotional literature states, "our team approach enabled Greer Laboratories to develop the ELISA inhibition procedure for measuring extract relative potency . . . it's become one of the most powerful tools in our industry's drive for batch consistency and accurate labeling."<sup>33</sup>

FDA regularly sought the advice of the Allergenic Products Advisory Committee on grass pollen extract standardization issues. At the February 4, 1991 public meeting, FDA representatives discussed standardization of allergenic products and implementation of potency testing. FDA representatives made presentations on the status of standardization of grass extracts, and asked the Committee whether FDA should require a clinical skin test bioassay on initial lots of grass extracts submitted with a licensing application, or whether a laboratory test result would be sufficient. The Advisory Committee voted unanimously not to require skin testing.<sup>34</sup> Representatives of Greer Laboratories and Antigen Laboratories, both members of APMA, presented statements related to standardization at the meeting, and an APMA representative attended and presented a statement on another issue under consideration.<sup>35</sup>

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<sup>29</sup> *Id.* at 197-211.

<sup>30</sup> *Id.* at 47-48, 208-10.

<sup>31</sup> The Paul Ehrlich Seminar is a forum for representatives of government, industry, and science to discuss problems of manufacturing and controlling allergenic extracts, to promote the standardization of allergenic products, and to advance harmonization in the implementation of rules and regulations for allergenic extracts. The Seminar was initiated in the late 1970s when the Federal Republic of Germany, due to reform of their drug registration law, began to regulate allergenic products. In order to obtain information regarding this product area, members of the Paul Ehrlich Institute, the German regulatory authority, contacted FDA to organize an international forum for discussion of the relevant regulatory issues concerning allergenic products. The first meeting was in 1977, with subsequent meetings approximately every three years. See Siefert, G., Review of the Past Paul Ehrlich Seminars, *Arb. Paul Ehrlich Inst., Bundesamt Sera Impfstoffe Frankf., A.M.*, 1988; 82: XII-XV.

<sup>32</sup> Esch, R.E., Role of Proteases on the Stability of Allergenic Extracts, *Arb. Paul Ehrlich Inst. Bundesamt Sera Impfstoffe Frankf. A.M.* 1992, 85:171-79.

<sup>33</sup> Greer Laboratories, promotional literature, "Optimization (in Research)".

<sup>34</sup> Transcript of Proceedings, Allergenic Products Advisory Committee Meeting, February 4, 1991, at 151.

<sup>35</sup> *Id.* at 25-33, 43-47, 249-256.

At the December 13, 1991 meeting, a public meeting announced in advance in the Federal Register,<sup>36</sup> FDA summarized the development of laboratory test methods for standardization. The Advisory Committee recommended that FDA continue to move toward standardized potency testing for grass pollen extracts under 21 C.F.R. § 680.3 (e).<sup>37</sup> Committee members stressed that variations in the potency of grass pollen extracts could pose a safety problem.<sup>38</sup> A representative of one allergenic product manufacturer (a member of APMA) appeared and gave a statement regarding standardized cat extract.<sup>39</sup>

At the July 20, 1993 meeting, attended by industry members, FDA discussed new testing procedures for the standardization of grass pollen allergenic extracts. The Advisory Committee recommended that each grass extract should be available in two dose forms: 100,000 and 10,000 BAU/mL (Bioequivalent Allergy Unit per milliliter). FDA advised the Committee that, pursuant to 21 C.F.R. § 680.3(e), it intended to advise manufacturers of eight grass pollen extracts that there was available a potency test capable of measuring the allergenic activity of those allergenic products. That standardization method involved skin testing, which would be performed by FDA as the developer of the initial reference standards, and laboratory testing, which would be performed by manufacturers. Manufacturers would test their products to assure that the products conformed to reference samples. See Section I.D.3. The Advisory Committee and FDA approved FDA's proposal to phase in standardization requirements over a two year period.<sup>40</sup> Representatives of two APMA-member companies made comments during the meeting.<sup>41</sup>

Moreover, FDA met with APMA once a year to discuss standardization and other regulatory issues. On October 17, 1991, FDA and APMA representatives discussed, among other things, approvals of supplements to product licenses for standardized grass pollen extracts.<sup>42</sup> In the October 15, 1992 meeting, APMA representatives stated that APMA members were anxious to continue the momentum of the standardization effort.<sup>43</sup> At the October 20, 1993 meeting, APMA requested an update on the proposals related to standardized grass pollen extracts, and inquired about future standardization candidates and FDA skin testing of various reference preparations for standardized products.<sup>44</sup>

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<sup>36</sup> 56 Fed. Reg. 58701, 58702 (Nov. 21, 1991).

<sup>37</sup> Transcript of Proceedings, Allergenic Products Advisory Committee, December 13, 1991, at 18-59.

<sup>38</sup> One panel member noted, "as far as I know, almost all of the immunotherapy deaths in the United States involve grass extracts, a very large percentage, if not almost all." *Id.* at 53-54.

<sup>39</sup> *Id.* at 12.

<sup>40</sup> Transcript of Proceedings, Allergenic Products Advisory committee Meeting, July 20, 1993, at 111-66.

<sup>41</sup> *Id.* at 166-69.

<sup>42</sup> Agenda, CBER-APMA Information Exchange Meeting, October 17, 1991.

<sup>43</sup> Agenda, APMA/FDA Information Exchange Meeting, October 15, 1992.

<sup>44</sup> Agenda, APMA/CBER Information Exchange Meeting, October 20, 1993.

Two months later, in December, 1993, when it became clear that standardization of grass pollen extracts, in accordance with 21 C.F.R. §§ 610.10 and 680.3(e), was feasible, FDA held joint workshops with grass pollen extract manufacturers.<sup>45</sup> The subject of the workshops was the ELISA potency assay and calculation of relative potency. Ten allergenic product manufacturers participated.

**2. Pursuant to 21 C.F.R. § 680.3(e), FDA Advises Grass Pollen Manufacturers of the Existence of a Test Capable of Measuring the Potency of Eight Grass Pollen Extracts.**

As noted on page 1, by letters dated April 8, 1994, FDA notified grass pollen extract manufacturers of the existence of a grass pollen standardization method to measure the allergenic activity of eight grass pollen extracts.<sup>46</sup> FDA stated:

In accordance with 21 C.F.R. § 680.3(e), we are notifying all manufacturers that suitable testing methods which measure the allergenic activity of these eight grass pollen extracts are available. We are therefore requiring that final containers of each grass pollen extract be labeled with a potency that reflects the allergenic activity of the product. We are recommending that each of these eight grass pollen extracts be standardized by comparison against the respective FDA Reference Extract and FDA Reference Serum Pool, or an equivalent FDA approved reference reagent and an equivalent FDA approved reference serum pool, utilizing either the Radioallergosorbent Test ("RAST") or the Enzyme-Linked Immunosorbent Assay ("ELISA"). These methods can be found in the Methods of Allergenic Products Testing Laboratory, 1993. We will accept equivalent testing methods that provide an equally reliable measure of the potency of the product.

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<sup>45</sup> You complain that "the agency did not publish notice of its workshops in the Federal Register." Citizen Petition at 40. These workshops were only one mechanism FDA used to communicate regarding its implementation of 21 C.F.R. § 680.3(e). In any event, at the outset, the agency announced in the Federal Register that it would "consider conducting more workshops as needed to assist manufacturers in performing specific potency tests for allergenic products." 52 Fed. Reg. at 37605 (Preamble to final rule establishing 21 C.F.R. § 680.3(e)). FDA maintained regular contact with industry members on these issues.

<sup>46</sup> This was not the first time technology became available to permit product standardization in accordance with FDA regulations. Over the past decade, four other types of allergenic products have been standardized: short ragweed, dust mite, cat dander, and insect venoms. These transitions proceeded without disruption of supply or significant safety problems. The standardized products have been widely accepted as improvements. See Norman, P., and Van Metre, T., *The Safety of Allergenic Immunotherapy*, *J. Allergy and Clinical Immunology*, 85:522 (1990); Committee on Allergen Standardization, *Position Statement: The Use of Standardized Allergen Extracts*, *J. Allergy and Clinical Immunology*, 99:583 (1997). For example, when potency testing for the major cat allergen, fel d I, became available, it was discovered that some extracts of house dust (intended for dust mite allergy) had more fel d I than did the cat dander extracts themselves. Chapman, M.D., Aalberse, R.C., Brown, M.J., Platts-Mills, T.A.E., *Monoclonal Antibodies to the Major Feline Allergen Fel d I*, *Journal of Immunology*, 140:812 (1988).

FDA recommended test methods, or equivalent test methods, should be submitted to FDA for review and approval prior to implementation.

**a. FDA Invites Submission of Alternative Standardization Methods, and Invites Comments on the Standardization Methodology, but Receives None.**

No manufacturer proposed an alternative method of measuring the potency of any of the eight grass pollen extracts, despite the direct invitation to do so contained in FDA's April 8, 1994 letters.

By Federal Register notice dated November 23, 1994, FDA announced the availability of a revision of "Methods of the Laboratory of Allergenic Products" dated March 1987. This document, "sets forth the in vitro and in vivo methods used in the [FDA/CBER] Laboratory of Immunobiochemistry for determining the identity and relative potency of investigational and approved allergenic extracts." The reason for the Federal Register notice was very clear:

FDA is requesting comments from interested parties concerning the methods document. These comments will be considered in determining whether further revision of the methods document is warranted.<sup>47</sup>

Despite the clear invitation, FDA received no comment from allergenic product manufacturers on the potency testing methods.

**b. FDA Extends the Deadline for Compliance with 21 C.F.R. §§ 610.10 and 680.3 (e)**

FDA and APMA representatives discussed the April 8th letters at a August 17, 1994 meeting, and again at the annual meeting on October 26, 1994.<sup>48</sup> At the November 22, 1994 Advisory Committee meeting, APMA proposed that there should be a two year phase-in period, from April 1996 to April 1998, during which both standardized and unstandardized grass pollen extracts could be sold. After careful consideration, the Advisory Committee voted that unstandardized grass pollen extracts should not be marketed after April, 1996.<sup>49</sup>

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<sup>47</sup> 59 Fed. Reg. 60362 (Nov. 23, 1994). FDA anticipates that, in the future, potency test methods will be developed for other allergenic products. FDA intends to notify manufacturers of the existence of a potency test measuring the allergenic activity of an allergenic product, and that the potency test represents one way to meet the requirements of 21 C.F.R. 680.3(e), in accordance with the procedures set out in 21 C.F.R. 10.115.

<sup>48</sup> Throughout the period of transition to standardized grass pollen extracts, FDA continued its annual meetings with APMA.

<sup>49</sup> Transcript of Proceedings, Allergenic Products Advisory Committee Meeting, November 22, 1994, at 40-45.

At a public session of the Allergenic Products Advisory Committee, held on January 22, 1996, an APMA representative outlined the problems the industry had encountered in meeting the time frames set out in the April 8th letters.<sup>50</sup> FDA then informed the advisory committee that it planned to extend by fifteen months the date by which grass extract manufacturers would be required to comply with the FDA's call for standardized products, pursuant to 21 C.F.R. §§ 610.10 and 680.3(e).<sup>51</sup> By letter to grass pollen extract manufacturers dated April 5, 1996, FDA extended that deadline to July 8, 1997. In doing so, FDA was responding to letters from APMA and from the American Academy of Allergy, Asthma & Immunology, requesting that the deadline be extended. APMA had raised concerns about the impact on product supplies, and the American Academy had requested a two year transition period (April 8, 1996-April 8, 1998) to allow it to develop protocols for physicians to use in converting to standardized products. FDA concluded that "[t]he additional fifteen months will allow physicians and manufacturers to address any concerns."

FDA extended that deadline a second time, to January 8, 1998, by letter dated June 18, 1997, "in order to ensure an uninterrupted supply of grass pollen extracts." By letter to grass pollen extract manufacturers dated December 23, 1997, FDA extended that deadline a third and final time, to July 8, 1998. FDA noted that it had received a letter from the American Academy of Allergy, Asthma & Immunology dated December 17, 1997, and responded to APMA's request that the deadline be stayed, and to the American Academy's request that the deadline be extended. Both parties had "raised concerns that the current January 8, 1998 deadline for cessation of manufacture and distribution of non-standardized extracts may result in an inadequate supply of standardized grass pollen extracts." After full consideration, FDA determined:

an extension of six months from the January 8, 1998 deadline is appropriate in order to allow physicians and manufacturers to address any concerns . . . related to the transition from non-standardized to standardized grass pollen extracts. During the six month extension period (even after approval of a product license supplement to manufacture [ . . . ] standardized grass pollen extracts) manufacturers may continue to distribute non-standardized grass pollen extracts. However, on July 8, 1998, new lots of the eight grass pollen extracts, introduced into interstate commerce, will be considered safe and effective and not misbranded only if the new lots are standardized such that the product's potency has been measured under FDA approved procedures and FDA has approved the labeling.

By July 8, 1998, FDA had approved amendments to the product license applications of all grass pollen extract manufacturers, reflecting the change to production of standardized products of measurable potency.

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<sup>50</sup> Transcript of Proceedings, Allergenic Products Advisory Committee Meeting, January 22, 1996, at 8-10.

<sup>51</sup> *Id.* at 11-13.

### **3. The FDA-Recognized Grass Extract Standardization Method**

The grass pollen standardization method recognized by FDA consists of three phases. The first involves FDA's selection of a lot of grass pollen extract to serve as a reference standard for each grass pollen allergenic product. The second involves manufacturers' laboratory testing of their products and samples of the reference standard to assure that their allergenic products have a potency comparable to the reference standard. The third phase occurs when supplies of a reference standard or serum pool for use in laboratory testing run low, and FDA and industry representatives use laboratory testing to select a new generation of reference standard or serum pool. Under the standardization method recognized by FDA, there would be no need for manufacturers to conduct skin testing of their products on patients. Manufacturers would standardize their products by conducting laboratory tests to compare them to a reference standard, rather than by conducting the more difficult skin testing.

#### **a. Selection of a Reference Standard**

To identify a reference standard, FDA first used laboratory methods to measure allergenically important proteins in a variety of grass extracts. If the tests showed that an extract contained a wide range of allergenically important proteins in a quantity detectable by laboratory tests, the extract was suitable for clinical testing as a candidate reference standard.

For the clinical testing, skin testing, as briefly described in Section I.A., was performed on a panel of 15 subjects who were selected because they were highly allergic to the grass extract allergenic product under study. A clinician used a dilution prepared from a candidate reference to perform the skin testing. The clinician measured the size of the skin reaction (erythema) to each dilution administered. After statistical analyses, the skin test dilutions and the measurement of the skin reaction at each dose served as an estimate of the potency of that candidate reference standard. An FDA standard that elicited a 50 millimeter erythema at a mean allergen dilution between 13 to 15 three-fold dilutions (about  $1.6$  to  $14.4 \times 10^6$  - fold dilution) was defined as containing 100,000 Bioequivalent Allergy Units ("BAU") per milliliter. FDA adjusted the concentration of the references to reflect the consensus potency targets, 10,000 and 100,000 BAU/mL, then designated grass pollen extract from the lot tested as a reference standard. FDA stored the reference standards awaiting shipment to manufacturers under conditions where most proteins are highly stable and therefore unlikely to lose potency during storage.

#### **b. Laboratory Testing**

Manufacturers would then conduct the second evaluation, which involved an estimate of the potency of the manufacturers' lot of allergenic extract relative to the reference standard. If the results obtained by testing the allergenic product conformed to those obtained by testing the reference standard, then the potency of the allergenic product would be measurable and predictable.

Using FDA-supplied reference standard samples and pooled serum reagents, manufacturers would conduct laboratory testing to assure that their products were equivalent to the reference standard. By testing their product using the ELISA or RAST ("radioallergosorbent test") inhibition tests,<sup>52</sup> and comparing those test results to those obtained by testing the reference standards, manufacturers would calibrate the potency of their products to the reference standards.

Both the ELISA and the RAST use as reagents serum containing human antibodies. For many years, we have known that allergies are mediated by a subset of antibodies called IgE. The specific characteristics of an individual's IgE determine whether an allergen will cause allergy symptoms in that individual. When an individual makes IgE specific for a particular allergen, the IgE becomes attached to specific receptors on mast cells loaded with granules. When the allergen falls on mucosal surfaces, the allergens dissolve in the secretions and eventually come in contact with, and bind to, IgE. This binding reaction triggers the mast cells to release granules containing large amounts of histamine and other inflammation mediators, causing allergy symptoms.

Grass pollen extracts are complex mixtures of allergens. Each allergen has its corresponding IgE antibody. In order to reflect this complex mixture, the grass pollen standardization method uses pooled serum that has been collected from many allergic subjects. The range of contributors assures that the serum pool will include IgE specific to a wide range of the allergens present in grass pollens. Each major allergen is represented in the reactivity of the pool. By using IgE specific to the many allergens present, the testing reproduces the reaction that occurs in the tissues of subjects who are highly sensitive to grass allergens. Thus, the test assays grass allergens based on their content of biologically relevant allergens.

APMA member Greer Laboratories developed the ELISA for this purpose. The ELISA is performed as follows. The technician mixes a sample of the test allergenic product with pooled serum containing human IgE that recognizes the allergen. The technician adds the mixture to a microtiter plate, in wells coated with immobilized reference allergenic product. The antibodies in the pooled serum are allowed to bind to the allergens either in the test allergenic product or the reference standard. If there are more allergens in the test product, then fewer antibodies will bind to the immobilized allergen on the wells of the microtiter plate.

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<sup>52</sup> As you note, "Both of these methods provide a quantitative assessment of the amount of antigen in the test extract by measuring, directly or indirectly, the amount of antigen bound to allergen-specific antibodies fixed on a solid substrate." Citizen Petition at 9-10. Numerous examples of bioassays based on ELISA testing have demonstrated the reliability and reproducibility of the assay in a number of different laboratories. For example, ELISA assays are used in all United States blood banks to test for transfusion-transmitted diseases such as hepatitis and AIDS. More than eight million blood units are tested each year, with an accuracy of about 99.9%. The safety of the United States blood supply depends on the accuracy and reproducibility of ELISA, which can be performed with equivalent results by laboratories across the country.

The technician then washes off the microtiter plate, leaving only those antibodies that have bound to the well coated with immobilized reference allergenic product. To measure the amount of human antibody bound to the plate, the technician uses other antibodies that react specifically with human IgE (such as goat anti-human IgE) and that have been chemically linked to an enzyme. The technician adds this enzyme-linked anti-human IgE to the testing well containing the bound human IgE from the first step. The anti-human antibody reagent, along with its coupled enzyme, binds to the bound human IgE, and the technician washes off any unbound antibodies. The technician adds a colorless substrate, which the enzyme on the plate converts to a colored product. The greater the amount of enzyme that has bound to the testing well, the greater will be the intensity of color produced, measured in light absorbing units (absorbance). Thus the greater the number of antibodies bound to the reference allergenic product in the first step, the greater will be the absorbance formed in the last step.

The quantity of allergen in the test material affects the absorbance in the ELISA as follows: the greater the quantity of allergen in the test material, the smaller the quantity of human IgE antibody available to bind to the reference allergenic product on the plate. When a smaller quantity of human IgE antibody binds to the reference allergenic product on the plate, a smaller quantity of enzyme-linked anti-IgE binds to the plate. When a smaller quantity of enzyme-linked anti-IgE binds to the plate, a smaller amount of colorless substrate will convert to a colored product. When a smaller amount of colorless substrate converts to a colored product, the absorbance of the well in the final stage of the assay will be lower. By comparing this final signal over a range of concentrations of test allergen, the technician can determine a dose response curve for each sample. Thus, the relative potency of a sample of allergenic product can be determined by comparison with a reference standard.

Figure 1 provides an illustration of such a comparison. Each curve represents the ELISA results at multiple concentrations of each preparation of allergen. The curve on the right represents the reference standard, while the curve on the left represents a typical allergen sample. The horizontal shift between the two curves indicates, on a log scale, the relative potency. The curve on the right corresponds to less potent material, so more is needed to compete for antibody binding and to reduce the ELISA signal to the same optical density. If the horizontal difference between curves is 0.699 units on a log scale, the sample on the left is  $10^{.699}$ , five-fold more potent than the reference standard. Since the standard is defined as 100,000 BAU/mL, the sample must be 500,000 BAU/mL. To produce the desired potency of 100,000 BAU/mL, the manufacturer must dilute the sample five-fold.

If an important allergen were missing from a sample, the ELISA curve would exhibit incomplete competition, as shown in the curve marked  $C_B$  in Figure 2. The relative contribution of the missing allergen is shown by the height of the plateau in relation to the maximum signal. If a grass allergen failed to compete fully, as in this case, it would fail lot release specifications.

Such a failure would be appropriate, since the lot would lack an important allergen recognized by a significant number of grass-allergic individuals.<sup>53</sup>

**c. Development of Successive Generations of Serum Pools and Reference Standards; Participation by Manufacturers**

When supplies of a serum pool or reference standard near depletion, FDA and industry jointly test the next generation serum pool or reference standard. Manufacturers and FDA subject the candidate serum pool or reference standard to repeated assays in order to compare the candidates to the current pool or reference standard, in order to establish that the new generation is, indeed, equivalent to the previous one.

For example, grass pollen extract manufacturers actively participated in validating a new IgE serum pool for use in the ELISA assay. Figure 3<sup>54</sup> represents a joint effort of FDA and allergenic product manufacturers. The majority of the 97 data points were determined by manufacturers, with only 14 data points determined by FDA. Experiments such as this demonstrate the reliability of the ELISA potency assay, the ability of manufacturers to achieve consistent results using this assay, and the significant role and active participation of the manufacturers in developing and evaluating key reagents for the FDA grass standardization program.

In another example, as stocks of generation E10 of perennial rye grass reference standard<sup>55</sup> grew limited, FDA distributed samples of proposed reference standard E11-Rye. FDA and perennial rye grass pollen extract manufacturers then performed a battery of ELISA potency tests to determine the relative potency of reference standard generation E10-Rye and proposed reference standard E11-Rye. Those test results disqualified E11-Rye as a reference standard. FDA and the manufacturers then performed another series of tests to determine the relative potency of reference standard E10-Rye and proposed reference standard E12-Rye. The performance of both

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<sup>53</sup> As you note, "An acceptable extract should . . . fulfill the following demands: it should include all potential allergens in relevant ratios and in their appropriate forms. Moreover, all irrelevant material should ideally be absent." Citizen Petition at 5, n. 20 (quoting Ipsen, H., *et al.*, "Allergenic Extracts," in *Allergy Principles and Practice* at 540 (Middleton, E., *et al.*, eds., 4th ed. 1991)).

<sup>54</sup> Figure 3 shows the ELISA assay results for different lots of allergen tested with the old serum pool, denoted S4, on the X-axis, plotted against the results for the same allergen lot tested with a new serum pool, denoted S5 on the Y-axis. Each point compares the assay results of the same sample tested with one serum pool or the other. If the old serum pool gave a low result, while the new pool gave a higher result, then the points would fall above the 45° line of equivalence. But, as can be seen from the graph, the points fall very close to the line, indicating equivalence of the old and new serum pools. Thus, the new serum pool could be substituted for the old without changing potency results.

<sup>55</sup> For each of the eight grasses, the first reference standard was called E1, the next generation was called E2, and so on. Table II identifies the generation of reference standard calibrated by skin testing, and the generation currently in use. In each case, subsequent generations were calibrated against the previous generation by ELISA testing.

standards on the ELISA showed extremely close agreement, and E12-Rye was accepted as a reference standard. See Figure 4.<sup>56</sup>

Thus, FDA and the allergenic product manufacturers have been able to renew the supplies of pooled serum and reference standards with successive generations of equivalent potency.

#### **d. Manufacturers' Success in Using the Standardized Potency System**

Typical potency results for the standardized grass allergens made by one manufacturer are shown in Table III. The upper and lower 95% confidence limits for lot release are 1.431 and 0.699 times the potency of the reference standard. Two lots of each grass were tested, and every lot passed these criteria. The lot release limits were determined based on a rigorous statistical study of the range of ELISA potency results when the same sample was tested more than 200 times, giving a standard deviation of 0.1375 (log scale). The 95% confidence interval sets the first of two screens for potency relative to the standard in FDA's testing protocol.<sup>57</sup>

All nine manufacturers who have been approved to manufacture Standardized Grass Pollen Extracts have achieved results comparable to those in Table III with standardized grass allergens. The difference between Table I (for unstandardized grasses) and Table III shows the superior quality control of the standardized grasses. Standardized allergens vary less than twofold, while the unstandardized allergens varied by up to 60-fold in potency.

#### **4. Measuring the Potency of Grass Pollen Extracts by Measuring the Potency of Key Allergenic Components**

Grass pollen extracts are complex mixtures of allergens. For certain other allergens, such as ragweed and cat dander, it has been possible to identify key components of the allergen which account for the majority of activity in the extracts. Once identified, IgG antibodies specific for these components can be used instead of IgE for standardization,<sup>58</sup> and the composition can be

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<sup>56</sup> Each point on the graph in Figure 4 represents a plot of potency of E10 on the X-axis vs. potency against that of E12 on the Y-axis. If there were drift in E10, so that the new E12 standard were more potent than the previous E10, the samples would show lower potency relative to E12 than to E10, and the points would fall below the 45° line of equivalence. Conversely, if the E12 standard were less potent, the points would fall above the line. Neither of those circumstances occurred. In fact, the experimental points yield a regression line very nearly superimposable on the 45° line of equivalence.

<sup>57</sup> See Testing Limits in Stability Protocols for Standardized Grass Pollen Extracts (Draft Guidance) (August, 1997), available at <http://www.fda.gov/cber/gdlns/grass.txt>.

<sup>58</sup> If a key allergenic component can be identified and purified, it is often possible to inject animals with the purified component and to elicit from the animals IgG antibodies specific for that individual allergenic component. The usefulness of IgG antibodies depends on independent verification that the purified component that elicited the antibodies is a major allergen causing symptoms in most allergic subjects and that it alone can account

expressed in terms of the mass (weight in milligrams) of key components. In the case of grass allergens, available data do not support the identification of any single component as an adequate measure of the overall activity of the extract, as you yourself note.<sup>59</sup> The identification of a single major allergen for grass pollen extracts may prove especially difficult:

To use assay of a single allergen to standardize an extract, that allergen must be either an allergen that is an important quantitative component of all extracts from that source and to which most, that is,  $\geq 80\%$  of allergic individuals respond, or an allergen that is present in all extracts in a consistent relationship to other components of the extract . . . .

Problems arise if an extract contains several important allergens that are present in different proportions in extracts produced from different material or by different manufacturing techniques. With pollens, the source material is relatively consistent and can be checked for purity; however, different extraction procedures or processing may alter the ratio of different constituents.<sup>60</sup>

Thus, the grass standardization method recognized by FDA links standardization of grass allergens to IgE reactivity, rather than to a measure of concentration of key components as suggested in the citizen petition.

## **II. FDA Promulgated Section 680.3 of the Code of Federal Regulations in Accordance with the Administrative Procedure Act.**

### **A. FDA Promulgated the Regulation Pursuant to Notice and Comment Rulemaking.**

In your petition, you assert that, in developing a rule on potency testing for allergenic products, FDA did not engage in notice and comment rulemaking in accordance with the procedures set out in the Administrative Procedures Act ("APA").<sup>61</sup> On this basis, you argue that FDA's actions were fatally flawed. The agency rejects these contentions. The agency promulgated the applicable regulation in accordance with the notice and comment rulemaking provisions of the APA.

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for the majority of allergenic activity in the extract. This evidence is currently lacking for any grass allergen. Thus, at present, no available IgG antibody could replace an IgE test. Current evidence suggests that the grass allergens are complex, so that quantitation would require a mixture of IgG antibodies, including some as yet unknown allergens.

<sup>59</sup> See Citizen Petition at 6 ("because many allergens have not been sufficiently characterized to identify all of the significant allergenic components, it is difficult to establish a uniform compositional formula or ratio.")

<sup>60</sup> Platts-Mills, T.A.E. and Chapman, M.D., Allergen Standardization, *J.Allergy Clinical Immunology* 87:621, 623 (1991).

<sup>61</sup> See 5 U.S.C. § 553.

Substantive rules must be promulgated through notice and comment rulemaking.<sup>62</sup> Accordingly, FDA strictly adhered to those APA provisions when it promulgated the following rule:

*Potency.* The potency of each lot of each Allergenic Product shall be determined as prescribed in § 610.10 of this chapter. Except as provided in this section, the potency test methods shall measure the allergenic activity of the product. Until manufacturers are notified by the Director, Center for Biologics Evaluation and Research, of the existence of a potency test that measures the allergenic activity of an allergenic product, manufacturers may continue to use unstandardized potency designations.<sup>63</sup>

You do not contend that this regulation was not promulgated in accordance with the APA.<sup>64</sup> Instead, you challenge the actions FDA took to implement this properly promulgated regulation. Specifically, you argue that FDA's letters of April 8, 1994, and FDA's subsequent letters extending the time line for implementation of the potency testing required by 21 C.F.R. § 680.3(e), constitute a substantive rule that should have been promulgated pursuant to the APA's notice and comment rulemaking provisions.

However, FDA did not create a new substantive rule by issuing the April 8, 1994 letters. FDA addressed those letters to individual companies, and simply reiterated the rule and policy set out in 21 C.F.R. § 680.3(e). They created no new substantive rule.

Under 5 U.S.C. § 551(4), a rule is "the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency." As the D.C. Circuit noted many years ago, "[this broad definition obviously could be read literally to encompass virtually any utterance by an agency, including statements of general policy."<sup>65</sup> If that is the case, the important issue becomes, not whether a communication constitutes a rule, but whether the communication was in fact a substantive rule, and not an interpretive rule or policy statement.<sup>66</sup> Indeed, even if you contend that the April 8th letters share

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<sup>62</sup> *Id.*

<sup>63</sup> 21 U.S.C. § 680.3(e).

<sup>64</sup> Indeed, this regulation was also promulgated in accordance with the Regulatory Flexibility Act and the Paperwork Reduction Act. Since the letters merely implemented this regulation, and were not new regulations, the letters did not require additional analysis under these provisions. Your suggestion to the contrary, Citizen Petition at 51 n.147, is meritless.

<sup>65</sup> "Pacific Gas & Elec. Co. v. Fed. Power Comm'n, 506 F.2d 33, 37 (D.C. Cir. 1974).

<sup>66</sup> *Id.* at 38; see also Alcaraz v. Block, 746 F.2d 593, 613 (9th Cir. 1984).

characteristics with both interpretive rules and policy statements, that does not trigger a requirement for notice and comment rulemaking.<sup>67</sup>

In American Mining Congress v. Mine Safety & Health Administration,<sup>68</sup> the court reviewed the legal status of Program Policy Letters issued by the Mine Safety and Health Administration. The Program Policy Letters defined a regulatory term that, when applicable, triggered a reporting requirement. The court identified four criteria, any one of which, if met, meant the agency action was a substantive rule and required notice and comment rulemaking procedures:

- (1) whether in the absence of the rule there would not be an adequate legislative basis for enforcement action or other agency action to confer benefits or ensure the performance of duties,
- (2) whether the agency has published the rule in the Code of Federal Regulations,
- (3) whether the agency has explicitly invoked its general legislative authority, or
- (4) whether the rule effectively amends a prior legislative [*i.e.*, substantive] rule.<sup>69</sup>

The Court of Appeals held that since the Program Policy Letters met none of these criteria, the Letters did not constitute a substantive rule. The Program Policy Letter at issue was an interpretive rule.<sup>70</sup>

Similarly, the agency's April 8th letters regarding the potency provisions contained in 21 C.F.R. §§ 680.3 and 610.10 meet none of the above criteria. The substantive regulations themselves provide sufficient basis for the action, and the letters did not add anything to that authority.<sup>71</sup> The agency did not publish in the Code of Federal Regulations the interpretation contained in the

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<sup>67</sup> Interpretive rules and statements of policy are specifically exempted from notice and comment rulemaking requirements under § 553(b)(A) of the APA. The § 553(b)(A) exemptions for interpretive rules and policy statements "accommodate situations where the policies promoted by public participation in rulemaking are outweighed by the countervailing considerations of effectiveness, efficiency, expedition and reduction in expense. Guardian Fed. Sav. and Loan Ass'n v. Fed. Sav. and Loan Ins. Corp., 589 F.2d 658, 662 (D.C. Cir. 1978). Such considerations are critically important, "If the mere delegation of rule-making authority meant all subsequent agency determinations were legislative, and had to meet the notice and comment requirements of the APA, agency functioning would be hamstrung." Metropolitan School District of Wayne Township v. Davila, 969 F.2d 485, 492 (7th Cir. 1992), *cert. denied*, 507 U.S. 949 (1993).

<sup>68</sup> 995 F.2d 1106 (D.C. Cir. 1993).

<sup>69</sup> *Id.* at 1112.

<sup>70</sup> *Id.*

<sup>71</sup> See Clinical Reference Lab., Inc. v. Sullivan, 791 F. Supp. 1499, 1504 n.6. (D. Kan. 1992), *aff'd in part, rev'd in part on other grounds*, 21 F.3d 1026 (10th Cir. 1994) ("The decision to initiate enforcement proceedings against CRL amounted only to a determination that [its] containers were subject to regulation under the FDCA, a determination the FDA was entitled to make without resort to judicial or administrative hearings") (citing CIBA Corp. v. Weinberger, 412 U.S. 640, 643-44 (1973)); National Pharmaceutical Alliance v. Henney, 47 F. Supp.2d 37, 41 (D.D.C. 1999) ("The statute on its face provides all the 'legislative basis' that is necessary for the agency's action.")

letters,<sup>72</sup> nor did the agency invoke its rulemaking authority. Lastly, the agency's letters did not amend, repudiate, or conflict with a prior substantive rule.<sup>73</sup> Accordingly, like the Program Policy Letters at issue in American Mining, FDA's April 8th letters do not have the "force of law" and are exempt from notice and comment rulemaking requirements.<sup>74</sup>

Similarly, as "policy statements," FDA's letters would be distinguishable from substantive rules.<sup>75</sup> As the Court of Appeals for the District of Columbia Circuit has noted:

An agency policy statement merely represents an agency position with respect to how it will treat – typically enforce – the governing legal norm. By issuing a policy statement, an agency simply lets the public know its current enforcement or adjudicatory approach. The agency retains the discretion and the authority to change its position – even abruptly – in any specific case because a change in its policy does not effect the legal norm.<sup>76</sup>

In the April 8th letters, FDA simply informed the recipients of its enforcement approach. Indeed, rather than establishing a legal norm, the April 8th letters emphasized that methods other than the FDA recommended method could be used to meet the obligations imposed by 21 C.F.R. §§ 610.10 and 680.3(e):

We will accept equivalent testing methods that provide an equally reliable measure of the potency of the product. CBER recommended test methods, or equivalent test methods, should be submitted to CBER for review and approval prior to implementation. If you would like to pursue an equivalent reference reagent or an equivalent reference serum

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<sup>72</sup> In any event, the publication-in-the-CFR criterion is only slight evidence of agency intent. See Health Ins. Ass'n. of America v. Shalala, 23 F.3d 412, 423 (D. C. Cir. 1994), cert. denied, 513 U.S. 1147 (1995) (CFR publication as no more than "snippet" of evidence of agency intent).

<sup>73</sup> FDA rejects your suggestion that the effect of the April 8th letters "is to amend § 680.3 to exclude nonstandardized grass pollen extracts." Citizen Petition at 32-33. It is section 680.3(e) itself that operates to require standardization of allergenic products; it is not FDA's letters.

<sup>74</sup> See also Syncor Int'l Corp. v. Shalala, 127 F.3d 90, 95 (D.C. Cir. 1997) ("substantive rule modifies or adds to a legal norm based on the agency's own authority" (emphasis in original)); Shalala v. Guernsey Memorial Hosp., 514 U.S. 87, 100 (1995) (holding that notice and comment were not required for interpretive rule because it did not effect a substantive change in existing regulations).

<sup>75</sup> Interpretive rules and general statements of policy share many of the same attributes, Pacific Gas & Electric, 506 F.2d at 37 n.14., and can be difficult to differentiate. See Professionals and Patients for Customized Care v. Shalala, 56 F.3d 592, 601-602 (5th Cir. 1995) (finding that the challenged FDA rule could fit either definition). FDA's letters have the characteristic of an interpretive rule, because they interpret the relevant provisions of 21 C.F.R. §§ 680.3 and 610.10, and the characteristic of a general statement of policy in that it identified one standardization method that met regulatory requirements, while inviting the submission of other such methods.

<sup>76</sup> Syncor, 127 F.3d at 94.

pool, CBER requests that a meeting be held to discuss your in vivo and in vitro analytical data and the conditions necessary for approval of this testing method.<sup>77</sup>

In light of FDA's announced intention to consider other methods, your suggestion that FDA would only permit use of the FDA recommended standardization method is puzzling.

In any event, whether FDA's letters regarding standardization methods are characterized as letters reiterating a previously established regulatory position, as an interpretive rule, or as a policy statement, the letters are exempt from the APA's notice and comment rulemaking requirements. The agency's April 8, 1994 letters neither have the "force of law" that turns an interpretive rule into a substantive rule subject to notice and comment rulemaking requirements,<sup>78</sup> nor limit the discretion of agency decision makers so as to turn a policy statement into a binding rule of law.<sup>79</sup>

#### **B. FDA's Actions Were Consistent with the Public Health Service Act and FDA Regulations.**

You raise a second legal challenge by asserting that the Public Health Service Act and FDA regulations required FDA to implement its regulations, 21 C.F.R. §§ 610.10 and 680.3(e), only by issuing additional regulations. Once again, your argument ignores the fact that FDA promulgated its standardization and potency regulations by notice and comment rule making.<sup>80</sup> Instead you focus only on the steps FDA subsequently took to implement those regulations.

First, you assert that "the agency's framework for implementation of the PHS Act requires designation of specific test methods for measurement of potency for each type of biological product."<sup>81</sup> However, the most important part of "the agency's framework for implementation" is FDA's own regulations, issued under notice and comment procedures. That "framework" did not require designation of specific test methods. The applicable regulation, 21 C.F.R. § 680.3(e), prescribed the very process that FDA followed here.<sup>82</sup>

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<sup>77</sup> April 8, 1994 Letter to Grass Pollen Extract Manufacturers at 1.

<sup>78</sup> American Mining Congress, 995 F.2d at 1109 (citing National Latino Media Coalition, 816 F.2d 785, 787-788 (D.C. Cir. 1987)).

<sup>79</sup> Community Nutrition Inst. v. Young, 818 F.2d 943, 946-48 (D.C. Cir. 1987).

<sup>80</sup> You go so far as to state that "the agency did not engage in rulemaking, but rather issued letters to affected manufacturers imposing the new requirements as conditions of product licensure." Citizen Petition, Introduction at 2.

<sup>81</sup> Id. at 4.

<sup>82</sup> Given the explicit provisions of 21 C.F.R. § 680.3(e), your suggestion that FDA failed to comply with FDA regulations simply by following § 680.3 (e) is puzzling. Your argument appears to rest on a significant misunderstanding of the regulations. For example, citing 21 C.F.R. § 610.10, you state, "FDA regulations provide that the agency will designate a method of potency testing for each type of biological product." Citizen Petition at

Moreover, your assertion that "[o]n its face, the language of the PHS Act clearly indicates that standards of potency may only be issued by regulation,"<sup>83</sup> is without support.<sup>84</sup> You rely on a single provision of the Public Health Service Act, now deleted from the statute. That provision provided:

Licenses for the maintenance of establishments for the propagation or manufacture and preparation of [biological products] may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations, and licenses for new products may be issued only upon a showing that they meet such standards.<sup>85</sup>

This provision is silent about how detailed any implementing regulations should be. Congress did not express an intent on this point; instead it left the question to the discretion of the agency charged with administering the provision. Accordingly, FDA's regulations implementing this provision are entitled to substantial deference. If FDA's actions were before a reviewing court, such a court would defer, and refrain from "substitut[ing] its own construction of a statutory provision for the reasonable interpretation made by the administrator of an agency."<sup>86</sup>

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12. Section 610.10 says no such thing. That regulation simply describes, in general terms, the standards which potency tests used in biological products should meet.

<sup>83</sup> Citizen Petition at 18.

<sup>84</sup> The Food and Drug Administration Modernization Act of 1997 ("FDAMA") was enacted approximately four months after you filed your petition. That law amended many of the provisions of the Public Health Service Act you rely upon.

<sup>85</sup> 42 U.S.C. § 262(d)(1) (1997). The current provision, enacted in FDAMA, provides, in pertinent part, that FDA shall establish by regulation requirements for the approval, suspension, and revocation of biologics licenses. 42 U.S.C. § 262 (a)(2)(A).

<sup>86</sup> Chevron, U.S.A., Inc. v. Natural Resources Defense Council, 467 U.S. 837, 844 (1984). Accord Christensen v. Harris County, \_\_\_ U.S. \_\_\_, 120 S.Ct. 1655 (2000) ("Of course, the framework of deference set forth in Chevron does apply to an agency interpretation contained in a regulation."); Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 416 (1971) ("[T]he court must consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment. Although this inquiry into the facts is to be searching and careful, the ultimate standard of review is a narrow one. The court is not empowered to substitute its judgment for that of the agency"); Contact Lens Mfrs. Ass'n v. FDA, 766 F.2d 592, 597 (D.C. Cir. 1985), cert. denied, 474 U.S. 1062 (1986)(stating that the court must defer to the agency's decision even though it agreed there was "substantial merit" to the challenge before it, because FDA "acted within an area of its expertise, it ruled in a manner at least arguably consistent with the statutory scheme, and it considered the matter in a detailed, adequately reasoned fashion.")

Indeed, FDA's implementation of the provision was reasonable. FDA issued a general standard in a regulation entitled "Potency,"<sup>87</sup> and an additional potency standard for allergenic products;<sup>88</sup> both standards are quoted above in section I.C. Those provisions, and the definition of "potency" provided in 21 C.F.R. § 601.3(s), provide that potency standards and potency tests be "specifically designed for each product,"<sup>89</sup> that the product have the "specific ability or capacity . . . to effect a given result,"<sup>90</sup> and that the product "measure the allergenic activity of the product."<sup>91</sup> Thus, FDA exercised its discretion to devise a useful definition of potency, recognizing that potency must be evaluated on a product-by-product basis. FDA's exercise of this discretionary authority is due considerable deference, since it is making a scientific decision within the agency's particular area of expertise.<sup>92</sup>

Moreover, FDA has considered adopting a practice of issuing individual regulations for each individual potency test required by statute and regulation,<sup>93</sup> and has rejected that approach for several reasons.

First, FDA determined that it was impractical to codify in a specific regulation each new potency test procedure. Such an approach would require literally thousands of new regulations:

[A]pproximately 1,800 to 2,000 generic allergenic products are marketed. Therefore, FDA believes that it is impractical to codify a description of each new specific potency test procedure for a product as the procedure is developed[.]<sup>94</sup>

Second, if FDA codified each potency test, it would increase the period of time between development of any improved test, and its implementation. FDA's actions might unduly delay implementation of product improvements. Indeed, a delay in implementation of technological advances might even discourage technological development.<sup>95</sup>

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<sup>87</sup> 21 C.F.R. § 610.10.

<sup>88</sup> 21 C.F.R. § 680.3(e).

<sup>89</sup> 21 C.F.R. § 610.10.

<sup>90</sup> 21 C.F.R. § 600.3(s).

<sup>91</sup> 21 C.F.R. § 680.3(e).

<sup>92</sup> Community Nutrition Inst. v. Young, 773 F.2d 1356, 1363 (D.C. Cir. 1985), cert. denied, 475 U.S. 1123 (1986).

<sup>93</sup> In 1982, 21 C.F.R. § 680.4, FDA's regulation requiring potency testing for short ragweed, became effective. 46 Fed. Reg. 39129, 39135 (July 31, 1981). In 1985, FDA proposed to revoke that rule, see 50 Fed. Reg. 30211, 30213 (July 24, 1985), and finally revoked the rule effective November 9, 1987. 52 Fed. Reg. at 37607.

<sup>94</sup> 50 Fed. Reg. at 30212.

<sup>95</sup> Cf. "Revocation of Certain Regulations; Opportunity for Public Comment," 60 Fed. Reg. 53480, 53482 (Oct. 13, 1995) (revoking regulations not at issue here; "[t]he codification by regulation of many of the additional

Finally, your suggestion that, since FDA promulgated regulations containing more detailed standards of potency eighty years ago, it should do so here,<sup>96</sup> is baseless. It may be that, early in the twentieth century, the agency charged with regulating the relatively few biological products then available issued more specific potency regulations for a few products other than grass pollen extracts. However, current regulations, issued in accordance with notice and comment rulemaking procedures, provide a different approach.

In sum, the agency promulgated the standardization and potency regulations in accordance with the Public Health Service Act and FDA's own regulations.

### C. FDA's Implementation of the Regulation Was Not Arbitrary or Capricious.

In your petition, you contend that, in identifying a standardization method that satisfied the requirements of 21 C.F.R. §§ 610.10 and 680.3(e), FDA failed to gather and analyze the relevant scientific and other information to support the identification of that standardization method.<sup>97</sup> Under the APA, your contention would be evaluated by a court under the arbitrary and capricious standard of review.<sup>98</sup> This "highly deferential standard of review presumes agency action to be valid."<sup>99</sup> An agency decision is arbitrary and capricious only if the agency "has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise."<sup>100</sup>

Where the action involves an interpretation by the agency of its own statute and regulations, a court should be especially deferential.<sup>101</sup> The arbitrary and capricious standard also mandates heightened deference to the agency's judgment where, as here, a court is asked to review scientific decisions made by the agency.<sup>102</sup>

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standards for biologicals sometimes does not allow for the flexibility necessary to keep abreast of technological advances in science.")

<sup>96</sup> Citizen Petition at 19.

<sup>97</sup> Id., Introduction at 2.

<sup>98</sup> 5 U.S.C. § 706(2)(A).

<sup>99</sup> Int'l Fabricare Inst. v. EPA, 972 F.2d 384, 389 (D.C. Cir. 1992)

<sup>100</sup> O'Keeffe's Inc. v. Consumer Prod. Safety Comm'n, 92 F.3d 940, 942 (9th Cir. 1996) (quoting Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983)); see also Overton Park, 401 U.S. at 416; Contact Lens Mfrs., 766 F.2d at 597.

<sup>101</sup> See United States v. Rutherford, 442 U.S. 544, 553 (1979); Providence Hosp. of Toppenish v. Shalala, 52 F.3d 213, 216 (9th Cir. 1995); United States v. Algon Chem. Inc., 879 F.2d 1154, 1159 (3d Cir. 1989).

<sup>102</sup> See Mount Graham Red Squirrel v. Espy, 986 F.2d 1568, 1571 (9th Cir. 1993); Int'l Fabricare, 972 F.2d at 389; Community Nutrition Inst. v. Young, 773 F.2d 1356, 1363 (D.C. Cir. 1985), cert. denied, 475 U.S.

FDA's actions regarding the standardization method were rational and well supported by the administrative record, and therefore were not arbitrary and capricious.

**1. Allergenic Product Manufacturers Have Had Regular and Meaningful Opportunities to Comment on FDA's Promulgation and Implementation of the Standardization Regulations**

You assert, "the affected industry has had little opportunity to provide meaningful input to the standardization process."<sup>103</sup> This statement is inaccurate. FDA's approach to the standardization process cannot fairly be characterized as suffering from an "absence of full public participation."<sup>104</sup> The record establishes that FDA welcomed participation and comment by the public, including the medical community and manufacturers.

In fact, FDA regularly invited public participation. FDA's frequent communications took the form of Federal Register notices, open advisory committee meetings, meetings with industry representatives, including annual meetings with APMA and joint workshops, as well as regular correspondence. We summarize these regular communications in sections I.C. and I.D.1 and 2. Moreover, grass pollen extract manufacturers continue to play an important role in the development of reference standards and serum pools. See discussion in section I.D.3.C. Finally, on three occasions, in response to requests of the American Academy of Allergy, Asthma & Immunology and grass pollen extract manufacturers, and in order to be certain of an adequate supply, FDA extended the deadline for compliance with 21 C.F.R. § 680.3(e), for a total of 27 months.

**2. FDA Gathered and Analyzed Scientific Information Relevant to its Decision.**

You suggest that FDA did not appropriately gather and analyze the relevant scientific and other information to support the standardization method it recognized.<sup>105</sup> In addition to FDA's regular communication with the public on these issues, FDA scientists consulted with outside experts from academia, industry, and in clinical practice before embarking on standardization, through its communications with the Allergenic Products Advisory Committee, APMA, and the American Academy of Allergy, Asthma & Immunology. The issues related to grass standardization received intense attention internationally at meetings such as the International Paul Ehrlich Symposia in 1987, 1990, and 1993, which FDA representatives attended, and at the

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1123 (1987); Somerset Pharm., Inc. v. Shalala; 973 F. Supp. 443, 453 (D. Del. 1997); see also Fed. Power Comm'n v. Florida Power and Light Co., 404 U.S. 453, 463-66 (1972).

<sup>103</sup> Citizen Petition, Introduction, at 3.

<sup>104</sup> Id. at 41.

<sup>105</sup> Id., Introduction at 2.

1996 International Paul Ehrlich Symposium, which FDA hosted. Moreover, throughout the standardization process, FDA sought guidance, first from the Allergenic Extracts Panel, and then from the Advisory Committee.

FDA considered fully the relevant issues before adopted this course of action. Of course, the only alternative course of action that APMA has proposed is inaction. Taking no action to standardize widely variant grass extract allergenic products was simply unacceptable to FDA.

Indeed, FDA specifically recognized "the many sources of variability in clinical response to allergen extracts."<sup>106</sup> The Panel Report acknowledged those variables in clinical response,<sup>107</sup> and proceeded to recommend that allergenic products be standardized.<sup>108</sup> FDA adopted the Allergenic Extract Panel's common sense recommendation to limit through standardization the variability of the product administered. Standardized allergens will provide more consistent clinical results by removing an important source of variability.

### 3. FDA's Development of, and Reliance Upon, Skin Test Data Was Appropriate.

You criticize FDA's recognition of a standardization method that relies on skin testing to calibrate the original reference standards. You have identified no alternative calibration method. You argue that skin testing does not correlate the bioequivalent allergenic unit measure to a particular clinical effect in individual patients.<sup>109</sup>

You acknowledge that two views have been expressed in the scientific literature regarding the value of skin testing to calibration of reference standards. One of those views clearly supports the use of skin testing. You characterize that view as follows:

because potency units should indicate biological response, and in light of the variation in patients reactivity, standardization must be based on in vivo evaluation in allergic patients, i.e., skin testing[.]<sup>110</sup>

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<sup>106</sup> Id. at 60.

<sup>107</sup> See, for example, 50 Fed. Reg. at 3086.

<sup>108</sup> Id. at 3112-13. See also id. at 3095 ("Education of physicians and technicians regarding proper testing techniques, proper use of allergens of high potency, identification of patients at greater risk, and standardization of extracts by the manufacturers are factors which would minimize the frequency of reactions following diagnostic skin testing." (emphasis supplied).)

<sup>109</sup> Citizen Petition at 43-48.

<sup>110</sup> Id. at 43.

In fact, the use of skin testing in order to calibrate reference standards is now widely accepted. The 1997 European Pharmacopoeia advocates skin testing:

Where possible, the biological potency of the [reference preparation] is established by in vivo techniques such as skin testing, and expressed in units of biological activity."<sup>111</sup>

In any event, the complaints you make about skin testing provide an inadequate basis for FDA to indefinitely defer standardization, which is the course you urge. Indeed, since it exercised its scientific judgment in implementing the standardization provisions of 21 C.F.R. § 680.3(e), FDA's decision is entitled to a high degree of deference.<sup>112</sup>

You appear to contend that, because only 15 patients were involved in the skin testing, the skin test results were unreliable.<sup>113</sup> However, each of the 15 subjects was selected because the subject was highly allergic to grass allergens. The subjects were not chosen to represent the population as a whole, since the population as a whole includes many people who are not allergic to grass allergens. Each subject had a history of grass allergy, as well as a reproducible response to grass allergens. If the major grass allergens were present in a sample, the subjects would react to them.

FDA acknowledges that, as you note in the Citizen Petition,<sup>114</sup> the Allergenic Extracts Panel identified six complications inherent in the use of skin testing as part of a standardization method.<sup>115</sup> However, these comments were written prior to identification of the standardization method recognized by FDA. In developing the skin test methodology, FDA addressed each of the six complications enumerated by the Panel.

According to the Panel Report:

Estimation of the potency of an extract by [direct skin titration] is complicated by (1) the lack of a generally accepted skin test procedure, (2) the different levels of sensitivity to a given extract within the patient population, and (3) the inherent variability of biological

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<sup>111</sup> European Pharmacopoeia, Allergen Products, at 1063 (1997).

<sup>112</sup> Weinberger v. Bentex Pharm., Inc., 412 U.S. 645, 654 (1973) ("threshold questions within the peculiar expertise of an administrative agency are appropriately routed to the agency, while the court stays its hand"); Stauber v. Shalala, 895 F. Supp. 1178, 1189 (W.D. Wis. 1995) ("[W]hen a decision goes to the core of an agency's expertise, generally the court must defer to the agency's more-informed judgment."). See also Tri Bio Lab., Inc. v. United States, 836 F.2d 135, 142 (3d Cir. 1987), cert. denied, 488 U.S. 818 (1988) ("in evaluating scientific evidence in the drug field, the FDA possesses an expertise entitled to respectful consideration by the] court.") See also Young v. Community Nutrition Inst., 476 U.S. 974, 981 (1986) ("view of the agency administering the statute is entitled to considerable deference.")

<sup>113</sup> Citizen Petition at 46.

<sup>114</sup> Id. at 44-45.

<sup>115</sup> See Panel Report, 50 Fed. Reg. at 3109.

assays. Other problems in estimating potency by skin testing include the following: (4) Different skin test sites vary in their reactivity; (5) deposition of an exact volume in each skin test site is difficult; and (6) criteria for setting an end point. Regarding the latter, it is necessary to express it in terms of the dose of extract required to induce a reaction of a particular size.<sup>116</sup>

FDA considered each of these six items as follows:

(1) The Panel submitted the Panel Report to FDA on March 13, 1981.<sup>117</sup> By April 8, 1994, allergenic product manufacturers had already accepted and used the skin test identified by FDA to develop skin test data in support of license applications for standardized cat and dust mite allergenic extracts. The method was generally accepted.

(2) FDA recognized that different patients would have different levels of sensitivity. The method identified by FDA controlled for variability in sensitivity in two ways: a) For products from the same allergen source, the method required determining relative potency within subjects. Products claimed to have equivalent potency were expected to have the same relative potency regardless of the sensitivity of the patient. b) For products from different allergen sources, the method required determining relative potency in subjects maximally reactive to each allergen, thus reducing the variability in sensitivity of the subjects tested to those most sensitive to the allergen of interest.

(3) FDA considered the inherent variability of biological assays by selecting a method that set clinical and statistical criteria for acceptable dose-response lines based on skin testing. These criteria placed defined limits on the variability of the assay.

(4) FDA recognized that different skin test sites may vary in their reactivity. The method recognized by FDA provided for random assignment of the doses to be tested to the skin test sites. Random assignment prevented variation in skin reactivity at a particular site from biasing the response at a specific dose, because the site would vary for each dose tested in each subject tested.

(5) Although the deposition of an exact volume in each skin test site may be difficult, in the skin test method identified by FDA, the investigators were required to inject a defined volume of 0.05 mL at each test site.

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<sup>116</sup> Id. at 3109.

<sup>117</sup> Id. at 3083.

(6) The recognized method defined an end point as the D50, the calculated dilution for a 50 mm sum of erythema response.<sup>118</sup>

Similarly, in developing that methodology, FDA considered the considerations that Dr. Yunginger described in his 1991 article that you reference in your Petition.<sup>119</sup> Dr. Yunginger noted:

Universal acceptance of skin testing as the primary method of allergen standardization has been hampered, however, by [(1)] controversies over the method of patient selection (unselected versus highly sensitive patients); [(2)] the method of skin testing (puncture versus intradermal); [(3)] the response to be measured (wheal or erythema); [(4)] the standard used for comparison testing (allergen or histamine); [(5)] the occasionally arcane methods used for statistical analysis of the results; and, finally, [(6)] the unitage in which the results are expressed."<sup>120</sup>

FDA's response to Dr. Yunginger's points may be summarized as follows:

(1) FDA recognized a skin test method that used highly sensitive subjects, because such subjects best facilitate evaluation of product safety. Highly sensitive subjects are at highest risk of having severe allergic disease related to the allergen of interest and are at highest risk of experiencing a serious adverse event, if they inadvertently receive an overdose. If less sensitive subjects were used to define potency, the safety of doses well tolerated in less sensitive subjects could not be assumed to be safe for administration to highly sensitive subjects. Moreover, other investigators have recognized the need to use suitably sensitive subjects to estimate allergen potency.

(2) FDA recognized a skin test method that required both puncture and intradermal skin test data, in order to assure that the doses associated with both routes are well tolerated. The skin test assay used to define potency in BAUs is based primarily on the intradermal route, since it is more sensitive, precise, and accurate in determining the dose of allergen administered. Other investigators have confirmed this opinion. The package inserts for the allergenic products describe allergen doses and allergic responses associated with both the puncture and intradermal routes of administration.

(3) The recognized skin test method captured both wheal and erythema data. FDA has concluded that, to estimate potency, an investigator should analyze the skin test variable

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<sup>118</sup> See Memorandum of Medical Officer, Immediate Office of the Director, DBPAP, OVRP, FDA (1/10/00), regarding FDA Response to Skin Testing Complications Identified in the Panel Report.

<sup>119</sup> See Citizen Petition at 44, n.130.

<sup>120</sup> Yunginger, J.W., Standardization of Allergenic Extracts, *Annals Allergy* 66:108 (1991) (numerals added).

most responsive to differences in allergen dose. Erythema is more responsive than wheal to differences in allergen dose. Accordingly, the method recognized by FDA uses erythema to determine potency. Other investigators have recognized that erythema is more responsive to dose than the wheal. The package inserts for the allergenic products include both wheal and erythema data.

(4) The recognized method requires independent measurement of skin test responses to both allergen and histamine, but does not require that histamine be used as a standard against which allergen responses are compared. Skin test response to allergen is not wholly attributable to histamine. Other investigators have criticized the use of histamine as a standard against which allergen potency is estimated.

(5) The FDA recognized method avoids arcane statistical methods and instead employs standard statistical calculations such as parallel line assay and linear regression. Other investigators have used these statistical calculations for analysis of skin test dose-response lines.

(6) The BAU is a measure of allergen potency that reflects bioequivalence; therefore, similar doses of standardized extracts should elicit similar responses, regardless of the manufacturer of the standardized allergen. Both manufacturers and allergen standardization experts have commented that a single biologically based unit is preferable to the confusing plethora of proprietary units used in Europe by each manufacturer.<sup>121</sup>

Members of the scientific community appeared to view favorably the skin test standardization process identified by FDA. In a position paper released in 1989, the European Academy of Allergology and Clinical Immunology recommended the skin test method recognized by FDA "as the standard method for estimation of the relative potency of allergenic preparations in relation to a given standard",<sup>122</sup> and recognizing the skin test component as the only method "that has been thoroughly validated."<sup>123</sup> In September, 1993, Professor A.L. de Weck, of the Institut für Immunobiologie in Bern, Switzerland, presented a paper at the Seventh International Paul Ehrlich Meeting, in which he concluded that the skin testing component of the standardization method recognized by FDA was preferable to the HEP technique, another type of skin test used in Northern Europe:

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<sup>121</sup> See Memorandum of Medical Officer, Immediate Office of the Director, DBPAP, OVRR, FDA (1/10/00), regarding FDA Response to Yunginger's Points.

<sup>122</sup> Subcommittee on Skin Tests of the European Academy of Allergology and Clinical Immunology, Skin Tests Used in Type I Allergy Testing (S. Dreborg, ed.), *Allergy*, 44:10 at 44 (1989).

<sup>123</sup> *Id.* See also *id.* at 49, 50.

A method such as the HEP standardization technique, combining prick testing, evaluation of skin reactions by wheal area and reference to a histamine standard is therefore the worst of possible alternatives. The US method, based on intradermal injection of various dilutions of allergen and evaluation of erythema, seems to us more adequate and reproducible for quantitative biological standardization of allergen extracts by skin testing.<sup>124</sup>

On March 6, 1994, FDA presented a scientific poster, "Measurement of Relative Potency by ELISA Competition" at the 50th Annual Meeting of the American Academy of Allergy and Immunology. At the 1996 International Paul Ehrlich meeting, Dr. Jan Dorpema, a regulatory official in the Netherlands, commented that FDA was "successful in the establishment of [reference] preparation."<sup>125</sup>

Furthermore, data presented by one manufacturer at the Eighth International Paul Ehrlich Seminar confirmed that the potency of CBER's grass pollen reference extracts, as determined by the ID<sub>50</sub>EAL skin test method, correlated with the mean potencies of that manufacturers' products, as determined by the competitive ELISA.<sup>126</sup> This confirmed not only that the two techniques were comparable; but that the reference extracts chosen by CBER, which were intended to be representative of the allergenicity of the native allergens, could be produced by the manufacturers using established methods.

In challenging FDA's actions, you rely on a 1991 article by John W. Yunginger, M.D.<sup>127</sup> However, you ignore the fact that Dr. Yunginger became chairman of FDA's Allergenic Products Advisory Committee on November 22, 1994. In that capacity, he actively supported FDA's standardization of grass pollen extracts.<sup>128</sup>

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<sup>124</sup> de Weck, A.L. and Derer, T., Critical Evaluation of the Use of Skin Tests and Cellular Tests in Standardization of Allergens, *Arb. Paul Ehrlich Inst. Bundesamt Sera Impfstoffe Frankf. A.M.* 1994, 87:89-117. Dr. de Weck is editor-in-chief of *Allergy & Clinical Immunology International*, the Official Organ of the International Association of Allergology and Clinical Immunology (the world allergy organization) and official publication of the International Association of Asthmology. He is on the Executive Committee of each of these latter two organizations. He has been a member of the International Union of Immunological Societies Allergen Standardization Committee which has interacted with the World Health Organization on allergen standardization issues. He is an internationally recognized expert on allergen standardization.

<sup>125</sup> Dorpema, J.W., Biological Reference Preparation for Allergens, *Arb. Paul Ehrlich Inst. Bundesamt Sera Impfstoffe Frankf. A.M.* 1997, 91:111-9.

<sup>126</sup> Esch, R.E. and White, W., Standardization: Dreams, Myths, and Reality, *Arb. Paul Ehrlich Inst. Bundesamt Sera Impfstoffe Frankf. A.M.* 1997, 91: 134-37.

<sup>127</sup> See Citizen Petition at 44 n.130.

<sup>128</sup> See Transcript of Proceedings, Allergenic Products Advisory Committee Meeting, November 22, 1994, at 43 (when clinicians begin to use standardized extracts, "it's going to get the improved, safer, hopefully more effective, and certainly more rational dosage schedules being used for the patients, the ultimate consumers here".)

Indeed, Dr. Yunginger has written, "In theory, skin testing is the most clinically relevant measure of the potency of an allergenic extract, and no specialized or expensive equipment is necessary."<sup>129</sup>

Moreover, you misrepresent Dr. Platts-Mills' and Dr. Chapman's complaint about the difficulty of patient selection in order to conduct reliable skin-testing. You quote the physicians as describing patient selection as "a situation that can easily become circular, that is, that an extract is used for skin testing to define who should be used to test the potency of the extract,"<sup>130</sup> Platts-Mills and Chapman actually limited that statement to "house dust allergens, fungi, and many less common pollens" for which "it is difficult to define typical symptoms." In contrast:

For patients with seasonal hay fever caused by a pollen that has a distinct season and is common in a particular area, it is relatively easy to identify highly allergic patients and to confirm by skin reactivity.<sup>131</sup>

This comment is applicable to grass pollens, which have distinct seasons and are common to a particular area.

Finally, the agency has determined that the identified standardization method adequately captures the "potency" of the allergenic product, which is defined as "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." 21 C.F.R. § 600.3(s). FDA rejects your suggestion that the standardization method is "inconsistent with the agency's own definition of 'potency.'"<sup>132</sup>

**4. FDA's Decision Not to Await Future Technological Developments or International Agreement to Implement its Potency Standardization Regulations was Rational.**

You suggest that future advances in the characterization of the allergenic components of grass pollens could lead to a superior method of standardizing grass pollen extracts.<sup>133</sup> However, FDA has determined that it is not in the interest of the public health to wait indefinitely for some unknown best system to be developed. The standardization methods implemented under 21 C.F.R. 680.3(e) have led to a greatly reduced variability of potency in standardized extracts.

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<sup>129</sup> Yunginger, J.W., Standardization of Allergenic Extracts,, *Annals Allergy* 66:107-08 (1991).

<sup>130</sup> Citizen Petition at 44 (citing Platts-Mills, T.A.E. and Chapman, M.D., *Allergen Standardization*, 87 *J. Allergy Clinical Immunology* 621, 622 (March, 1991)).

<sup>131</sup> Platts-Mills, T.A.E. and Chapman, M.D., *Allergen Standardization* 87 *J. Allergy Clinical Immunology* at 622.

<sup>132</sup> Citizen Petition at 60-61.

<sup>133</sup> Id. at 47.

Current standardized extracts exhibit less than a 2-fold variation in potency - a significant improvement over the potency of unstandardized extracts, which varied as much as 60-fold.

Although you suggest that FDA should "work toward development of a more reliable system of standardization in conjunction with other regulatory authorities,"<sup>134</sup> FDA has determined that this matter should not await the development of international consensus. The public health would be ill served by inaction, and ill served by waiting for international action that might never occur. In any event, FDA stays abreast with international developments. FDA has held numerous discussions with regulators from the European Community, and FDA regularly participates in the Paul Ehrlich meetings, held every three years for the past decade. Indeed, FDA hosted the 1996 Paul Ehrlich meeting in Bethesda, Maryland.

#### **5. FDA Appropriately Considered Issues Surrounding "Reference Standard Drift".**

You raise the specter of "reference standard drift," an alleged alteration in the composition of the reference standard samples provided to grass pollen extract manufacturers by FDA.<sup>135</sup> You assert that, due to this "drift," grass pollen extract manufacturers are required to "aim at a moving target" as the reference standard samples change over time.<sup>136</sup> However, you have proffered no evidence of a "drift" in the composition of the grass pollen extract reference standards, nor have you identified factors that suggest that such a drift is likely to develop over time.<sup>137</sup>

You base your contention on reported drift in the reference standard for house dust mite extract, which reportedly has changed as successive generations of the reference standard are prepared.<sup>138</sup> However, even if dust mite allergens may be subject to degradation or antigenic variation over time, there is no reason to assume that grass pollen extracts might be subject to similar variation.

The potential for degradation of mite allergens is much greater than that for the grass standards. Mite extract is prepared from the total body and feces of dust mites. In contrast, grass pollen extracts are prepared from 99% pure pollen. Mite extract has been shown to contain more proteases, enzymes that may degrade protein allergens, than grass pollen extracts.<sup>139</sup> In addition, mites are grown in culture, and the composition of mite allergens may vary as culture conditions

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<sup>134</sup> Id. at 48.

<sup>135</sup> Id. at 51-52.

<sup>136</sup> Id. at 52.

<sup>137</sup> Indeed, as of September, 1999, first generation reference standards were still used for four of the eight grass pollen extracts.

<sup>138</sup> Citizen Petition at 51-52, n.148.

<sup>139</sup> Esch, R. E., Role of Proteases on the Stability of Allergenic Extracts, Arb. Paul Ehrlich Inst. Bundesamt Sera Impfstoffe Frankf. A.M. 1992, 85:171-79

change. For example, the age and nutritional status of the mites and their growth rate may affect the composition of the allergens.

The grass pollen extract reference standards appear to remain stable over time. As shown in Table IV, relative potencies for reference standards re-constituted up to 3 years prior to testing were virtually the same as for freshly reconstituted standards. Thus, the unit of potency did not drift over the three years of the study. On the contrary, it remained consistent over time.

Moreover, we have demonstrated consistency between generations of reference standard extracts. FDA has performed extensive testing to compare successive generations of grass pollen extract reference standards. As described in section I.D.3.c, each new generation of reference standard is validated in a joint effort by FDA and the manufacturers, using the ELISA assay.<sup>140</sup> For example, prior to the introduction of the most recent replacement grass reference standard (E-12 for Perennial Rye Grass), a battery of ELISA potency tests were performed by both FDA and the manufacturers (Figure 4). Several different lots of perennial rye allergen were tested for relative potency compared to either the old standard E10-Rye or the proposed new standard E12-Rye. Each point on the graph represents a plot of potency of E10 on the X-axis vs. potency against that of E12 on the Y-axis. If there were drift in E10, so that the new E12 standard were more potent than the previous E10, the samples would show lower potency relative to E12 than to E10, and the points would fall below the 45° line of equivalence. Conversely, if the E12 standard were less potent, the points would fall above the line. In fact, the performance of both standards showed extremely close agreement, and the experimental points yield a regression line very nearly superimposable on the 45° line of equivalence.

These results demonstrate FDA's ability to renew the grass standards at the same level of potency. They also demonstrate the lack of drift in the old standard, up to the time when it was replaced. Moreover, these results demonstrate that intra-laboratory and inter-laboratory variability do not impede the selection of successive generations of grass pollen extract reference standards.<sup>141</sup> FDA has determined that both intra-laboratory and inter-laboratory variability are low. Based on a review of over 200 ELISA tests performed by at least three different FDA technicians, FDA concluded that the standard deviation was 0.1375, representing a low level of intra-laboratory variability. Similar results were obtained after a review of intra-laboratory variability during selection of the E12-Rye reference. Similarly, inter-laboratory variability is quite low. In a study comparing ELISA assays performed by eight different laboratories (seven APMA members and FDA), the results obtained using the E10 reference were similar to those

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<sup>140</sup> You state that the agency "has not implemented any standard procedure to calibrate new supplies of reference standards to the existing standards to ensure that the target potency level remains constant with each successive 'generation' of reference extracts," Citizen Petition at 51. However, FDA has implemented such a procedure, with input from industry. See Laboratory of Immunobiochemistry Standard Operating Procedures Number 12 and 13.

<sup>141</sup> See Citizen Petition at 52 and n.149.

obtained using E12, as reflected in the agreement between the experimental line and the predicted line (Figure 4).

Based on its review of this evidence, and in the absence of contrary evidence, FDA has reasonably concluded that there is every reason to expect that successive generations of reference standards will be equivalent to prior generations.

**6. FDA and Grass Pollen Extract Manufacturers Provided for Appropriate Physician Education and Other Steps to Ease the Transition to Standardized Grass Pollen Extracts.**

By October 8, 1987, the date that FDA promulgated the standardized potency rule, 21 C.F.R. § 680.3(e), grass pollen extract manufacturers should have known that standardization of their products was on the horizon. The Allergenic Extracts Panel had already recommended standardization in its report, published in the Federal Register in 1985. Moreover, standardization was discussed regularly in the scientific community. As you note,<sup>142</sup> the American Academy of Allergy issued a position statement in 1980 supporting the need for standardization.<sup>143</sup>

By letters dated April 8, 1994, FDA advised manufacturers that they should comply with 21 C.F.R. § 680.3(e) by April 8, 1996. FDA subsequently extended that compliance date three times, until the final date, July 8, 1998, was set. That date was four years and three months after FDA's April 8, 1994 letters, and ten years and nine months after FDA promulgated the standardized potency rule. The grass pollen extract manufacturers were not rushed into compliance. Rather, they had plenty of time to ease the transition to standardized grass pollen extracts. Rather than a two year transition period during which both types of extracts would be available, manufacturers and practitioners had almost eleven years to prepare for the advent of standardized grass pollen extracts.

Moreover, throughout this implementation period, FDA listened to concerns expressed by medical practitioners. In two of the three extensions of the compliance date, FDA acted in response to concerns expressed by the American Academy of Allergy, Asthma & Immunology. On one occasion, the American Academy requested additional time to allow it to develop protocols for physicians to use in converting to standardized products; FDA granted a one year extension for this purpose. On the second occasion, the American Academy requested additional time to avoid the development of product shortages; FDA granted a six month extension for this purpose. After July 8, 1998, with the implementation of standardization finally complete, FDA

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<sup>142</sup> Citizen Petition at 8 n.29.

<sup>143</sup> American Academy of Allergy, Position Statement on Allergen Standardization (No. 6), *J. Allergy Clinical Immunology* 66:431 (1980).

received no reports of product shortages associated with the implementation of 21 C.F.R. § 680.3(e).

Despite the long time frame for implementation of standardized potency designations, and despite the smooth transition process, you warn of potential ill effects.<sup>144</sup> Those ill effects have not materialized. There is no reason that physicians should have been confused by the advent of the "Bioequivalent Allergy Unit" (BAU) potency unit. Although allergenic product manufacturers no longer describe the potency of the product by reference to "W/V" or "PNU" on product labels, package inserts accompanying such products contain data comparing the relative potency of products previously distributed by the manufacturer labeled "W/V" or "PNU" designations, with standardized grass pollen extracts labeled in BAU.<sup>145</sup>

Moreover, FDA and the grass pollen extract manufacturers have taken measures to facilitate the easy introduction of standardized grass pollen extracts. When standardized products were ready to be licensed, FDA reviewed and approved letters to be sent by manufacturers to physicians who used their products.<sup>146</sup>

On May 11, 1998, FDA sent out a "Dear Doctor" letter informing the medical community of the advent of standardized grass pollen extracts, and directing physicians to the package insert for:

directions on how to perform skin testing with these extracts in order to make a diagnosis of grass pollen allergy, how to select a safe dose when switching from nonstandardized to standardized extracts, and how to initiate immunotherapy. . . .

The package insert contains full prescribing information.

Standardized grass pollen extracts labeled in BAUs are not directly interchangeable with grass pollen extracts labeled in Allergy Units (AU/mL) or with non-standardized extracts labeled in PNU/mL or the extraction ratio (e.g., 1:10 weight by volume). However the package insert does show the potency of the previously available non-standardized

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<sup>144</sup> Citizen Petition at 52-56.

<sup>145</sup> Thus, since the "W/V" and "PNU" reference is available in the package insert, it is simply not true that, "the agency's standardization system requires manufacturers to delete from product labeling the W/V and PNU units of potency that allergists have traditionally used, [and] physicians will have no system of reference to assist in interpreting the new bioequivalent allergy units." *Id.* at 52-53. Manufacturers have been given permission to provide information on how W/V or PNU designations of lots in current use compare to standardized grass pollen lots in BAU to facilitate safe switching from nonstandardized to standardized extracts.

<sup>146</sup> You state that "there is no assurance that physicians will read or fully comprehend these materials before using the new standardized products." *Id.* at 54. This argument is, in effect, an argument in favor of never making any changes. FDA has rejected it, in favor of a practice of appropriate and effective communication.

extracts, for comparison with the standardized lots currently available. It also provides guidance for switching patients to the new standardized extracts.<sup>147</sup>

To facilitate communication regarding the standardized extracts, FDA has placed additional information regarding the transition on its web site,<sup>148</sup> and published an article, "Important New Product Prescribing Information on Standardized Grass Pollen Extracts," in the summer 1998, volume 28, number 1, issue of the FDA Medical Bulletin, a publication FDA made available to health professionals by subscription and on its web site.<sup>149</sup> Both FDA and the manufacturers have made presentations at clinical allergy meetings designed to inform physicians about the advantages of the BAU units as compared to unstandardized designations.<sup>150</sup>

Manufacturers are now manufacturing a better product. Standardized grass pollen extracts are more consistent than unstandardized extracts. As shown in Table I, non-standardized allergenic extracts labeled identically differed by over five-fold in potency from one lot to the next, and extracts of different grasses differed by up to 60-fold. Standardized extracts are measured by reference to IgE reactivity, instead of by the weight of total proteins, including non-allergenic proteins, or by the weight of matter extracted by a given volume of liquid, as measured by the PNU and W/V designations. Accordingly, doses based on BAU can be expected to elicit clinical responses more consistently. Now that reliable potency testing is available, it would be unreasonable to turn back the clock and subject allergic patients to the risk of receiving a dose of unstandardized product that is 10 to 15 times stronger than the dose implied by the label.

#### **7. FDA's Decision to Require Stability Testing of Standardized Grass Pollen Extracts Was Rational.**

Manufacturers have consistently asserted that grass extracts stored in 50% glycerin at 2-8°C are stable for at least three years. To back up this claim, manufacturers must demonstrate that three year stability period by conducting three year stability studies. Throughout the three year study, manufacturers test retained product samples using the ELISA potency assay, which is capable of detecting changes in the product over time.

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<sup>147</sup> May 11, 1998 "Dear Doctor" letter at 2;  
<http://www.fda.gov/cber/ltr/grassltr.pdf>.

<sup>148</sup> See, e.g., December 23, 1997 letter extending the deadline for compliance to July 8, 1998, <http://www.fda.gov/cber/ltr/grassl22397.pdf>; 1997 and 1998 Biological License Application Supplement Approvals for Standardized Grass Extracts for Allergy Diagnosis and Treatment, <http://www.fda.gov/cber/appr1997/1997grass.htm> <http://www.fda.gov/cber/appr1998/1998grass.htm>; May 11, 1998 Dear Doctor letter, informing medical community about the transition to standardized grass pollen extracts, <http://www.fda.gov/cber/ltr/grassltr.pdf>.

<sup>149</sup> The summer, 1998 FDA Medical Bulletin may be found at <http://www.fda.gov/medbull/summer98.html>.

<sup>150</sup> See, e.g., List of Presentations, 1986-1999, by Paul C. Turkeltaub, M.D.

You object that "FDA's potency testing system requires that at each stability testing interval, the extracts must continue to meet the same standard of potency applied to initial lot release."<sup>151</sup> You argue that FDA should instead follow "European regulations regarding allergen extract stability testing [and] establish limits which account for product degradation, requiring that products must retain at least 30% of their initial potency at the end of shelf life."<sup>152</sup> FDA rejects this approach. The standardization program established in 21 C.F.R. § 680.3(e) is designed to prevent a major discrepancy between the last dose a patient receives from an old vial of an allergenic product, and the first dose he receives from a new vial. Widely varying stability limits could result in significant overdosing and could needlessly expose the patient to the risk of anaphylaxis. In addition, since immunotherapy depends on the amount of allergen received, a dose that was 30% of the intended dose could reduce the consistency of effect. Reliable and consistent dosing is an important benefit of the grass standardization program. This benefit would be lost if widely varying stability limits were allowed.<sup>153</sup>

You have also expressed concern about other sources of instability, such as improper storage conditions in a physician's office, or storage in dilute solutions.<sup>154</sup> FDA has determined that these hazards do not exempt manufacturers from delivering a product that will be stable when handled under optimal conditions by the most skilled practitioners, and these hazards do not exempt manufacturers from accompanying that delivery with a package insert specifying appropriate storage conditions.

Similarly, although you object to conducting stability testing "for multiple lots of each formulation and strength of each extract,"<sup>155</sup> this method has worked well for licensed manufacturers. As shown in Table III, the method assures that an adequate number of samples will be available for testing at each time point to make a statistically reasonable estimate of stability. If fewer samples were put on study, more frequent sampling would be needed to make a statistical estimate.

#### **8. FDA's Decision to Implement Standardization in 10,000 and 100,000 BAU Was Rational.**

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<sup>151</sup> Citizen Petition at 49.

<sup>152</sup> Id. at 49-50.

<sup>153</sup> In any event, FDA has issued a draft guidance related to stability test criteria. See Testing Limits in Stability Protocols for Standardized Grass Pollen Extracts (Draft Guidance) (August, 1997), available at <http://www.fda.gov/cber/qdlns/grass.txt>.

<sup>154</sup> Citizen Petition at 48 and n.141.

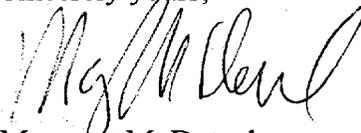
<sup>155</sup> Id. at 50.

You complain that FDA has not recognized a reference standard for allergenic product containing up to 1,000,000 BAU/mL.<sup>156</sup> However, FDA sought the advice of the Advisory Committee, which recommended that each grass extract be available in two dose forms: 100,000 and 10,000 BAU/mL. Rather than making this decision "arbitrarily,"<sup>157</sup> FDA made this decision on the advice of the Advisory Committee, after a full discussion of the issues at a meeting APMA representatives attended.

### **III. Conclusion**

Your request that FDA withdraw certain requirements pertaining to the standardization of eight grass pollen extracts is denied.

Sincerely yours,



Margaret M. Dotzel  
Associate Commissioner  
for Policy

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<sup>156</sup> Id. at 57.

<sup>157</sup> Id. at 61.

**Table I. Range of Relative Potency of Unstandardized Grass Pollen Extracts Labeled as Aqueous 1:10 W/V and Glycerinated 1:20 W/V, as Compared to a 100,000 BAU/mL Reference by the ELISA Potency Assay**

Grass Pollen Extract	Number of Lots	Tested	Range of Relative Potency	Ratio of Highest to Lowest Relative Potency
<b>Kentucky Bluegrass</b>	27	Aqueous 1:10 W/V	0.51-4.49	9
	27	Glycerinated 1:20 W/V	0.32-1.50	5
<b>Meadow Fescue</b>	21	Aqueous 1:10 W/V	1.28-11.32	9
	25	Glycerinated 1:20 W/V	1.29-3.78	3
<b>Orchard</b>	23	Aqueous 1:10 W/V	0.24-2.42	10
	25	Glycerinated 1:20 W/V	0.66-1.32	2
<b>Redtop</b>	22	Aqueous 1:10 W/V	0.18-15.02	83
	26	Glycerinated 1:20 W/V	0.13-2.19	17
<b>Perennial Rye</b>	21	Aqueous 1:10 W/V	0.25-2.13	9
	23	Glycerinated 1:20 W/V	0.53-1.95	4
<b>Timothy</b>	29	Aqueous 1:10 W/V	0.46-4.49	10
	23	Glycerinated 1:20 W/V	0.43-1.49	3
<b>Sweet Vernal</b>	14	Aqueous 1:10 W/V	0.75-2.56	3
	20	Glycerinated 1:20 W/V	0.64-2.01	3
<b>Bermuda<sup>158</sup></b>	19	Aqueous 1:10 W/V	0.08-0.40	5
	28	Glycerinated 1:20 W/V	0.04-0.16	4

Source of Information: Manufacturers' Package Inserts

<sup>158</sup> Bermuda grass pollen extracts were approximately ten times less potent than those of the other grass pollen extracts at equal protein content or weight to volume. The discovery of this variation among grass pollen extracts from different species of grass was a notable scientific result of the allergen standardization program. Currently, Bermuda grass pollen extracts are distributed only in a 10,000/BAU/mL concentration.

**Table II. Skin Tested Reference Standards and the Current Generation of Reference Standards**

<b>Grass</b>	<b>Skin Tested Lot</b>	<b>July 1998 Reference</b>	<b>Sept. 1999 Reference</b>	<b>Conclusion</b>
<b>Bermuda</b>	E4-Ber	E4-Ber and E5-Ber	E5-Ber	one generation removed
<b>Kentucky (June) Bluegrass</b>	E3-Jkb	E3-Jkb	E5-Jkb	one generation removed <sup>159</sup>
<b>Meadow Fescue</b>	E4-Mf	E4-Mf	E4-mf	same generation
<b>Orchard</b>	E4-Or	E4-Or	E4-Or	same generation
<b>Redtop</b>	E4-Rt	E4-Rt	E4-Rt	same generation
<b>Perennial Rye</b>	E10-Rye	E12-Rye	E12-Rye	one generation removed
<b>Sweet Vernal</b>	E4-Sv	E4-Sv	E4-Sv	same generation
<b>Timothy</b>	E6-Ti	E7-Ti	E7-Ti	one generation removed

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<sup>159</sup> E4-Jkb was also skin-tested, but it was rejected for use as a reference standard. E5-Jkb was standardized to E3-Jkb.

**Table III. Typical ELISA Relative Potency Results from a Manufacturer of Standardized Grass Pollen Extracts at 100,000 BAU/mL (Except Bermuda at 10,000 BAU/mL)**

<b>Grass</b>	<b>Lot A</b>	<b>Lot B</b>
<b>Bermuda</b>	0.93	0.95
<b>Kentucky (June) Bluegrass</b>	0.88	1.39
<b>Meadow Fescue</b>	0.97	0.72
<b>Orchard</b>	1.05	1.27
<b>Perennial Rye</b>	0.91	0.9
<b>Redtop</b>	1.14	0.77
<b>Sweet Vernal</b>	0.98	0.84
<b>Timothy</b>	0.88	0.9

Note: For all grasses, both lots passed

**Table IV. Relative Potencies of CBER Lyophilized Grass Pollen References Reconstituted at Various Times, Stored at 2-8 C, and Tested in July, 1997**

Reference	Relative Potency of grass pollen that was reconstituted 7/94, then stored for three years	Relative Potency of grass pollen that was reconstituted 7/95, then stored for two years	Relative Potency of grass pollen that was reconstituted 7/96, then stored for one year	Relative Potency of freshly reconstituted grass pollen
Bermuda E4-Ber	0.935	1.052	0.922	0.898
Sweet Vernal E4-SV	0.727	0.762	0.84	1.078
Timothy E6-Ti	0.702	0.742	0.733	1.032
Meadow Fescue E4-Mf	0.833	1.193	1.277	1.316
June E3-JKB	0.975	1.033	0.942	0.92
Orchard E4-Or	0.933	0.927	1.081	1.361
P. Rye E10-Rye	0.714	0.789	0.916	1.209
Red Top E4-Rt	0.816	0.774	0.943	0.895

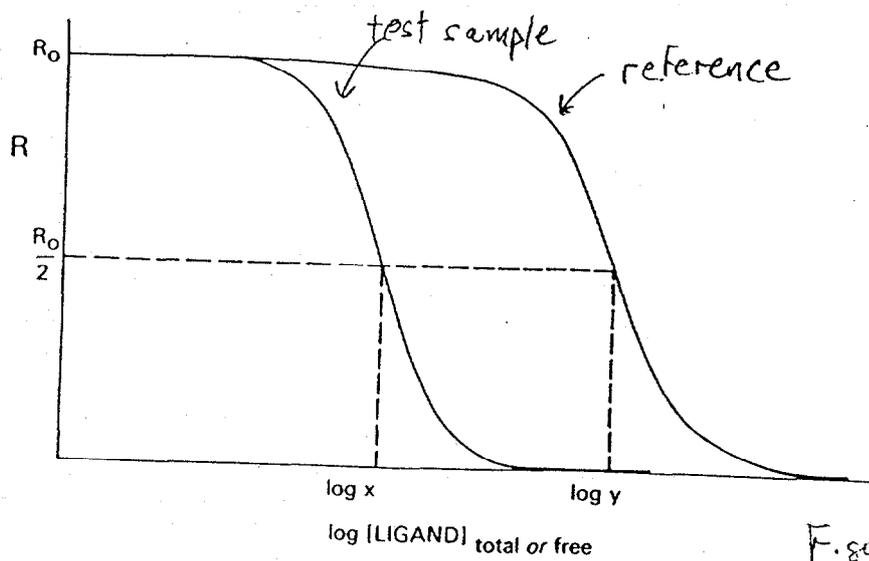


Figure 1

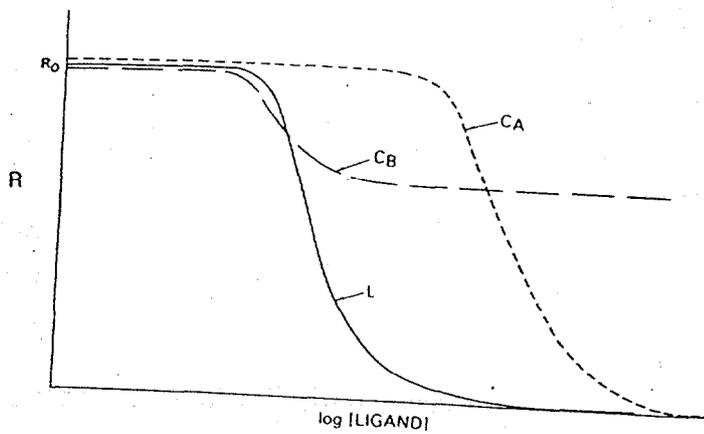


Fig 2

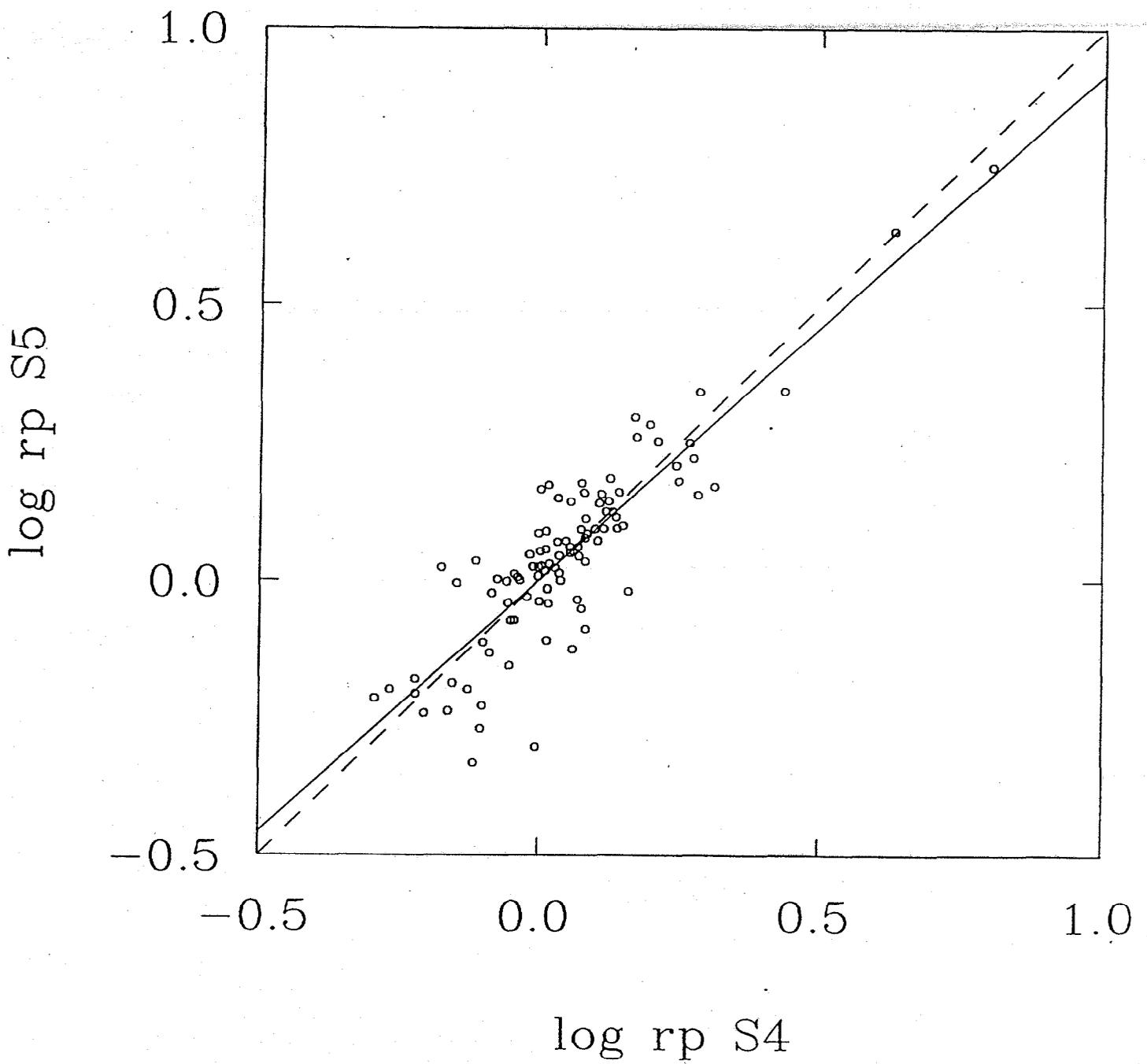


Figure 3.

Fig. 4. Sample log RP: A Comparison of E12-Rye vs. E10-Rye

