



# Oral Immunotherapy for Food Allergy—a US Regulatory Perspective

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## Abstract

The recent approval of Palforzia for treatment of peanut allergy by the US Food and Drug Administration (USFDA) predicts that additional products for oral immunotherapy (OIT) are on the horizon. In this article, the authors review the legal framework by which the USFDA regulates products for OIT of food allergy and the clinical data that demonstrated that the safety and effectiveness profile of Palforzia supported approval and conclude with a discussion of oral food challenge (OFC) as a clinical endpoint to demonstrate safety and effectiveness of OIT products.

**Keywords** Food allergy · Oral immunotherapy · Oral food challenge · US Food and Drug Administration · Anaphylaxis

## Introduction: Definitions and Overview of the Review Process

Upon establishing the concept of oral immunological tolerance, immunologists and allergists recognized that the oral route can be exploited to desensitize food-allergic patients. The first published report of oral immunotherapy (OIT) was an uncontrolled trial of 19 food-allergic patients in 1984 [1]. The first US report was in 2007, a proof-of-concept uncontrolled trial of seven egg-allergic children [2]. Although the first US randomized controlled trials were reported in 2012 [3, 4], adoption of OIT by some clinicians prompted a debate as to whether OIT was ready for “prime time” [5], and questions to regulatory authorities whether foods used to desensitize or tolerize food allergic patients should be considered as “foods” or should be regulated as “drugs.”

The answer to this question can be found in the Food Drug and Cosmetic Act. (FD&C Act). The FD&C Act

Section 321(g)(1)(B) defines “drugs” in part as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.” In addition, the Code of Federal Regulations (CFR), which carries the authority of law (amended March 20, 2020), defines a “biological product” in 21CFR 600(1)(h) as a “virus, therapeutic serum...allergenic product, protein or analogous product... applicable to the prevention, treatment, or cure of a disease or condition of human beings.” Note that all these definitions refer to the intended use. Thus, the intended use of a product in a clinical study determines whether the product fits within the drug definition. When used in OIT to treat allergic individuals, products traditionally considered foods are biologics regulated by the FDA’s Center for Biologics Evaluation and Research (CBER).

A clinical investigation intended to evaluate the effect of a food on a disease requires an Investigational New Drug application (IND) (21 CFR Part 312). An IND is a request to administer an investigational drug to humans. Thus, an IND is required to administer products intended for OIT [6•]). Under the IND, a sponsor (a person who takes responsibility for and initiates a clinical investigation) conducts clinical investigational studies to demonstrate safety and effectiveness, two critical parameters that determine whether the drug can be licensed. Typically, pre-licensure clinical studies are divided into three phases: phases 1, 2, and 3. The purpose of phase 1 studies is to evaluate the safety of an investigational drug and the dosage in (usually) a small set of subjects. In phase 2 studies, the investigational drug’s safety profile is further evaluated, including determination of common side effects, and preliminary evidence suggesting effectiveness is obtained.

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This can include establishing dosing and defining the treatment effect. Data from phase 2 studies are applied to the design of “pivotal” phase 3 studies. Phase 3 study design not only includes such factors as safety and effectiveness monitoring, but determination of study size based on expected treatment effect (often referred to as a “power” analysis). The data from phase 3 studies usually provide the safety and effectiveness data necessary to evaluate the overall benefit risk relationship of a drug to support a Biologics License Application (BLA).

## Product Considerations

In addition to clinical studies, the IND process includes establishing parameters for manufacturing the drug as well as validated measures of purity and potency, which are collectively referred to as “Chemistry, Manufacturing, and Control” (CMC) parameters. CMC data are required to assure the proper identification, quality, purity, and strength of the investigational drug. CMC data include, but are not limited to, descriptions of the source materials (from which the drug is derived), the drug substance (the active ingredient), and the drug product (drug substance with inactive ingredients such as sweeteners, fillers, etc.), and criteria for acceptance of a manufactured lot to be distributed to study subjects (e.g., purity, potency). The amount of information required will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available.

While the product used in investigational studies must be manufactured according to good manufacturing practices, specifications for product acceptance often narrow as studies progress from phase 1 to phase 3. Final specifications for the drug substance and drug product are expected at the time of submission of a marketing application. Since much of the clinical data demonstrating safety and effectiveness included

in a license application is generated in phase 3 studies, the study drug used in such studies should be manufactured according to the same process and controls as the product intended for licensure, usually in the same manufacturing facility and with the same instruments and machinery.

Standardization is the process by which potencies of similar products from different manufacturers can be compared—Amb a 1 content in ragweed pollen extracts, for example. For allergenic extracts, standardization is a lengthy process in which CBER determines validated methods and stocks reference reagents for distribution to manufacturers. Allergenic extracts that are not standardized are defined only by mass (g/mL) or protein nitrogen units (PNU). Consequently, consistency cannot be ensured by potency testing for most allergen extracts manufactured in the USA. Although Palforzia is not standardized to a CBER reference, it must be characterized with measures of potency by the manufacturer in order to ensure that the product is consistent across manufactured lots and to measure stability of manufactured lots through expiry. Standard techniques such as immunoassay (i.e., “sandwich” and competitive ELISAs) are informative, but it is CBER’s expectation that manufacturers of products for OIT choose complementary (often referred to as orthogonal) methods towards characterization of their products. For example, among the methods shown in Table 1, manufacturers may elect to use ELISA and HPLC to identify and measure presence of a set of allergens.

For any method manufacturers employ, they must have reference reagents to which manufactured lots are compared, as well as plans for replacing reference reagents that include “bridging” studies. For example, a reference reagent may be one lot of product that is kept at  $-20$  or  $-80$  °C divided into aliquots that are used once and discarded. Ideally, as the reference reagent is depleted, manufacturers choose a replacement from a manufactured lot that is most similar to the original,

**Table 1** Methods to measure product consistency and stability

| What is measured                                            | Method                                              | Comments                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Content of specific allergens (e.g., mg allergen/g protein) | Enzyme-linked immunosorbent assay (ELISA)           | Measures specific allergens<br>Laborious to create specific mAb or pAb                                                                                                                                                                                         |
| IgE binding activity                                        | Competitive ELISA                                   | Overall IgE binding activity with no attribution to specific allergens                                                                                                                                                                                         |
| Protein content (e.g., g protein/g peanut flour)            | Chemical (e.g., BCA) or physical (Kjeldahl) methods | Does not detect protein degradation                                                                                                                                                                                                                            |
| Individual proteins                                         | High-performance liquid chromatography (HPLC)       | Distinguished according to, e.g., mass, hydrophobicity or isoelectric point<br>Can be precise and reproducible<br>No indication about integrity of antigenic sites<br>May be difficult to distinguish different proteins with similar chemical characteristics |
| Individual proteins or signature peptides                   | Mass spectrometry                                   | Very precise and sensitive<br>Expensive technology                                                                                                                                                                                                             |

and the original and replacement standards are used together to “bridge” from the original to the replacement.

### **PALFORZIA as an Example for Approval of a Drug for OIT**

This section will review the Allergenic Products Advisory Committee (APAC) discussion that led to the use of oral food challenge (OFC) outcomes as the primary endpoint for assessment of effectiveness of OIT products and summarizes the data that demonstrated the safety and effectiveness of Palforzia. Further information about the approval of Palforzia including the package insert, medication guide, and supporting reviews can be found here: <https://www.fda.gov/vaccines-blood-biologics/allergenics/palforzia>

An APAC meeting was convened on January 21, 2016 to obtain advice regarding the design of investigational studies for treatment of IgE-mediated food allergy and to discuss safety and efficacy endpoints, including OFC study endpoints, to support licensure of OIT products. In particular, the committee was asked to comment on the use of OFC to assess efficacy. The discussion included the following issues regarding the use of OFCs: objective criteria for determining the eliciting dose, particularly in children less than 5 years of age, clinically meaningful parameters including amplitude of response, safety considerations for the food challenge, approaches other than OFC studies to demonstrate effectiveness of immunotherapy products, and specific safety monitoring for signs and symptoms of allergic reactions.

At the 2016 APAC meeting, the committee discussed the goal of immunotherapy: ideally to induce full tolerance so that patients may ingest the culprit food ad lib. However, since data from available studies have not shown induction of full tolerance by oral immunotherapy, the committee agreed that diminishing the risk of a life-threatening allergic reaction after accidental exposure is a clinically meaningful goal of immunotherapy. To this end, the goal of OIT is to incrementally increase the dose of the OIT product to a final fixed daily dose, referred to as the “maintenance dose.” The goals of OIT are to desensitize individuals and to mitigate the risk of a severe allergic reaction following accidental exposure to the food allergen, for example, after ingesting a cookie. Therefore, patients with a history of life-threatening anaphylaxis are those who may benefit most from this treatment.

In addition to this goal, the committee also agreed that OFC is an acceptable option to determine whether a treatment is effective. The alternative, a randomized, controlled field study (in subjects practicing allergen avoidance), in which the primary objective is reduction of the rate and/or severity of reactions following accidental food exposure in the treated subjects, may require larger cohorts and longer study durations to detect statistically significant differences. While OFCs have risks, the committee agreed that they are reduced by ensuring

that clinical investigators are allergists experienced in the field of food allergy who have been trained to recognize and treat allergic reactions.

Palforzia, the first OIT product licensed in the USA for treatment of IgE-mediated peanut allergy was approved on January 31, 2020 using the results of OFCs as the primary endpoint. Palforzia is indicated as a treatment to reduce the incidence and severity of allergic reactions, including anaphylaxis, after accidental exposure to peanut in patients 4 through 17 years of age with a confirmed diagnosis of peanut allergy. Palforzia is manufactured from defatted peanut (*Arachis hypogaea*) flour and provided in capsules at five dosage strengths (0.5, 1, 10, 20, and 100 mg peanut protein) and in a sachet at one dosage strength (300 mg peanut protein). The dosing regimen is complex and consists of three periods: initial dose escalation (IDE), up-dosing, and maintenance. Product dosing begins with an initial dose escalation of 0.5 to 6 mg of Palforzia over 1 day under the supervision of a qualified healthcare professional trained in the diagnosis and treatment of allergic diseases and in a health care setting equipped to manage severe allergic reactions. Subsequently, up-dosing begins at 3 mg Palforzia and continues, as tolerated, with up-dosing every 2 weeks until reaching 300-mg daily maintenance treatment. Like the IDE, the first dose of each new level in the up-dosing schedule and the first maintenance dose are administered under supervision of a qualified healthcare professional in a healthcare setting.

The Biologics License Application (BLA) for Palforzia contained data from four main clinical studies. These studies included one controlled phase 3 efficacy study (ARC003), a phase 3 controlled safety study (ARC007), and two uncontrolled studies (ARC004 and ARC011), both of which were follow-on studies for ARC003 and ARC007, respectively. While adults 18–55 years of age participated in ARC003, the majority of participants in the four clinical studies were pediatric subjects 4–17 years of age. Therefore, this discussion will focus on pediatric subjects in controlled studies ARC003 (efficacy and safety) and ARC007 (safety).

ARC003 was a phase 3, randomized, double-blind, placebo-controlled study that enrolled 499 subjects, 4–17 years of age. A screening double-blind, placebo-controlled oral food challenge (DBPCFC) with up to 100 mg peanut protein was performed to confirm true peanut allergy. Subjects with severe or uncontrolled asthma, a history of eosinophilic esophagitis (EoE), and severe/life-threatening anaphylaxis 60 days prior to screening were excluded from the study. The primary efficacy endpoint was the proportion of subjects 4–17 years of age who tolerated a single highest dose of at least 600 mg (1043 mg cumulative) of peanut protein with no more than mild symptoms at the Exit DBPCFC. Subjects who tolerated 600 mg (considered equivalent to the ingestion of two peanuts) were considered responders for the primary efficacy analysis. Subjects who did not have an Exit

DBPCFC were considered non-responders for the purpose of this analysis.

The point estimate of the primary efficacy analysis was the difference in responder proportions between treatment groups (Palforzia—placebo). The pre-specified criterion for study success was demonstrated if the lower bound of the corresponding 95% CI of the difference of response rates was greater than 15%. Key secondary endpoints included the proportion of subjects 4–17 years of age who tolerated a single highest dose of at least 300 mg or 100 mg of peanut protein with no more than mild symptoms at the Exit DBPCFC, and the proportion of subjects 4–17 years of age who tolerated a single highest dose of at least 300 mg of peanut protein with no more than mild symptoms at the Exit DBPCFC. Most of the ARC003 participants were white (78.4%), male (57.3%), and resided in North America (81.0%). The majority of subjects had additional food allergies (65.5%). Other common atopic conditions included allergic rhinitis (71.8%), asthma (52.8%), and atopic dermatitis (62.1%). Subjects with these conditions were equally distributed between the treatment and placebo groups.

The safety population (which included subjects from ARC007) reflected the demographics of subjects in study ARC003. However, participants in ARC007 did not undergo an Entry DBPCFC to confirm peanut allergy. In study ARC003, 21.4% of subjects treated with Palforzia discontinued treatment compared with 8.0% of placebo recipients. Reasons for discontinuation of Palforzia included adverse events (9.1%) and withdrawal of consent (8.3%). In the placebo group, 8% of subjects discontinued, most commonly due to withdrawal of consent. Study ARC003 met the primary efficacy objective for the subject population 4–17 years of age with a treatment difference (efficacy) estimate of 63.2% (95% CI: 53.0, 73.3).

The main safety concern in subjects treated with Palforzia is allergic reactions due to the nature of the treatment approach, which is to expose individuals with IgE-mediated peanut allergy to peanut proteins in order to decrease immunologic hyperresponsiveness upon accidental exposure to peanut proteins in routine daily life. Palforzia-treated pediatric subjects in the controlled safety population (studies ARC003 and ARC007) reported an increased number of allergic reactions, including systemic allergic reactions, compared with placebo-treated subjects. A total of 9.4% of subjects taking Palforzia had a systemic allergic reaction during IDE and up-dosing compared with 3.8% of placebo subjects. This imbalance was seen during the maintenance phase as well, with 8.7% versus 1.7% of Palforzia and placebo subjects, respectively, having a systemic allergic reaction. During the maintenance period, 7.7% of Palforzia-treated subjects used epinephrine compared with 3.4% in the placebo group. The incidence of systemic allergic reactions in treatment and placebo study

groups during the three study periods is summarized in Table 2.

Within the ARC003 “completer” population (those who completed the exit DBPCFC), the rates of systemic allergic reactions in Palforzia and placebo recipients were 14.2% and 11.8%, respectively. During up-dosing, 8.5% vs. 6.4% reported systemic allergic reactions and 8.7% vs. 7.1% reported reactions during the maintenance period. While limited by small numbers, these data suggest that subjects included in the ITT population, which included subjects who dropped out or did not complete the exit DBPCFC, were less tolerant (i.e., reported more systemic allergic reactions regardless of severity) to Palforzia than those in the “completer” population. In addition, there was no association between sensitivity (or minimum reactive dose) on entry DBPCFC (for study ARC003) and reports of systemic allergic reactions, epinephrine use, or study discontinuation for any reason. There were no meaningful differences in the reported frequency and severity of adverse events among subjects with asthma, allergic rhinitis, or atopic dermatitis. However, differences may be observed following use of Palforzia in a larger population of peanut-allergic patients.

Overall, the efficacy data from study ARC003 supported the effectiveness of Palforzia. Among Palforzia recipients, there was a strong treatment effect and dose-response to 300, 600, and 1000 mg of peanut protein during the exit DBPCFC as well as a reduction in the overall severity of allergic symptoms during the exit DBPCFC compared with placebo recipients. The increased risks of Palforzia treatment (systemic allergic reactions/anaphylaxis and allergic reactions requiring epinephrine as a rescue medication) necessitated a risk evaluation and mitigation strategy (REMS) program modeled after study procedures for risk mitigation in the clinical protocols as well as clear information conveyed through the prescribing information (PI) and medication guide. Due to the complex nature of Palforzia administration, treatment should be limited to those patients/caregivers who fully understand the risks, benefits, and lifestyle/time commitment involved with this therapy; some patients may decide against Palforzia treatment and instead choose only to continue a peanut avoidant diet. However, with proper education and risk mitigation, Palforzia represents a treatment option for peanut-allergic children 4 to 17 years of age who are also practicing peanut avoidance.

### Role of OFC in Demonstration of Effectiveness of OIT Products

As exemplified by FDA’s approval of Palforzia, randomized double-blind placebo-controlled OFCs have been used to confirm and measure severity of food allergy and to demonstrate safety and efficacy of biological products to treat food allergy. While OFC is considered an acceptable measure of reactions

**Table 2** Summary of systemic allergic and anaphylactic reactions in subjects 4 through 17 years of age: controlled safety population

|                                                      | Palforzia recipients <i>N</i> (%) | Placebo recipients <i>N</i> (%) |
|------------------------------------------------------|-----------------------------------|---------------------------------|
| Initial dose escalation <sup>a</sup> :               | --                                | --                              |
| Total subjects in population                         | 709                               | 292                             |
| Number of systemic allergic reactions <sup>b</sup>   | 5                                 | 1                               |
| Number of systemic allergic reactions by trigger     | --                                | --                              |
| Study product                                        | 5                                 | 0                               |
| Food allergen                                        | 0                                 | 1                               |
| Non-food allergen                                    | 0                                 | 0                               |
| Unknown                                              | 0                                 | 0                               |
| Severity of systemic allergic reaction <sup>c</sup>  | --                                | --                              |
| Mild                                                 | 5 (0.7)                           | 1 (0.3)                         |
| Moderate                                             | 0                                 | 0                               |
| Severe (anaphylaxis)                                 | 0                                 | 0                               |
| Considered serious adverse event                     | 0                                 | 0                               |
| Used epinephrine to treat reaction                   | 3 (0.4)                           | 1 (0.3)                         |
| Location of reaction                                 | --                                | --                              |
| Other than study site <sup>b</sup>                   | 0                                 | 1 (0.3)                         |
| Study site                                           | 3 (0.4)                           | 0                               |
| Up-dosing:                                           | --                                | --                              |
| Total subjects in population                         | 693                               | 289                             |
| Number of systemic allergic reactions <sup>b</sup>   | 76                                | 10                              |
| Number of systemic allergic reactions by trigger     | --                                | --                              |
| Study product                                        | 63                                | 1                               |
| Food allergen                                        | 8                                 | 9                               |
| Non-food allergen                                    | 5                                 | 0                               |
| Unknown                                              | 0                                 | 0                               |
| Severity of systemic allergic reactions <sup>c</sup> | --                                | --                              |
| Mild                                                 | 24 (3.5)                          | 4 (1.4)                         |
| Moderate                                             | 35 (5.1)                          | 6 (2.1)                         |
| Severe (anaphylaxis)                                 | 4 (0.6)                           | 0                               |
| Considered serious adverse event                     | 2 (0.3)                           | 0                               |
| Used epinephrine to treat reaction                   | 41 (5.9)                          | 8 (2.8)                         |
| Location of reaction                                 | --                                | --                              |
| Home                                                 | 33 (4.8)                          | 7 (2.4)                         |
| Study site                                           | 11 (1.6)                          | 1 (0.3)                         |
| Maintenance                                          | --                                | --                              |
| Total subjects in population                         | 310                               | 118                             |
| Number of systemic allergic reactions <sup>b</sup>   | 33                                | 2                               |
| Number of systemic allergic reactions by trigger     | --                                | --                              |
| Study product                                        | 28                                | 1                               |
| Food allergen                                        | 4                                 | 1                               |
| Non-food allergen                                    | 1                                 | 0                               |
| Unknown                                              | 0                                 | 0                               |
| Severity of systemic allergic reactions <sup>c</sup> | --                                | --                              |
| Mild                                                 | 12 (3.9)                          | 0                               |
| Moderate                                             | 14 (4.5)                          | 2 (1.7)                         |
| Severe (anaphylaxis)                                 | 1 (0.3)                           | 0                               |
| Considered serious adverse event                     | 1 (0.3)                           | 0                               |
| Used epinephrine to treat reaction                   | 19 (6.1)                          | 2 (1.7)                         |
| Location of reaction                                 | --                                | --                              |
| Other than study site                                | 18 (5.8)                          | 1 (0.8)                         |
| Study site                                           | 2 (0.6)                           | 1 (0.8)                         |

<sup>a</sup> *N* number of subjects<sup>a</sup> Administration of study product was done entirely in clinic during the initial dose escalation period<sup>b</sup> Number of systemic reactions occurring during the studies. This number does not denote the number of subjects in which systemic reactions occurred because a subject may have experienced more than one reaction<sup>c</sup> Anaphylaxis graded by severity by European Academy of Allergy and Clinical Immunology (EAACI) grading scale

to accidental exposure, clinicians and investigators have questioned whether FDA's reliance upon results of OFC as the primary endpoint for OIT clinical studies may hinder clinical development of OIT and other food allergy therapeutics. One concern is that as the number of clinicians who are administering OIT with products that are traditionally considered foods (e.g., peanut butter) increases, it may become increasingly difficult to recruit subjects to randomized trials. Second, patients and their families may be reluctant to undergo a procedure for which the endpoint is essentially an adverse reaction that is uncomfortable at best and potentially severe. Third, as demonstrated in the Palforzia clinical trials, OFC may be an insensitive predictor of adverse events, and fourth, OIT is time consuming and expensive.

An alternative to abandoning the outcome of OFC as an efficacy endpoint is to consider modifications to the procedure to increase its sensitivity and specificity. For example, Chinthrajah and colleagues reported that a history of exercise-induced asthma, elevated basophil CD63 levels, and decreased FEV<sub>1</sub> predicts a severe reaction to peanut allergen challenge [7•]. In addition, it was recently reported that a regimen of exercise increases sensitivity and specificity of OFC with omega-5 gliadin to diagnose wheat-dependent, exercise-induced anaphylaxis from 81%/71% to 91%/92% [8•]. Equally impressive, of 45 patients who did not react during standard OFC, 21 reacted when OFC was preceded by exercise. Similarly, Dua and colleagues reported that exercise reduced the threshold in 38% of patients tested with a reduction of ED<sub>50</sub> for peanut-allergic patients by 53% [9•].

Sensitivity of OFC may also be enhanced by using non-invasive measurements to detect parameters that may precede clinical respiratory symptoms. For example, impulse oscillometry may detect airway reactivity before the respiratory rate increases or the patient experiences shortness of breath [10•]. Similarly, changes in skin conductivity or even EEG activity may precede the sense of anxiety that accompanies a systemic allergic reaction. While it may be difficult to detect anxiety associated with a systemic reaction against the background of anxiety associated with the procedure, a “big data” analysis of many parameters may reveal criteria for stopping the OFC before the patient experiences symptoms.

Finally, assessment of threshold doses, as well as any comparative assessments, could benefit from adopting a harmonized protocol for OFC that takes into consideration variables such as dependency of time intervals between ingestion of the allergen and signs or symptoms of intolerance of the food allergen in question (e.g., milk versus egg, reviewed in [11]). While the procedure may take more time, we suggest that monitoring for allergic reactions of lower severity and determination of threshold doses with greater accuracy may address some of the difficulties cited with conducting OFC studies.

In conclusion, products used for OIT are drugs and regulated as biologics by the US FDA. As with other biologics,

manufacture of Palforzia is regulated to assure consistent quality and purity. The outcome of OFC has been used to provide data to demonstrate the effectiveness of OIT, and modifications to the procedure may improve its sensitivity and tolerability.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare no conflicts of interest relevant to this manuscript.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Disclaimer** This article is an informal communication that represents the authors' judgment. These comments do not bind or obligate FDA.

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- Of major importance

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