

**CBER CMC BLA Review Memorandum**

**BLA STN 125696**

**Peanut (*Arachis hypogaea*) Allergen Powder**

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**1. BLA#:** STN 125696

**2. APPLICANT NAME AND LICENSE NUMBER**

Applicant name: Aimmune

License number: 2109

**3. PRODUCT NAME/PRODUCT TYPE**

Proper name: Peanut (Arachis hypogaea) Allergen Powder-dnfp

Proprietary name: Palforzia

**4. GENERAL DESCRIPTION OF THE FINAL PRODUCT**

PALFORZIA is an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Initiation of PALFORZIA is approved in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy. PALFORZIA may be continued in patients 18 years of age and older.

Palforzia is presented in capsules and sachets with five capsule dosage strengths of 0.5, 1, 10, 20, and 100 mg, and one sachet dosage strength of 300 mg. The contents of the capsules and sachets are emptied and mixed with age-appropriate food for administration. The capsule shells are not intended to be swallowed.

The dosing regimen for Palforzia consists of three phases:

- Initial dose escalation consists of 5 single doses of 0.5, 1, 1.5, 3, and 6 mg given at 20- to 30-minute intervals as tolerated during a single day.
- Updosing consists of a dose escalation occurring approximately every 2 weeks with once-daily doses of 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day.
- Maintenance dosing involves once-daily doses of 300 mg/day

**5. MAJOR MILESTONES**

Submission date	December 21, 2018
Filing meeting	March 4, 2019
Allergenic products advisory committee meeting	September 13, 2019
Action due date	January 25, 2020

## 6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Philippa Hillyer	3.2.S.1 3.2.S.2 3.2.S.3 (except analytical method for (b) (4)) 3.2.S.4 (except protocols, validation protocols and validation reports for (b) (4)) [REDACTED] 3.2.S.5 3.2.S.6 3.2.S.7 3.2.P, except 3.2.P.2.- (b) (4) attributes and 3.2.P.7 – Container Closure
Debasis Panda (left the FDA, September 2019)	3.2.S.1 3.2.S.2 3.2.S.3 (Analytical method for (b) (4) are reviewed by DBSQC) 3.2.S.4 (Reviewed only (b) (4) method in 3.2.S.4.2, analytical procedure and 3.2.S.4.3, validation of analytical procedure. Other procedures are reviewed by Philippa Hillyer, Samuel Mindaye and members of DBSQC) 3.2.S.5 3.2.S.6 3.2.S.7
Sam Mindaye (currently CDER, formerly DBPAP)	(b) (4) method and validation 3.2.S.4.2 (b) (4) method and data 3.2.S.3.1 and 3.2.R
Lei Huang (intra-center consult, OBE)	Statistics for (b) (4), batch release specifications, stability and post marketing commitments

## 7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/N <sup>1</sup> )
None	N/A	N/A

**8. SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
25 January 2019	STN-125696/0	Reviewed
5 April 2019	STN-125696/4	Reviewed
23 April 2019	STN-125696/6	Reviewed
29 April 2019	STN-125696/9	Reviewed
2 May 2019	STN-125696/10	Reviewed
13 May 2019	STN-125696/13	Reviewed
13 May 2019	STN-125696/14	Reviewed
13 May 2019	STN-125696/15	Reviewed
3 June 2019	STN-125696/17	Reviewed
9 July 2019	STN-125696/22	Reviewed
10 July 2019	STN-125696/23	Reviewed
15 July 2019	STN-125696/24	Reviewed
6 August 2019	STN-125696/29	Reviewed
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9 September 2019	STN-125696/36	Reviewed
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23 Sept 2019	STN-125696/39	Reviewed
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11 October 2019	STN-125696/45	Reviewed
12 November 2019	STN-125696/48	Reviewed
12 November 2019	STN-125696/50	Reviewed
13 November 2019	STN-125696/52	Reviewed
18 November 2019	STN-125696/55	Reviewed
18 November 2019	STN-125696/56	Reviewed
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25 November 2019	STN-125696/59	Reviewed
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5 December 2019	STN-125696/62	Reviewed
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10 December 2019	STN-125696/66	Reviewed
6 January 2020	STN-125696/71	Reviewed
14 January 2020	STN-125696/74	Reviewed
27 January 2020	STN-125696/81	Reviewed

**9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)**

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 15463	Aimmune	Whole IND	No	Clinical development program for Palforzia, (known as AR101 during development).

## 10. REVIEWER SUMMARY AND RECOMMENDATION

### A. EXECUTIVE SUMMARY

On December 21, 2018, Aimmune Therapeutics Inc. submitted a BLA (STN 125696) for licensure of Peanut (Arachis hypogaea) Allergen Powder (Proprietary name: Palforzia). Based on the CMC review of the original submission and responses to informational requests, I recommend approval of Palforzia.

The source material is partially defatted peanut flour (b) (4), light roast) manufactured by (b) (4), from lightly roasted shelled peanuts. The source material is shipped to CoreRx, Clearwater, FL, who selects batches of source material based on (b) (4)

(b) (4), are performed before source material is released as drug substance. Based on stability data, shelf life of the drug substance is (b) (4) months from date of manufacture at (b) (4)

The drug product is also manufactured at CoreRx under GMP conditions. Drug product manufacturing involves the (b) (4)

(b) (4) fashion. Each dose, expressed as mg of peanut protein, has a different batch formula. The resulting powder (b) (4) are tested for (b) (4) and are then either filled into hydroxypropylmethyl cellulose (HPMC) capsules (0.5, 1, 10, 20, 100 mg doses) or foil laminated sachets (300 mg dose). Drug product release testing includes content uniformity, protein content, protein integrity by HPLC, and relative potency by ELISA. Based on real-time stability data, shelf life of the capsules is 24 months at 2 – 8°C, and shelf life of the sachets at 2 – 8°C is 18 months.

There were several review issues that required multiple information requests. The major issues were:

1. A change to the ELISAs used for determining relative potency of Ara h 1, Ara h 2 and Ara h 6 in (b) (4) drug product and a major change to the reference standard used for these ELISAs were both introduced immediately prior to testing of commercial drug product batches. (b) (4) are calculated to compare ELISA results from previous and future reference standard batches. Only limited release and stability data are available on commercial batches tested with the new ELISA method and reference standard.
2. Changes made to the drug product (b) (4) process prior to commercial production resulted in very different (b) (4) results for clinical and commercial batches. Only limited data are available on (b) (4) in commercial batches.
3. Aimmune plans to add (b) (4) testing to source material selection procedures to ensure greater consistency between batches of drug substance and drug product. No data have yet been provided on batches using the new selection procedure.

Although the current drug substance, drug product and (b) (4) acceptance criteria are acceptable to ensure product quality, due to the issues raised in 1,2 and 3 above, Aimmune agreed that specifications should be reset based upon additional commercial experience. Please see the agreements section at the end of this memo.

## **B. RECOMMENDATION**

### **I. APPROVAL**

#### **a. List of Drug Substance and Drug Product manufacturing facilities:**

Source material manufacturer: (b) (4) specialty division,  
(b) (4)

Drug substance and drug product manufacturer: CoreRx, 14205 Myerlake Circle,  
Clearwater, FL 33760, USA

#### **b. List of approvable Comparability Protocols:**

None

#### **c. List of Post-Marketing Commitments (PMCs)/Post-Marketing Requirements (PMRs):**

None

#### **d. Consideration for Inspectional Follow-up (e.g., flagging inspectional issues for future surveillance inspections):**

No CMC issues. Please see DBSQC review for facility issues.

#### **e. Lot release requirements**

Lot release protocols were provided for each dose in the 6 January 2020 submission and were acceptable.

### **II. COMPLETE RESPONSE (CR)**

N/A

### **III. SIGNATURE BLOCK**

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Philippa Hillyer, Staff Fellow, DBPAP, OVR, CBER	Concur	
Ronald L. Rabin, Lab Chief, DBPAP, OVR, CBER	Concur	
Jay E. Slater, Director, DBPAP, OVR, CBER	Concur	

## Review of CTD

### Table of Contents

3.2.S DRUG SUBSTANCE.....	1
3.2.S.1 Nomenclature, Structure and General Properties .....	1
3.2.S.2 Manufacture.....	2
3.2.S.2.1 Manufacturer(s).....	2
3.2.S.2.2 Description of Manufacturing Process.....	2
3.2.S.2.3 Control of Materials .....	3
Control of Raw Materials <u>NOT</u> of Biological Origin.....	9
Control of Raw Materials of Biological Origin .....	9
Control of Starting (i.e., Source) Material(s).....	9
3.2.S.2.4 Controls of Critical Steps and Intermediates.....	14
3.2.S.2.5 Process Validation and/or Evaluation .....	14
3.2.S.2.6 Manufacturing Process Development .....	14
3.2.S.3 Characterization.....	15
3.2.S.3.1 Elucidation of Structure and Other Characteristics.....	15
3.2.S.3.2 (b) (4) .....	17
3.2.S.4 Control of Drug Substance .....	22
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s) .....	22
Justification of specifications:.....	23
3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures .....	30
(b) (4) validation .....	32
Analytical comparability between clinical and commercial (b) (4) .....	37
(b) (4) storage.....	38
(b) (4) validation .....	38
3.2.S.4.4 Batch Analyses.....	46
3.2.S.5 Reference Standards or Materials.....	49
Selection of the new primary reference standard (b) (4) .....	50
Qualification of the new primary reference standard .....	51
Secondary reference standard .....	54
Reference standard (b) (4) correction factor for future batches .....	54
Batch number assignment, storage and stability of reference standard .....	54
3.2.S.6 Container Closure System .....	65
3.2.S.7 Stability.....	66
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data.....	66
Registration stability study .....	66
Stability protocol for drug substance lots used in PPQ batches.....	69
3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment .....	70
3.2.P DRUG PRODUCT .....	75
3.2.P.1 Description and Composition of the Drug Product .....	75
3.2.P.2 Pharmaceutical Development .....	77
3.2.P.2.1 Components of the Drug Product.....	77
3.2.P.2.1.1 Drug Substance.....	77
3.2.P.2.1.2 Excipients .....	77
3.2.P.2.2 Drug Product .....	78
3.2.P.2.2.1 Formulation Development.....	78

3.2.P.2.2.2 Overages .....	78
3.2.P.2.2.3 Physicochemical and Biological Properties .....	78
3.2.P.2.3 Manufacturing Process Development .....	79
3.2.P.2.4 Container Closure System .....	86
3.2.P.2.5 Microbiological Attributes .....	87
3.2.P.2.6 Compatibility .....	87
3.2.P.3 Manufacture .....	93
3.2.P.3.1 Manufacturer(s) .....	93
3.2.P.3.2 Batch Formula .....	94
3.2.P.3.3 Description of Manufacturing Process .....	96
Formulation blending .....	99
Encapsulation .....	102
Sachet filling .....	104
Blister packaging .....	104
Secondary packaging .....	104
Batch record numbering .....	105
3.2.P.3.4 Controls of Critical Steps and Intermediates .....	106
(b) (4) .....	106
(b) (4) .....	108
(b) (4) .....	108
(b) (4) .....	109
3.2.P.3.5 Process Validation and/or Evaluation .....	113
Powder blend - procedures .....	114
Powder blend – deviations .....	114
Powder blend - results .....	114
Encapsulation - procedures .....	115
Encapsulation – deviations .....	117
Encapsulation - results .....	117
Sachet filling - procedures .....	118
Sachet filling - deviations .....	118
Blister manufacturing process .....	118
3.2.P.4 Control of Excipients .....	120
3.2.P.4.1 Specifications .....	120
Excipients .....	120
Capsules .....	121
3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures ...	122
3.2.P.4.4 Justification of Specifications .....	122
3.2.P.4.5 Excipients of Human or Animal Origin .....	122
3.2.P.4.6 Novel Excipient .....	122
3.2.P.5 Control of Drug Product .....	124
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) .....	124
Appearance .....	129
Identity .....	129
Protein integrity .....	129
Relative potency .....	131
Assay for protein content .....	132



Uniformity of dosage units .....	132
(b) (4) .....	133
Deliverable Mass .....	133
Microbiological limits (b) (4) .....	133
(b) (4) .....	134
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures ...	140
Appearance .....	141
(b) (4) and protein integrity .....	141
Relative potency (ELISA).....	142
Assay (total protein content by combustion) .....	142
Deliverable mass .....	142
(b) (4) .....	143
Microbiological limits (b) (4) .....	144
(b) (4) .....	144
3.2.P.5.4 Batch Analyses .....	145
Changes to test methods .....	145
Appearance .....	146
Deliverable mass and (b) (4) .....	146
(b) (4) and protein integrity .....	146
Protein content and content uniformity .....	146
Potency.....	147
3.2.P.5.5 Characterization of Impurities.....	148
3.2.P.6 Reference Standards or Materials .....	149
3.2.P.7 Container Closure System .....	149
3.2.P.8 Stability.....	150
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data.....	150
Primary registration studies .....	150
Commercial stability studies.....	152
Stability study results .....	155
Additional supporting studies .....	158
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment .....	159
3.2.A APPENDICES .....	167
3.2.A.1 Facilities and Equipment.....	167
3.2.A.2 Adventitious Agents Safety Evaluation .....	167
3.2.A.3 Novel Excipients .....	167
3.2.R Regional Information (USA).....	167
Other eCTD Modules.....	172
Aimmune agreements .....	173

### **Module 3**

#### **3.2.S DRUG SUBSTANCE**

##### **3.2.S.1 Nomenclature, Structure and General Properties**

Aimmune referred to the drug product as AR101 during development and has used this term throughout this submission. The drug substance is sourced from peanuts (*Arachis hypogaea*). Raw peanuts are partially defatted and lightly roasted to obtain the drug substance (b) (4), light (b) (4) peanut powder. This drug substance is a complex natural product composed of multiple allergenic proteins. Since this drug substance is not a chemically synthesized, single well-defined substance, INN, BAN, USAN and IUPAC names are not available. Also, there is no CAS number for peanut powder.

As the drug substance is a natural product, structural and molecular formulas are not applicable. The drug substance is composed of multiple allergenic proteins such as Ara h 1, Ara h 2, Ara h 3 and Ara h 6. (b) (4) have been provided by the applicant for (b) (4).

The applicant has summarized the physicochemical properties of the drug substance based on the literature. Allergen-directed IgE levels against Ara h 1, Ara h 2 and Ara h 6 are high in peanut-allergic patients. These three clinically important allergens, Ara h 1, Ara h 2 and Ara h 6, are (b) (4). The applicant will control the drug substance for the presence as well as (b) (4).



### 3.2.P DRUG PRODUCT

#### 3.2.P.1 Description and Composition of the Drug Product

The drug product is an oral powder that is supplied either in pull apart hydroxypropylmethyl cellulose (HPMC) capsules (0.5 – 240 mg doses composed from a combination of 0.5mg, 1.0 mg, 10 mg, 20 mg and 100 mg capsules) or in foil laminate sachets (300 mg dose). Capsules are packaged in foil backed (b) (4) blister packs. The powder is intended to be administered orally after emptying the capsule or sachet and mixing with food.

There are three configurations of the drug product:

1. Initial dose escalation:

The 0.5, 1.0, 1.5, 3.0 and 6.0 mg doses are packaged into blister strips and presented together on one paperboard card. Each dose is to be delivered under medical supervision in succession on the first day of therapy.

2. Up-dosing:

For each increase in dose, capsules of 3, 6, 12, 20, 40, 80, 120, 160, 200 or 240 mg are provided in two forms. The first form is a single “physician’s sample” dose in a blister to be administered under medical supervision or to be given to the patient to provide doses until the patient receives the second form from a pharmacy. The second form is a daily dose pack with 15 capsules of the same dose packaged into two blister strips (7 in one strip and 8 in the other) which is used for daily dosing at home. The daily dose pack is presented in a paperboard card with child resistant features.

3. Maintenance:

The 300 mg sachets are provided in single dose physician samples for up-dosing or in paperboard cartons containing a 30-day at-home supply.

The composition of each dose of the drug product including the capsules is listed in Table 19 and the immediate containers are shown in Table 20. Note that the target weight for the drug substance is calculated from the (b) (4)

total weight per capsule is unchanged.

Table 19. Composition of drug product doses

Component (Grade)	Function	0.5 mg mg Conc. (b) (4)	0.5 mg Target Unit Weight (mg/capsule)	1 mg mg Conc. (b) (4)	1 mg Target Unit Weight (mg/capsule)	10 mg mg Conc. (b) (4)	10 mg Target Unit Weight (mg/capsule)	20 mg mg Conc. (b) (4)	20 mg Target Unit Weight (mg/capsule)	100 mg mg Conc. (b) (4)	100 mg Target Unit Weight (mg/capsule)	300 mg mg Conc. (b) (4)	300 mg Target Unit Weight (mg/sachet)
Peanut flour drug substance	Drug substance	(b) (4)											
Starch (b) (4)	(b) (4)												
Microcrystalline cellulose (b) (4)	(b) (4)												
(b) (4)	(b) (4)												
Magnesium stearate (b) (4)	(b) (4)												
<b>Total</b>													

Acceptable ranges for drug substance and microcrystalline cellulose are shown in parentheses.

Table 20. Drug product dose containers

Attribute	0.5 mg	1 mg	10 mg	20 mg	100 mg	300 mg
Container closure	Capsule	Capsule	Capsule	Capsule	Capsule	Sachet
Capsule Size	3	3	00	00	00	2.5 x 3 inch sachet
Capsule shell	Hydroxypropyl methylcellulose (b) (4)	Hydroxypropyl methylcellulose (b) (4)	Hydroxypropyl methylcellulose (b) (4)	Hydroxypropyl methylcellulose (b) (4)	Hydroxypropyl methylcellulose (b) (4)	foil laminate film complies with food regulations.
Colorant	(b) (4)					
(b) (4)						
Print ink						

### **3.2.P.2 Pharmaceutical Development**

#### **3.2.P.2.1 Components of the Drug Product**

The drug substance (b) (4) light roast peanut flour received from (b) (4) and released by Core Rx according to specifications in section 3.2.4.S.1) is a (b) (4)

(b) (4) of the final drug product, which aids both manufacture of the drug product and emptying of the capsules or sachets by the patients.

(b) (4) are the key characteristics of the drug substance that influence the quality of the final drug product.

##### **3.2.P.2.1.1 Drug Substance**

□ (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

### 3.2.P.2.2 Drug Product

#### 3.2.P.2.2.1 Formulation Development

Both capsules and sachets are used to deliver a powder-based formulation of drug product into a food matrix. The composition of each of the doses is the same for clinical and commercial batches, however the doses used changed during clinical development. Phase 2 studies used 0.5, 1, 10, 100, 300, (b) (4) and 1000 mg doses, but the 20 mg dose was added in phase 3 to reduce both the number of capsules necessary and the burden on the subject. In addition, the (b) (4) and 1000 mg doses were removed for phase 3, (b) (4). The maintenance dose for phase 2 was either 300, (b) (4) or 1000 mg, but for the phase 3 study and commercial distribution the maintenance phase is 300 mg.

Capsules were selected to deliver low doses and low volumes of drug product that are initially required in the OIT treatment regimen. The use of a set number of dose sizes that in different combinations can make up an array of different dose levels gave the flexibility required for OIT dosing protocols. Sachets were selected as a patient-friendly mechanism to deliver the higher volumes required for the maintenance dose of OIT.

#### 3.2.P.2.2.2 Overages

There are no overages used in the manufacturing of this product.

#### 3.2.P.2.2.3 Physicochemical and Biological Properties

##### □ Physicochemical properties

The addition of excipients ensures the (b) (4) of the drug product, so (b) (4) is the only critical property of the drug substance that is relevant to the drug product. The specification (b) (4) of the drug product has been used throughout clinical development and microbial growth has not been seen.

□ **Biological properties**

To ensure consistent potency of the drug product, allergen composition and content specifications are set by (b) (4) HPLC and ELISA for three allergens: Ara h 1, Ara h 2 and Ara h 6. While these three allergens contribute most of the allergenic activity, individual patients may react to allergens in the peanut flour that are not routinely measured (in particular, (b) (4) In Module 3.2.S.3.1, Aimmune provided (b) (4) showing consistency of (b) (4) .

Information regarding the critical nature of the protein content of the drug product was not provided in the original submission. CBER requested further information in comment 5 of the IR sent on March 14, 2019, and additional information was provided by the applicant on April 5, 2019, which is summarized below:

Since there are multiple allergens present in this drug product, the protein content is the method by which dose strength is labelled and controlled. Protein content specifications are set to ensure uniformity of incorporation of (b) (4) in the final drug product (b) (4) by sampling at various locations in the (b) (4) . Specifications for protein content are also used to ensure content uniformity of the final filled capsules and sachets.

**3.2.P.2.3 Manufacturing Process Development**

Since it was determined that phase 1 and pre-clinical studies were not required, development of this drug product began at phase 2. The composition of each dose of drug product has not changed from the time the clinical studies were initiated (see Table 19 in section 3.2.P.1 above). The manufacturing process involves blending (b) (4)







(b) (4)

(b) (4)

See DMPQ memo for detailed review of encapsulation.

Aimmune provided batch release results tables for several capsule batches manufactured using the clinical and commercial processes. All meet specifications. Graphs and statistical analyses of these data were requested in an information request dated 30 July 2019. In the response received 6 August 2019, Aimmune stated that these are available in the comparability section of this module (see below for review).

#### ❑ **Blister packaging**

Blisters used for packaging the clinical and commercial drug product capsules differed slightly.

(b) (4)

Commercial blisters have up to eight cavities per strip, and each cavity is completely filled (see Table 27 in section 3.2.P.3.3 of this review) (b) (4)

(b) (4) the blister cavity. The clinical blisters and commercial IDE and daily dosing blisters use the same materials and are dispensed by pushing them through the foil layer. The individual blisters (referred to as “physician’s samples”) have an additional layer, which is peeled back prior to pushing the capsule through the foil. This additional safety feature is not expected to affect the quality of the drug product or to confer any additional protection to the drug product.

See DMPQ memo for complete review of blister packaging.

#### ❑ **Sachet filling**

Filling the drug product powder (b) (4) into foil laminate sachets uses commercially available sachet filling machines. Phase 3 studies used a (b) (4) filling machine. For commercial lots, a (b) (4) filling machine equipped with (b) (4) and an (b) (4) was used (b) (4) use an (b) (4) for filling the sachets – (b) (4)

See DMPQ memo for review of the sachet filling.

The foil laminate film used for the clinical and commercial products, while of similar foil-laminate construction was not identical. See Table 21 for details of the differences between clinical and commercial sachets and Figure 5 for a diagram of the commercial sachet.

1 page determined to be not releasable: (b)(4)

❑ **Comparability studies for the clinical and commercial manufacturing processes**

For each dose, the sponsor provided graphical comparisons of results between batches of drug product produced using the clinical and commercial manufacturing processes. It is unclear how these results were obtained. An IR clarified that these were results from batch release testing on (b) (4) (and not a direct comparison, see comments in summary section below).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

**3.2.P.2.4 Container Closure System**

The container closure for the drug product is either capsules in blisters or sachets as shown in Table 23.

*Table 23. Drug product container closure by dose*

<b>Dose Level</b>	<b>Capsules Strength(s) Used for Dose Level</b>	<b>Capsule color and size</b>	<b>Packaging</b>
0.5 mg	1 × 0.5 mg	White size 3	Initial day escalation blister
1 mg	1 × 1 mg	Red size 3	Initial day escalation blister
1.5 mg	1 × 0.5 mg 1 × 1 mg	White size 3 Red size 3	Initial day escalation blister
3 mg	3 × 1 mg	Red size 3	Initial day escalation blister
6 mg	6 × 1 mg	Red size 3	Initial day escalation blister
12 mg	2 × 1 mg 1 × 10 mg	Red size 3 Blue size 00	Single, seven and eight count blisters
20 mg	1 × 20 mg	White size 00	Single, seven and eight count blisters
40 mg	2 × 20 mg	White size 00	Single, seven and eight count blisters
80 mg	4 × 20 mg	White size 00	Single, seven and eight count blisters
120 mg	1 × 20 mg 1 × 100 mg	White size 00 Red size 00	Single, seven and eight count blisters
160 mg	3 × 20 mg 1 × 100 mg	White size 00 Red size 00	Single, seven and eight count blisters
200 mg	2 × 100 mg	Red size 00	Single, seven and eight count blisters
240 mg	2 × 20 mg 2 × 100 mg	White size 00 Red size 00	Single, seven and eight count blisters
300 mg	3 × 100 mg	-	Sachets

In this submission, capsules have been described as excipients. Since they are not part of the dose, the capsules are not excipients, however since the information is provided within the excipients section, the materials and suitability of the capsules as a primary container for the drug product are reviewed in 3.2.P.4.

**Blisters**

As shown in Table 23 above, there are four different configurations of blisters. The foil for these blisters is of two types; either the capsules are removed from the blister by pushing through the foil (IDE, seven and eight count) or by peeling a layer back then pushing through the foil (single count).

Phase 2 and early phase 3 studies provided doses to the subjects in individual (b) (4) with each day's dose. Aimmune introduced blisters for patient convenience and to reduce the opportunity for dosing errors.

The primary consideration for the blisters is to protect capsules from breakage and moisture ingress. The sponsor used a (b) (4) simulation to determine the most suitable material based on (b) (4) laminate than those tested to ensure an additional safety margin. This grade of (b) (4) film was used for all clinical and commercial blister processes. The sponsor provided results of testing to demonstrate that the blister base material conforms to (b) (4).

Aimmune appears to have considered the capsules as part of the dose form when writing this submission even though the capsules are not swallowed and should be considered primary packaging, however the regulations concerning materials that are part of the dose form are more stringent than those that are primary packaging (which according to the FDA container closure guidance only have to comply with FDA food contact material regulations). Furthermore, the blisters have been considered as primary packaging and comply with the food contact material regulations, when they are not in contact with the dose form. The materials for the sachets also comply with food contact regulations. This is acceptable.

### 3.2.P.2.5 Microbiological Attributes

Defer to DMPQ reviewer.

### 3.2.P.2.6 Compatibility

Aimmune tested the (b) (4) the drug product after mixing with apple sauce or chocolate pudding for (b) (4). These are two of the foods recommended for mixing the product before consumption. Apple sauce and chocolate pudding differ in both pH and fat content. They found no differences in peanut protein content when measured with a commercial (b) (4) kit for peanut protein or by (b) (4) for Ara h1, Ara h2 and Ara h6.

#### **Overall Reviewer's Assessment of Section 3.2.P.2:**

Several deficiencies were identified and satisfactorily resolved.

The comment is provided followed by the reviewer's summary and assessment of the response in italics. All responses were acceptable.

IR#1, dated 14 Mar 2019

Responses received 5 and 23 April 2019

CBER comment 5

In section 3.2.P.2 you discuss the biological properties of the drug product. Please amend this section to include discussion of the protein content as it is critical to the performance of the product.

*In the response received on 05 April 2019, Aimmune provided a description of how protein content relates to the performance of the product. The label claim is based on protein content*

*rather than allergen measurement because peanuts have several major allergens. Aimmune also described why relative potency, identity and protein integrity methods are important.*

IR#17 dated 30 July 2019

Responses received on either 6 or 14 August 2019.

CBER comment 1

In Section 3.2.P.2.3 – manufacturing process development, you provided a summary and results from (b) (4) testing designed to evaluate (b) (4) of the manufacturing process. Please address the following comments:

(b) (4)

*Aimmune responded that their results included the outlier. A new analysis was provided which excludes the outlier. Removal of the outlier did not change the overall conclusion of the study.*

CBER comment 2

In Tables 16 – 21 and Figures 3 – 7 of section 3.2.P.2.3 – manufacturing process development you have provided results from (b) (4) testing of clinical and commercial batches. Please provide the following information:

- a. Provide a legend for each of the figures stating what is plotted in each figure.

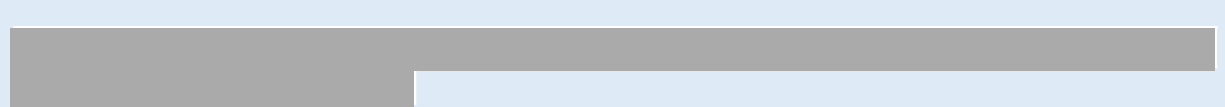

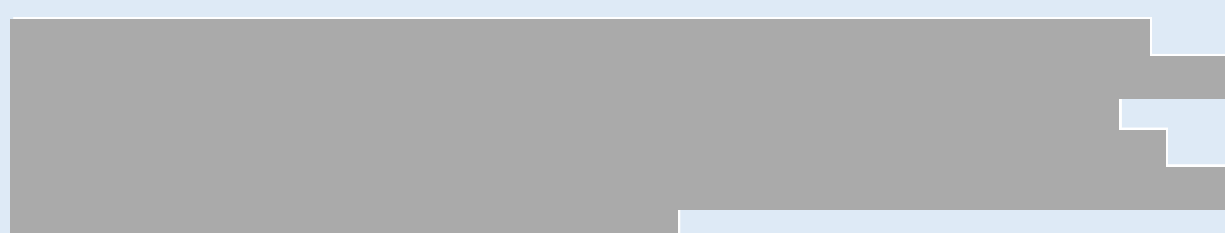
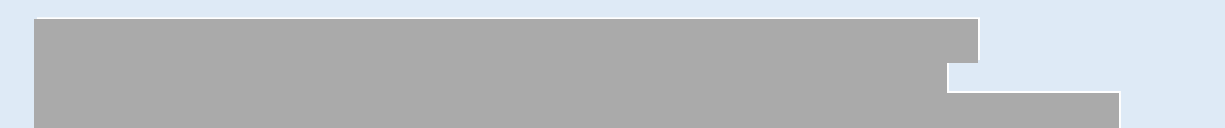
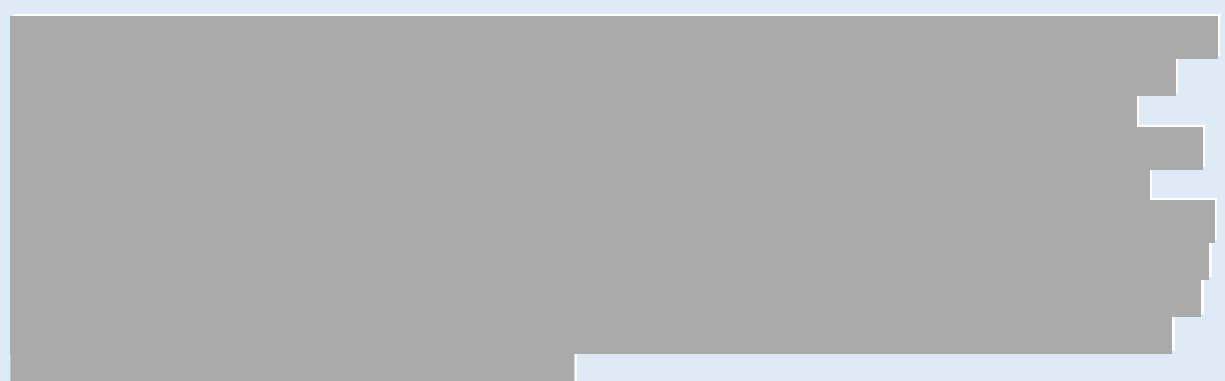

*Updated figures were provided showing that mean  $\pm$ SD were plotted and that the mean and SD of all commercial batches were within the initial proposed acceptance criteria*

- b. Your acceptance criteria for (b) (4) should be set based upon statistical analysis of existing data. Please explain your calculations for determining the acceptance criteria



ranges and RSDs for (b) (4) testing. Your currently proposed ranges and RSDs appear wider than the commercial batches warrant.

(b) (4)



CBER comment 3

Please provide graphical and statistical analysis of the batch release results described on page 65 of section 3.2.P.2.3 – manufacturing process development to demonstrate comparability of the clinical and commercial encapsulation processes.

*Aimmune provided the locations of this information in the BLA application. These were reviewed in the comparability studies section of the memo above).*

CBER comment 4

In Section 3.2.P.2.3 – manufacturing process development, you provide information regarding the performance qualification runs for the blister packaging on the IDE, 12 mg, 20 mg and 200 mg dose sizes. You describe that the blister cavities (b) (4)

during qualification runs and if so, then provide the relevant results, conclusions, and any resulting changes to the in-process parameter ranges.

*Aimmune provided information regarding how the blisters are formed (b) (4)*

but no further changes were necessary.

CBER comment 5

In Tables 75 and 84 of section 3.2.P.2.3 – manufacturing process development, you compare the in-process controls for blister packaging for Phase 3 clinical and commercial manufacturing. The tables have different acceptance criteria for the clinical (b) (4) tests. Please explain.

*Aimmune clarified that there was a mistake in the acceptance criteria for the clinical blisters in table 84, but table 75 was correct. Table 84 should read (b) (4)*

CBER comment 6

There are many development batches listed in section 3.2.P.2.3 - manufacturing process development, but no information is provided regarding their history. Please provide a table of all batches used during manufacturing process development including their dosage strength, lot numbers for drug substance, blend, encapsulation and bulk packaging, the dates of blending, encapsulation and sachet filling, the manufacturing scale and use.

*Aimmune provided tables of the history of the development batches, which list source material, drug substance and drug product batch numbers, manufacturing dates for each process, and their uses. Most development batches were produced from one of (b) (4) lots of drug substance produced in 2017 and were either used for feasibility studies prior to scaling up to commercial production (b) (4) only) (b) (4)*

*These lots are appropriate to include as supportive data for commercial batches.*

CBER comment 7

You have provided a comparison of clinical and commercial manufacturing batch release results. Please state whether the testing in this comparison was performed on bulk capsules and sachets or after packaging and please state whether the method versions used in the testing were the same for all batches since several methods have been updated or revalidated for commercial product.

Aimmune (b) (4)

*ELISA methods and reference standards and their impact on batch release results have been detailed elsewhere in this memo. See text of this section for details pertinent to this comparison.*

IR#38 dated 8 November 2019

Response received 26 November 2019

CBER comment 6

In your submissions dated 2 August 2019 and 14 August 2019, you provided graphs of your (b) (4) results. Please explain why the number of batches plotted for each dose differs in each submission even after the removal of development batches is accounted for.

*Aimmune has provided a detailed description of which batches were used for which set of submitted data. Several early commercial development batches and subsequent clinical batches from follow-on studies were removed from the statistical analysis, but Aimmune did not explain why. See comment 16 of IR#48.*

CBER comment 7

In your 14 August 2019 submission, you stated that you (b) (4) doses for statistics on (b) (4) results. Please state which tests you used to determine whether data sets were suitable for (b) (4).

*Aimmune explained that (b) (4)*

CBER comment 8:

In your 14 August 2019 submission, you responded to comment 7 from our 30 July 2019 information request by providing the location of the tables describing the test method changes and which lots used which versions of the methods. Since several batches used in the (b) (4) testing comparability study in module 3.2.P.2.3 are not listed in these tables, they are incomplete. Please provide a table that includes all the batches used for the comparability study.

*Aimmune clarified that powder (b) (4) have different batch numbers from the drug product batches and has provided the information pertinent to the protein content assay used for (b) (4) testing. This shows that all powder (b) (4) batches from batch (b) (4) onwards*

*(which includes all commercial and some recent clinical batches) used the more recent and less variable version 6 of the protein content assay method. This is acceptable.*

IR#48 dated 20 December 2019

Response received 6 January 2020

CBER comment 4

In response to comment 2b (of IR#17), you provided updated (b) (4) specifications in which you narrowed the % RSD but left the range of individual results as “% label claim” the same as previously proposed. Please address the following comments:

a. You performed statistical analysis for (b) (4) using two-sided tolerance intervals at (b) (4) coverage of sample population and (b) (4) confidence level. For all future analysis of (b) (4), please use the 99/95 TI approach that we previously recommended.

*Aimmune agreed.*

b. Narrowing the % RSD for your new acceptance criteria means that within a batch there is little variability, but the unchanged acceptance ranges means that there may still be large differences between batches. This is particularly an issue for the lower doses where the acceptance criteria ranges are set very wide to include the variability between clinical and commercial batches. Since a low number of commercial batches are currently available, we agree that acceptance criteria for all doses of (b) (4) should be re-evaluated when additional experience with commercial batches has been gained. However, we expect that the acceptance criteria will be set based on statistical analysis of commercial data and that this may result in rejection of some non-conforming batches to ensure consistency of product.

*Aimmune agreed and plans to submit data on (b) (4)*

*as the data becomes available.*

*See end of this memo for text of CMC agreement with Aimmune.*

CBER comment 16

In your response to comment 6 (of IR#38), you provided a detailed description of which batches were used for setting (b) (4) acceptance criteria in each of your two responses to IR#17 received on 2 August 2019 and 14 August 2019. However, it is unclear why the batches used were changed. Please explain the reasons behind removing certain clinical batches and certain commercial development batches.

*Aimmune provided their justification for removal of some batches. (b) (4)*

(b) (4)

All deficiencies were resolved satisfactorily. See CMC agreements at the end of this memo regarding reanalysis of (b) (4).

### 3.2.P.3 Manufacture

#### 3.2.P.3.1 Manufacturer(s)

Table 24. Manufacturing sites and responsibilities for drug product

Facility Information	Responsibility
CoreRx, Inc. 14205 Myerlake Circle Clearwater, Florida 33760 USA	Manufacturing (blending, encapsulation, and sachet filling) and release of bulk drug product Release and stability testing of drug product (appearance, (b) (4), deliverable mass, assay, content uniformity, identification, protein integrity, and relative potency) Testing of excipients Storage of bulk drug product
(b) (4)	Manufacturing (blister packaging of capsules, secondary packaging, and labeling of blistered capsules and sachets) Storage of finished drug product
Aimmune Therapeutics, Inc. 8000 Marina Boulevard, Suite 300 Brisbane, California 94005 USA	Disposition of finished drug product as an oversight activity
(b) (4)	Release and stability testing of drug product (microbiological limits and (b) (4))
(b) (4)	Release and stability testing of drug product (b) (4)
(b) (4)	Release and stability testing of drug product (appearance, deliverable mass, microbiological limits, (b) (4)) Stability storage of drug product

(b) (4) perform drug product testing under a contract with CoreRx. Excipients are received by CoreRx and tested by (b) (4) to CoreRx specifications to ensure compliance with the (b) (4). Testing is performed under a contract with CoreRx and this is listed as a CoreRx responsibility. See comment in summary section.

All sites have DUNS numbers, and all sites except (b) (4) and Aimmune have FEI numbers. Aimmune does not require an FEI number since no manufacturing is conducted at the Aimmune site. (b) (4) testing is performed at the (b) (4) under a memorandum of understanding with the FDA and no FEI number is required.

### 3.2.P.3.2 Batch Formula

Table 25. Batch Formula for commercial batches of each dose of AR101 drug product

Component (Grade)	0.5 mg capsule Conc. (b) (4)	0.5 mg capsule Quantity per lot (b) (4)	1 mg capsule Conc. (b) (4)	1 mg capsule Quantity per lot (b) (4)	10 mg capsule Conc. (b) (4)	10 mg capsule Quantity per lot (b) (4)	20 mg capsule Conc. (b) (4)	20 mg capsule Quantity per lot (b) (4)	100 mg capsule Conc. (b) (4)	100 mg capsule Quantity per lot (b) (4)	300 mg sachet Conc. (b) (4)	300 mg sachet Quantity per lot (b) (4)
Peanut flour drug substance	(b) (4)											
Starch (b) (4)												
Microcrystalline cellulose (b) (4)												
(b) (4)												
Magnesium stearate (b) (4)												
Total												
Capsule Size												
No. of units												

Acceptable ranges for drug substance and microcrystalline cellulose are shown in parentheses.

**Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:**

Several deficiencies were identified and communicated to Aimmune. The date of the IR and CBER's comment are followed in italics by a summary of Aimmune's response and the reviewer's assessment. All deficiencies were resolved and were acceptable.

IR#1 dated 14 Mar 2019

Responses received 5 and 23 April 2019

CBER comment 6

Please include any changes in the labeling during development in section 3.2.P.2.

*This was discussed with Aimmune in a telecon on 2 May 2019. Since there are no changes in labeling, no further action was necessary.*

CBER comment 7

In Table 1 of section 3.2.P.3.1, you list Aimmune as a manufacturer with responsibility for "disposition of finished drug product as an oversight activity." Please provide a complete description of Aimmune's exact role in all oversight and decision-making processes for this product.

*A list of the responsibilities of Aimmune regarding oversight of CoreRx and (b) (4) was provided in the 5 April 2019 submission. The quality agreements regarding responsibilities of Aimmune and each contractor were reviewed during the inspection of CoreRx and were found to be acceptable.*

CBER comment 10c

Please include the testing of excipients in your tables of contract manufacturers responsibilities in section 3.2.P.3.1.

*In the 5 April 2019 submission, Aimmune stated that CoreRx is responsible for excipient testing. This is because CoreRx reviews testing performed by the manufacturer of the excipient and the confirmatory testing to (b) (4) standards performed under contract to CoreRx by (b) (4). Quality agreements between Aimmune, CoreRx and each of the contractors were reviewed during the inspection of CoreRx and were found to be acceptable.*

IR#48 dated 20 December 2019

Response received 6 January 2020

CBER comment 20

Please review your submission and ensure that all companies and all sites used for manufacture, storage or testing (including (b) (4)) of the drug substance, all excipients and drug product are listed in the appropriate manufacturer's list.

*The following information was added to the table of manufacturers:*

- CoreRx: added responsibility for storage of drug product
- (b) (4) added responsibility for storage of drug product

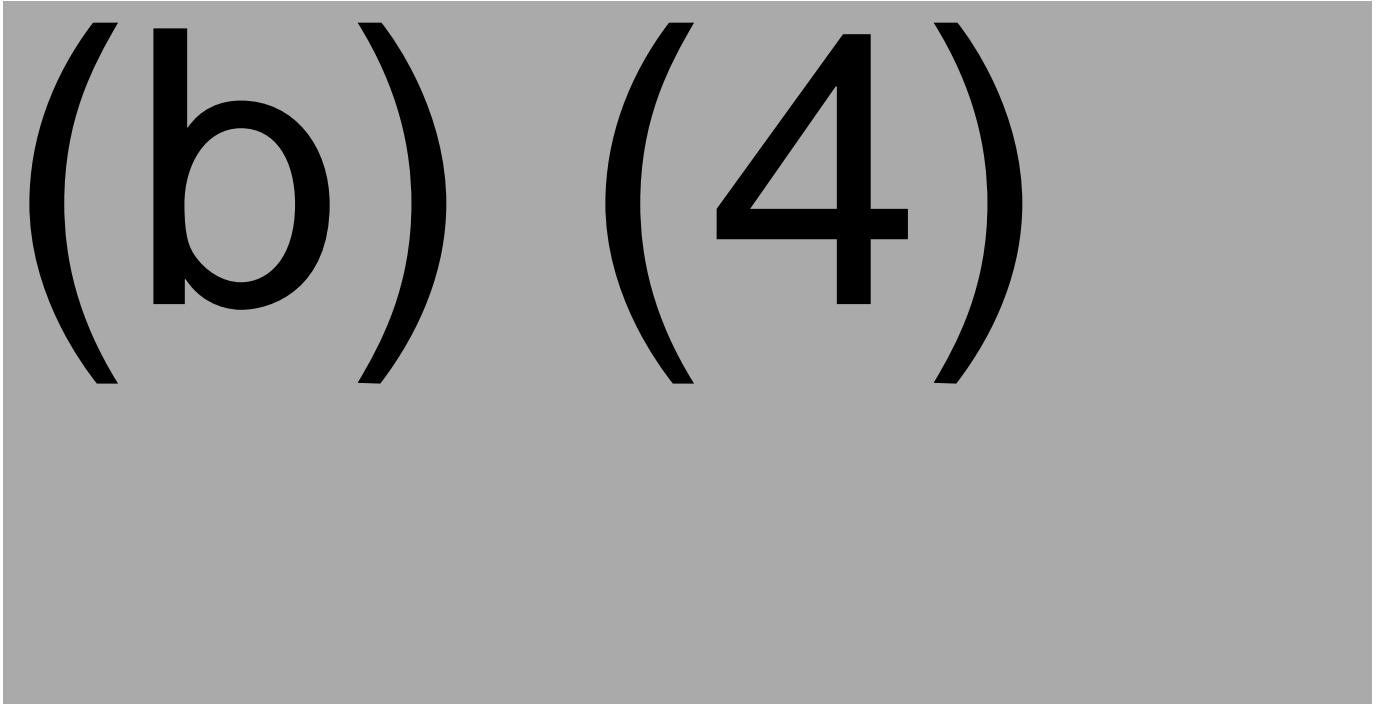
- (b) (4) added responsibility for stability storage of drug product

All deficiencies were resolved acceptably.

### 3.2.P.3.3 Description of Manufacturing Process

The manufacturing process consists of (b) (4) steps listed in Table 26 which take place at CoreRx (blending and encapsulation or sachet filling) and (b) (4) (packaging into blisters and secondary packaging).

Table 26. Manufacturing process steps



The drug product is packaged into one of two forms: 1) combinations of capsules of various doses in blisters or 2) 300 mg sachets (Table 26). There are four different forms of blister produced: 1) initial day escalation packs; 2) Individual physician samples for the first day of escalation; 3) Packs containing seven daily doses and; 4) packs containing eight daily doses. During secondary packaging, one seven- and one eight-dose pack are packaged together onto a card to make a 15-day daily dose pack. See section 1.14.1.1 of the original submission (Draft carton and container labels) for diagrams of the finished products.











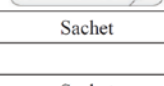
Aimmune did not define their date of manufacture for the drug product. See comment in section summary below.

In Comment 13 of the same IR (see comment in summary section below), we asked for clarification regarding how (b) (4) product hold times would affect the expiry date. The sponsor explained that since the expiry is 24 months after the date of manufacture, these hold times do not affect the expiry date, but just shorten the length of time that finished product is available for distribution. The



1 page determined to be not releasable: (b)(4)

Table 27. Drug product configurations



Dose Level	Capsules	Commercial Dose (Blister Strip) [1, 2]	
Initial Dose Escalation			
0.5, 1, 1.5, 3, 6 mg	0.5 mg: 1 × 0.5 mg		0.5 mg
	1 mg: 1 × 1 mg		1 mg
	1.5 mg: 1 × 0.5 mg 1 × 1 mg		1.5 mg
	3 mg: 3 × 1 mg		3 mg
	6 mg: 6 × 1 mg		6 mg
Up-Dosing (14 Day Treatment)			
3 mg	3 × 1 mg		
6 mg	6 × 1 mg		
12 mg	2 × 1 mg 1 × 10 mg		
20 mg	1 × 20 mg		
40 mg	2 × 20 mg		
80 mg	4 × 20 mg		
120 mg	1 × 20 mg 1 × 100 mg		
160 mg	3 × 20 mg 1 × 100 mg		
Dose Level	Capsules	Commercial Dose (Blister Strip) [1, 2]	
200 mg	2 × 100 mg		
240 mg	2 × 20 mg 2 × 100 mg		
300 mg	1 × 300 mg	Sachet	
Maintenance (30 Day Treatment)			
300 mg	1 × 300 mg	Sachet	

[1] Capsule drawings are intended to illustrate the numbers and occupancy (positions) of each capsule type in each blister cavity. The colors and markings of the capsules in these drawings are not accurate representations of actual commercial capsule colors and markings.

[2] The 0.5 mg dosage strength is a size 3 white capsule, 1 mg dosage strength is a size 3 red capsule, 10 mg dosage strength is a size 00 blue capsule, 20 mg dosage strength is a size 00 white capsule, 100 mg dosage strength is a size 00 red capsule.





(b) (4)



(b) (4)

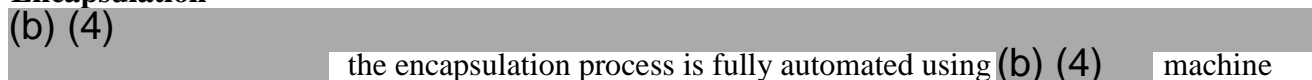


(b) (4)



#### **Encapsulation**

(b) (4)



the encapsulation process is fully automated using (b) (4) machine according to the flow diagram in Figure 8. Each dose is filled according to Table 29 below.



### **Sachet filling**

The sachet filling process for the 300 mg dose is fully automated using an (b) (4) machine, except for the (b) (4).

The sachets use the (b) (4)

is loaded into the sachet filling machine.

Defer to DMPQ for review of sachet filling.

Acceptable sachets are transferred to an appropriate bin labelled as acceptable sachets. In process samples are collected throughout the run for (b) (4)

testing. Product release samples are also taken at this stage. Once acceptable test results have been obtained, the sachets are (b) (4) (see section 3.2.P.3.4 for further details).

### **Blister packaging**

The blister packaging process is performed at (b) (4), where it is automated using an (b) (4) blistering machine. Drug product capsules are packaged into blister strips to obtain the different configurations required as shown in Table 27 (beginning of this section). The blister strips can be of four different types as described above. Each packaging configuration (dose and blister type) uses (b) (4) to form blister cavities of the appropriate number and size.

There was no information provided regarding the storage of finished blisters prior to secondary packaging. This information was requested on 30 July 2019 and Aimmune clarified in their response received on 6 August 2019 that the IDE, 7-count and 8-count blisters are stored a (b) (4) until they are put into the cards, while individual samples are stored (b) (4) prior to secondary packaging.

### **Secondary packaging**

The secondary packaging is performed at (b) (4) and there are two different methods depending on the required configuration.

1. The 8-count and 7-count blister strips are packaged into a single card to make a 15-day pack. Diagrams of cards are provided in section 1.14.1 – draft labeling.
2. Individual blisters and sachets are loaded into partially glued cartons. Loaded cartons are then glued into their final form. Diagrams of cartons are provided in section 1.14.1 – draft labeling.

Defer to DMPQ for detailed review of secondary packaging, shipping containers and shipping procedures.

It was unclear from the submission how many batches had been packaged using the commercial process. See comment in summary section for details of this IR request, which explained that although many commercial batches had been packaged into blisters, they had not yet been packaged onto cards. We noted that most of these batches will expire in mid-2020 and requested updated information regarding commercial lots that will be available for the product launch (including expiry dates). See comment in summary section below.

There are no reprocessing operations for manufacture of AR101.

**Batch record numbering**

CoreRx uses a 5-digit sequential numbering system for lots produced from each manufacturing process.

(b) (4)

(b) (4) . Lot numbers are assigned to each batch of each batch of bulk drug product capsules or sachets. (b) (4) uses a 7-digit sequential numbering system for the blistered lots.

See review of section 3.2.R.1 for comments regarding the representative executed batch records provided in this submission.

**Overall Reviewer's Assessment of Section 3.2.P.3.3:**

Several deficiencies were identified and communicated to Aimmune. The date of the IR is followed by the CBER comment with a summary of the sponsor's response and reviewer's assessment in italics. All deficiencies were resolved and were acceptable.

IR#1 dated 14 March 2019

Response received 5 April 2019

CBER comment 9

Please specify how you define the date of manufacture for each batch of drug product, as described in 21 CFR part 610.50.

*In their 5 April 2019 submission, Aimmune stated that the date of manufacture of the drug product is defined as the date that the (b) (4) . In a teleconference on 2 May 2019, Aimmune explained that this is a conservative date of manufacture since stability studies were generally not initiated until packaging into blisters or sachets, which could be (b) (4) after the date of manufacture that they defined. This is (b) (4) than the (b) (4) date that Aimmune used in stability studies and is acceptable.*

IR#17 dated 30 July 2019

Responses were received on 6 August 2019

CBER comment 8

You have provided a description of the blister packaging process in section 3.2.P.3.3. Please state how long the finished blisters are stored prior to packaging onto cards and into cartons and provide details of the container and conditions used for storage.

*The IDE, 7-count and 8-count blisters are stored at (b) (4) for up to (b) (4) until they are put into the cards, while individual samples are stored in (b) (4) also for up to (b) (4) prior to secondary packaging. This is acceptable.*

**CBER comment 9**

In section 3.2.P.3.3 you have provided a brief description of the secondary packaging process. Please provide further detail on this process including diagrams showing which steps are automated and which are manual.

*Aimmune provided flow diagrams for each process showing which steps were automated and which were manual. Both packaging methods have both a 100% automated vision inspection system and 100% inspection by (b) (4) operators prior to shipping. This is acceptable.*

**CBER comment 10**

Please provide a table of all batches of capsules packaged into blisters at (b) (4), including lot numbers, the use of each batch, which batches were packaged using the commercial process and if any batches were packaged differently from the commercial process explain how the packaging process differed. Please also state the secondary packaging used for each batch.

*Aimmune stated that separate clinical and commercial packaging lines are used at (b) (4) and provided (b) (4) of all the requested information. While all clinical batches have been packaged onto cards or into cartons, many commercial batches have been blistered, but not yet packaged into cards. as they are awaiting finalization of the text and design. Most of the capsule batches have a manufacture date of (b) (4). Since the expiry date for the capsules is 24 months, these lots will expire in (b) (4). See comment 2 of IR#48 below for resolution.*

IR#48 dated 20 December 2019

Response received 6 January 2020

**CBER comment 2**

Please provide a summary table of the status, including expiry date, of all commercial batches that you plan to have available for product launch.

*Aimmune provided a table showing the status of (b) (4) lots of commercial drug product that have been packaged into blisters. About half of the batches for each dose have been released and the remainder are under QA review. All have expiry dates of June – December 2021.*

All deficiencies in this section were resolved satisfactorily.

### 3.2.P.3.4 Controls of Critical Steps and Intermediates

There are (b) (4) intermediates which are the end results of (b) (4) different processes: (b) (4)

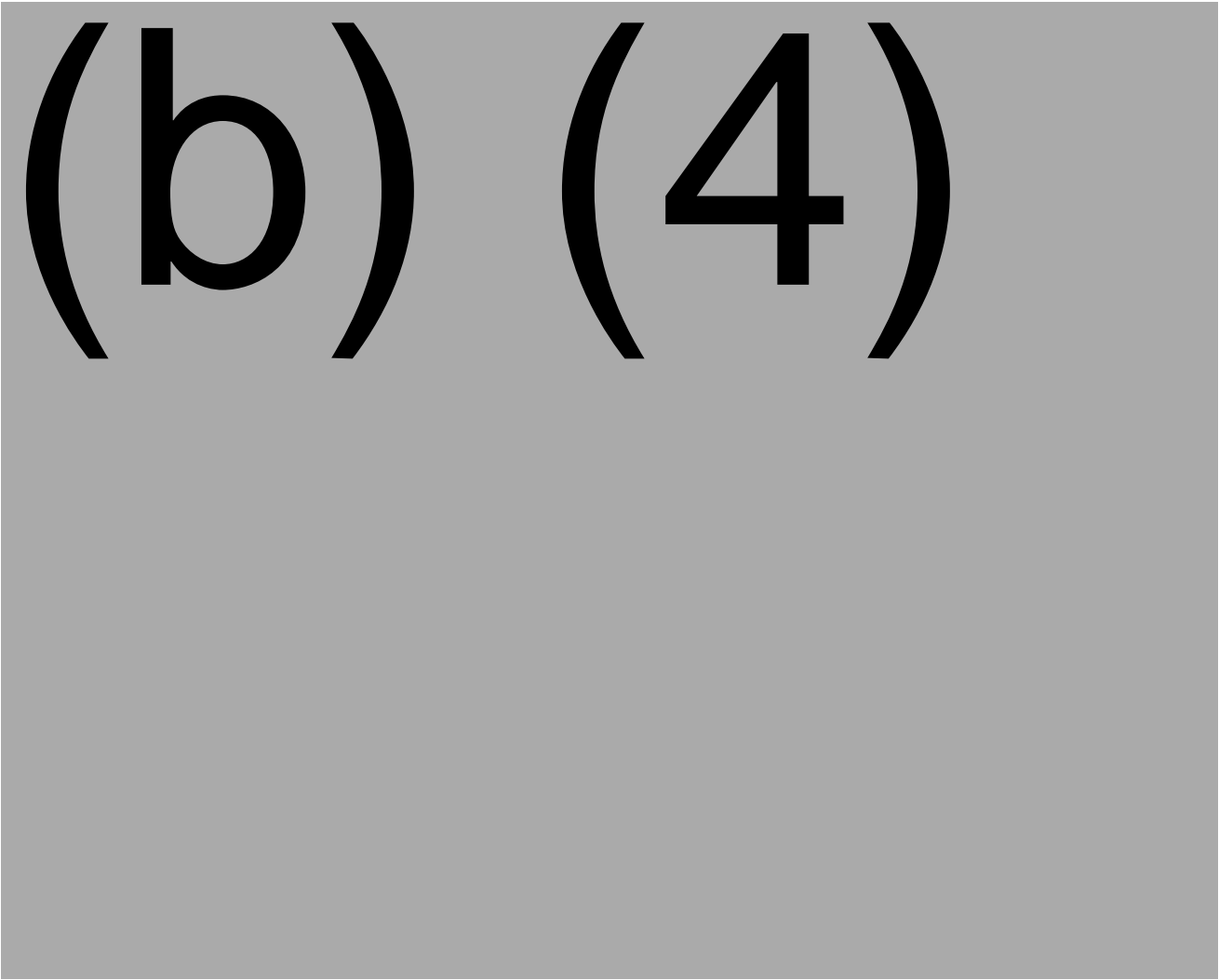
(b) (4) The control steps for each process and its intermediate will be addressed in sequence in this review.

(b) (4)






(b) (4)

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**3.2.P.3.5 Process Validation and/or Evaluation**

This section reviews text in the original application and Aimmune's July 9, 2019 response to a CBER IR dated June 26, 2019. The sponsor has performed process performance qualification (PPQ) on the first commercial scale batches in accordance with FDA and EU guidelines. Validation was performed on powder blending for each dosage strength, and on encapsulation and blistering for 0.5 – 100 mg doses and sachet filling for the 300 mg doses. Reports for each validation were provided in this section.

(b) (4)

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(b) (4)

### 3.2.P.4 Control of Excipients

#### 3.2.P.4.1 Specifications

The sponsor provided information regarding the capsules in this section. Since information on the capsules was submitted to this section, it will be reviewed here even though the capsules are not considered an excipient because the contents are emptied, and the capsules are not consumed.

#### Excipients

CoreRx releases the excipients after testing according to the (b) (4) Table 34.

Table 34. Compendial monographs for excipient release testing

Excipient	Compendial Monograph Reference
Microcrystalline Cellulose	(b) (4)
Partially Pregelatinized Maize Starch	
Colloidal Silicon Dioxide	
Magnesium Stearate	

In addition to testing according to the monographs, the excipient manufacturers perform tests on the physical characteristics (b) (4) of the excipients that impact (b) (4) the drug product as described in section 3.2.P.2.1.1 of this review. The tests performed are listed in Table 35.

*Table 35. Physical specifications for excipients*

Excipient	Quality Attribute	Acceptance Criteria
Microcrystalline Cellulose	(b) (4)	(4)
Microcrystalline Cellulose		
Partially Pregelatinized Maize Starch		
Partially Pregelatinized Maize Starch		
Colloidal Silicon Dioxide		
(b) (4)		
Magnesium Stearate		

In addition to these tests, each manufacturer confirms on the CoA (Section 3.2.R) that the product complies with (b) (4) guidance.

In comment 10 of IR #1 dated March 14, 2019, CBER inquired as to who performed the testing described in the certificates of analysis for excipients provided in section 3.2.R. We also requested a description and results of verification testing of the assay under actual conditions of use. See comment and Aimmune’s response in summary of this section.

### Capsules

Capsules used for the drug product are made from hydroxypropyl methylcellulose (HPMC) with (b) (4) dependent on the specific capsule. They are designed to pull apart so that the peanut allergen powder contained within can be sprinkled onto an appropriate food (see section 3.2.P.2.6 of this review for tested foods). Five different capsule sizes are used (0.5 mg, 1 mg, 10 mg, 20 mg and 100 mg). Each capsule is printed with the with the dose and “Aimmune”. The sizes of capsules, colorants and inks used are listed in Table 27 in section 3.2.P.1 of this review.

All capsules are received using the same procedure at CoreRx. The shipment is inspected in the warehouse to verify that the supplier information and material received are correct and that containers and labels are not damaged. The received lots of capsule shells are inspected for physical appearance, (b) (4) (using (b) (4) and defects to individual capsules according to AQL testing limits as defined in (b) (4), and the manufacturer’s CoA is checked to ensure that the lot provided met all the manufacturer’s release specifications. The capsule manufacture performs several tests for physical characteristics of the capsules including (b) (4) testing for capsule components, (b) (4) tests. No additional testing is performed at CoreRx and no validation is necessary since (b) (4) test is performed.

While each manufacturer has stated whether each component of the capsules complies with (b) (4), 21CFR, or FD&C, they did not specifically state with which chapters or regulations each component complies.

Details of the manufacturers, dimensions and catalogue numbers are shown in Table 36 below.

Table 36. Acceptance criteria for capsules

Dose	Capsule Description	Manufacturer	Dimensional (b) (4)	Part No.	DMF Reference
0.5 mg	Size 3 White Opaque (b) (4) Plus Capsule Shells with 0.5 mg/ Aimmune Print	(b) (4)	(b) (4)	(b) (4)	(b) (4)
1 mg	Size 3 Red Opaque (b) (4) Capsule Shells with 1 mg/ Aimmune Print				
10 mg	Size 00 Blue Opaque (b) (4) Plus Capsule Shells with 10 mg/ Aimmune Print				
20 mg	Size 00 White Opaque (b) (4) Capsule Shells with 20 mg/ Aimmune Print				
100 mg	Size 00 Red Opaque (b) (4) Plus Capsule Shells with 100 mg/ Aimmune Print [1]				

For each capsule size, the sponsor has provided an example of the component specification and result form completed during quality inspection of the capsules, the purchasing and receiving specification completed by the warehouse on receipt of the capsules and the certificate of analysis from the manufacturer for one capsule lot. Each manufacturer confirms on the CoA that the capsules conform with the (b) (4) guidance.

Several details regarding the capsules were missing. In an IR dated 30 July 2019, we asked for justification for the choice of capsules, how the capsules meet US regulations, whether there were any changes to capsules or their suppliers throughout development and why capsules from (b) (4) different manufacturers are used for commercial product. The sponsor addressed all questions and the capsules comply with regulations for human consumption, which are more stringent than those for food contact materials. This is acceptable. See comment and review of Aimmune's response in the summary of this section for further details.

### 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

See review of section 3.2.P.4.1 above.

### 3.2.P.4.4 Justification of Specifications

See review of section 3.2.P.4.1 above.

### 3.2.P.4.5 Excipients of Human or Animal Origin

No excipients of human or animal origin are used in this product.

### 3.2.P.4.6 Novel Excipient

No novel excipients are used in this product.

**Overall Reviewer's Assessment of Section 3.2.P.4:**

Several deficiencies were identified and communicated to the sponsor. The date of the IR is followed by the CBER comment with a summary in italics of the Aimmune's response and the reviewer's assessment. All deficiencies were resolved satisfactorily.

IR#1 dated 14 March 2019

Responses received 5 and 23 April 2019

CBER comment 10

In section 3.2.R, you provided Certificates of Analysis for all excipients used in the manufacturing process, and you state that the excipients are tested according to (b) (4) and CoreRx specifications. Please address the following:

- a. You provided documents from both CoreRx and other contract testing laboratories showing specifications and results of excipient testing. Please identify which entity (CoreRx or contract laboratory) performed the tests described in these documents.

*The sponsor stated in their response received 5 April 2019 that testing of excipients is performed at (b) (4) under contract to CoreRx. The tests are performed according to the (b) (4). CoreRx reviews the test results and compiles a certificate of analysis from the results, then appends the test results to the CoA. The excipients are released at CoreRx for manufacturing only if test results from (b) (4) meet the specifications in the monographs. This is acceptable.*

- b. Please state which tests are used to release each of the excipients and which entity is performing each test. If the tests are performed by a contract laboratory or manufacturer, please ensure that a description and results of verification testing of the assay under actual conditions of use are provided.

*In the response received 5 April 2019, the sponsor clarified that all excipient testing except microbial testing was performed at (b) (4) and suitability of (b) (4) for this testing has been verified under normal conditions of use since (b) (4) has successfully released many lots of the (b) (4) excipients. Verification reports of the microbial assays were provided. This is acceptable.*

IR#17 dated 30 July 2019

Responses received 6 August 2019

CBER comment 19

You have provided information regarding the capsules used for drug product in section 3.2.P.4. Please provide the following information regarding the capsules.

- a. Please justify your choice of the particular capsules you use for the drug product and explain how the capsules used for commercial product meet US regulations. Please refer to specific CFRs, including paragraph numbers or specific compendial methods or monographs.

*These capsules were chosen because (b) (4) materials, which are acceptable to patients with many different types of restrictive diet. All components comply with either FDA food color or food additive regulations and are fit for human consumption even though for this product they are not consumed. This is acceptable.*

b. Please document any changes to the capsules or their suppliers throughout pharmaceutical development.

*The capsule colors and manufacturers changed between the phase 2 and phase 3 clinical studies due to concerns regarding which food colorants are acceptable in the European Union. No other changes affect the composition of the capsule. This is acceptable.*

c. Please explain why you use different manufacturers for capsules for different doses and how this may affect the drug product.

*During phase 2, (b) (4) supplied all capsules, (b) (4). The capsules from (b) (4) have similar dimensions, fill weights, tolerances and locking mechanisms. Aimmune has not noted any differences between different capsule manufacturers during manufacture or stability studies. This is acceptable.*

d. The CoAs for capsules from (b) (4) conform with (b) (4) guidance, but the (b) (4) capsules do not appear to be tested for (b) (4), which should be tested for oral doses. Please explain.

*A letter from (b) (4) states that they monitor (b) (4) across batches, but do not test all batches. The monitoring indicates that their capsules comply with (b) (4). In addition, no metals are added during capsule manufacture and the capsules are not swallowed as part of the dose. This is acceptable.*

All deficiencies in this section were satisfactorily resolved.

### 3.2.P.5 Control of Drug Product

#### 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The release specifications for the drug product are shown in Table 37.

Aimmune provided a justification for the specifications for each test. (b) (4)





(b) (4)

**Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:**

Several deficiencies were identified and communicated to the sponsor. The date of the IR is followed by the CBER comment with a summary in italics of the Aimmune's response and the reviewer's assessment. While all acceptance limits are the same as or narrower than clinical specifications, sufficient experience has not been gained with the commercial manufacturing process and it may be possible to narrow specifications further. Drug product specifications should be reassessed after sufficient additional commercial batches have been manufactured to allow meaningful statistical analysis of commercial batches without including clinical batches. See CMC agreement with Aimmune regarding reanalysis of drug product specifications at the end of this memo.

IR#24 dated 9 September 2019

Responses received 11 October 2019 and 18 November 2019

CBER comment 1

According to section 3.2.P.5.6, Justification of Specifications, you set most of the specifications based on (b) (4) tolerance intervals (TIs). Please address the following:

a) (b) (4)


FDA comment 5

a. For some tests, you state that the specifications for commercial drug product have a wider range compared with those for the drug product used in your clinical studies (for example (b) (4))



CBER comment 7

(b) (4)



### **3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures**

The test methods used to evaluate the drug product are listed in Table 42. Several are the same as those used for the (b) (4) are described in that section.

Table 42. Analytical procedures for drug product analysis

Quality Attribute	Analytical Method	Method [1]	Location	Validation / Verification
Appearance	Visual	TM-0378	Included in this module	N/A
Identification	(b) (4)	TM-0067	Module 3.2.S.4.2, Section 2	Module 3.2.S.4.3, Section 1
Protein Integrity	HPLC	TM-0067	Module 3.2.S.4.2, Section 2	Module 3.2.S.4.3, Section 1
Relative Potency	ELISA	TM-0326	Module 3.2.S.4.2, Section 3	Module 3.2.S.4.3, Section 2
Assay	Combustion	TM-0066	Included in this module	Module 3.2.S.4.3, Section 3
Content Uniformity	Combustion (b) (4)	TM-0066	Included in this module	Module 3.2.S.4.3, Section 3
Deliverable Mass	Gravimetric	TM-0015	Included in this module	Included in this module
(b) (4)	(b) (4)	TM-0103	Module 3.2.S.4.2, Section 5	Module 3.2.S.4.3, Section 6
Microbiological Limits	(b) (4)	000004791	Included in this module	Module 3.2.S.4.3, Section 7
(b) (4)	(b) (4)	000004791	Included in this module	Module 3.2.S.4.3, Section 8
(b) (4)	(b) (4)	(b) (4)	Module 3.2.S.4.2, Section 8	Module 3.2.S.4.3, Section 9

[1] Testing performed at facilities listed in Module 3.2.P.3.1. For methods used at more than one facility, methods from one facility are provided. Equivalent methods from additional facilities are available on request.

HPLC, high-performance liquid chromatography; ELISA, enzyme-linked immunosorbent assay; (b) (4)

## Appearance

(b) (4) drug product doses are checked for (b) (4)

of the sachet is confirmed.

## (b) (4) and protein integrity

HPLC is used for the (b) (4) protein integrity tests. The (b) (4) test is performed by (b) (4)

and the protein integrity measures the (b) (4) for the same three allergens. (b) (4). The HPLC methods are validated for precision, robustness, specificity, sample/standard stability, and range. DBPAP reviewers defer to DBSQC for review of these methods and their validation.

### **Relative potency (ELISA)**

ELISA is used to measure the concentration of Ara h 1, Ara h 2 and Ara h 6 (b) (4) drug product by comparing against a reference standard. See review of the ELISA method and validation in section 3.2.S.4.2 of this review memo.

### **Assay (total protein content by combustion)**

The total protein content assay (Dumas combustion method) is used to confirm that the correct dose of peanut protein is present in the drug product. This assay is also used to test (b) (4)

#### **□ (b) (4)**

#### **□ Drug product protein content**

(b) (4) (10 – 300 mg doses) or (b) (4) capsules (0.5 and 1.0 mg) doses are (b) (4)

(b) (4)

The total protein method is validated for specificity, linearity, accuracy, precision, range and robustness. DBPAP reviewers defer to DBSQC for detailed review of this method and validation.

#### **□ Content uniformity**

As described above, the protein content assay is used to determine the content uniformity for the drug product. (b) (4)


For 0.5 and 1.0 mg doses, the label claim result and %RSD of the label claim are compared to the specifications in Module 3.2.P.5.1. DBPAP reviewers defer to DBSQC for detailed review of this method and validation.

### **Deliverable mass**

The deliverable mass is a measure of the amount of drug product (b) (4)


The test is performed (b) (4) dosage units.

(b) (4)




. The deliverable mass is calculated according to the following equation:

(b) (4)

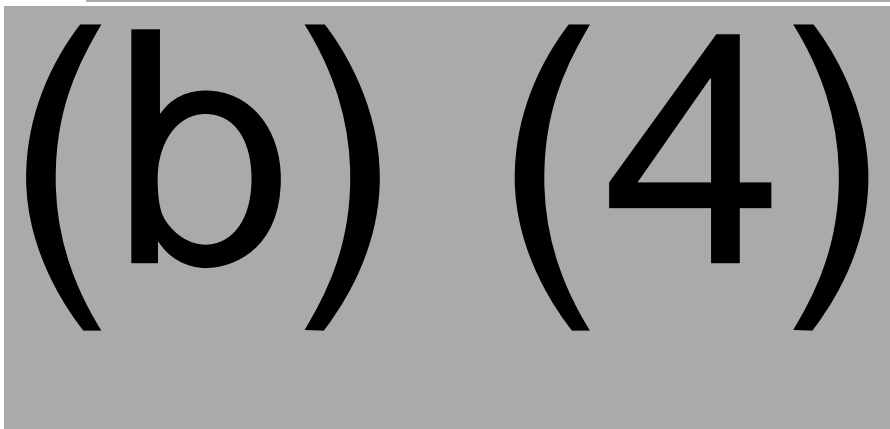


This assay has been validated for range, accuracy/precision and intermediate precision. All precision and intermediate precision results were well within the defined acceptance criteria of (b) (4) recovery and (b) (4) RSD across (b) (4) analysts and the range of doses.

(b) (4)



(b) (4)



CoreRx noted in an addendum to the verification report that the robustness of the assay was affected by (b) (4)



(b) (4) . This is acceptable.

**Microbiological limits (b) (4)**

(b) (4) were measured according to the (b) (4) method and the (b) (4) were measured according to the (b) (4) method. The method has been verified for recovery of microorganisms. DBPAP reviewers defer to DBSQC for detailed review of this method and validation.

(b) (4)  
A modified (b) (4) method based on (b) (4) is used to determine (b) (4) content of the drug product. The method and validation are reviewed in section 3.2.S.4.3 of this review memo.

**Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:**

Several deficiencies were identified and communicated to the sponsor. The date of the IR is followed by the CBER comment with a summary in italics of the Aimmune's response and the reviewer's assessment. These deficiencies were all resolved and responses were acceptable.

IR#1 dated 14 March 2019

CBER comment 11

Please provide the validation protocol for deliverable mass in section 3.2.P.5.3.

*This was provided in Aimmune's 5 April 2019 submission and no deficiencies were noted.*

IR#24 dated 9 September 2019

Responses received 8 October 2019

CBER comment 9

(b) (4)

*Aimmune confirmed this, which is acceptable.*

CBER comment 10

(b) (4)

*Aimmune stated that the results had been misinterpreted and that since then, (b) (4) have been obtained in (b) (4) and (b) (4) conditions, but they did not provide data to demonstrate this. See comment 11 of IR#38 below*



IR#38 dated 8 November 2019

CBER comment 11

In your response to CBER comment 10 in your submission dated 8 October 2019, you note that (b) (4) have been obtained during LOD testing under different conditions of (b) (4). Please provide a summary of this data.

*Aimmune provided a summary of data showing that (b) (4) had been obtained at (b) (4). Together with previous results (in response to comment 10 of IR#24, these show that the (b) (4) does not affect the LOD assay. This is acceptable.*

Deficiencies in this section were all resolved satisfactorily.

### 3.2.P.5.4 Batch Analyses

Batch analysis data are provided for the encapsulated drug product prior to packaging into blisters, and for the drug product packaged in foil laminate sachets. The batch analysis results provided are from phase 2 and 3 clinical batches including registration stability batches and from PPQ stability batches manufactured using the commercial process. Results from a total of (b) (4) batches have been provided. The purpose and number of lots of each type are documented in Table 43 below.

Table 43. Drug product batch usage summary

Dose	0.5 mg	1.0 mg	10 mg	20 mg	100 mg	300 mg
Phase 2 process - Clinical and stability	(b) (4)					
Phase 3 process - Clinical						
Phase 3 process - Development						
Phase 3 process - Registration stability						
Phase 3 process - TBD						
<b>Clinical Total</b>						
Commercial process – PPQ only						
Commercial process – Stability only						
Commercial process – PPQ and stability						
<b>Commercial Total</b>						
<b>Overall Total</b>						

While all tested batches met the acceptance criteria, eight lots of drug product had a borderline acceptable relative potency of (b) (4) for Ara h 1 or Ara h 6. Results for relative potency are reported to only (b) (4), which is not appropriate since a value of (b) (4) could be rounded up to (b) (4). The (b) (4) lots associated with these lots of drug product had low relative potency (b) (4) of the appropriate allergen).

### Changes to test methods

The sponsor provided graphs of the batch release results by date with notations of when new versions of the assays were introduced. Some of the changes are minor edits, while others have multiple changes and may involve revalidation of assays. In addition, the reference standard for the relative potency ELISA assay was updated during PPQ testing.

### Appearance

A product specific test method and a reference comparator for the capsules were introduced on 1 May 2018, during PPQ testing.

### Deliverable mass (b) (4)

There have been no significant changes since start of phase 3 production.

### (b) (4) protein integrity

The HPLC assay (TM-0067) was validated for phase 2 and 3 clinical batches, but the assay was updated and revalidated for TM-0067 version 5 prior to use for the PPQ drug product batches. The major changes were as follows:

- (b) (4)

(b) (4)

### Protein content and content uniformity

The total protein content assay (TM-066) was used for both phase 2 and phase 3 batches and was optimized and revalidated prior to the PPQ batches. The major changes were as follows:

- (b) (4)

Aimmune noted that they performed a bridging study to show comparability between the old and new versions of TM-066. The report for this study was requested in IR#38 dated 8 November 2109 and was provided in the response received on 26 November 2019. The report compared the results from each version of the test using (b) (4) different batches across the full range of doses from 0.5 mg – 300 mg (b) (4). The results provided show comparability between version 5 and version 6 of TM-066 and (b) (4) in data generated from version 6. This is acceptable.

## Potency

The ELISA assay to measure potency of Ara h 1, Ara h 2 and Ara h 6 was added at the start of phase 3 (TM-0129). The ELISA was further optimized (TM0326), revalidated, and implemented prior to testing PPQ batches (June 2018). A new reference standard batch (lot (b) (4)) was qualified and introduced during the PPQ batch testing. The change in reference standard was expected to affect potency measurements, since it was chosen for its similarity to recent batches of (b) (4), rather than comparability to the old reference standard. The major changes between TM-0129 and TM-0326 are:

- (b) (4)

A comparability study was performed to compare TM-0129 and TM-0326. The conclusion was that TM-0326 showed better accuracy and precision and results were comparable, however, few batches have been analyzed using this method and using the new reference standard at the time of submission. See review of ELISA method and validation in section 3.2.S.4.2 and 3.2.S.4.3 and review of the reference standard in section 3.2.S.5 for a complete detailed analysis of the effects of these changes.

In IR#24 dated 9 September 2019, we requested a table showing which reference standard was used for batch release and each time point of stability studies for (b) (4) drug product for phase 3 and commercial production. The sponsor provided this table and clarified that they have used two reference standards to date. Lot (b) (4) was the initial reference standard and Lot (b) (4) was introduced in June 2018, during PPQ testing and shortly after the adoption of ELISA method TM-0326 for commercial product. The tables show that for release of PPQ batches, the 10 mg, 20 mg (Ara h1 and 2 only) and 100 mg used the old reference standard, while all other tests and doses for release of PPQ and commercial batches used the new reference standard.

In IR#24, we also requested clarification regarding the annotations showing method changes on the figures of relative potency results and asked for the changes in reference standards to be added to the figures. In their response received 8 October 2019, Aimmune provided new plots with clear descriptions of the annotations and showing the reference standards used for each batch. This is acceptable.

In their assessment of method changes, Aimmune stated that the relative potency method change is category 2 (b) (4), but it produces equivalent test results). However, Aimmune did not assess how changing the reference standard affected the ELISA or any other method. Since reanalysis of data (provided across several responses to IR#24) introduced use of a (b) (4) to correct for differences between the old and new reference standards, and since a similar process will be in place moving forward, future changes in reference standards should have little impact on future batch release results.

### 3.2.P.5.5 Characterization of Impurities

Impurities including (b) (4) are measured in the (b) (4) are discussed in Section 3.2.S.4.3.

(b) (4)

#### **Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:**

Several deficiencies were identified and communicated to the sponsor. The date of the IR is followed by the CBER comment with a summary in italics of the Aimmune's response and the reviewer's assessment. These deficiencies were all resolved and responses were acceptable.

IR#24 dated 9 September 2019

Responses received 8 October 2019

CBER comment 6

We note that you replaced your original primary reference standard with a new primary reference standard. Please provide tables showing which batch of reference standard was used for batch release and each time point of stability studies for drug substance and drug product produced for phase 3 and commercial production. Please also state which are primary or secondary reference standards.

*Aimmune provided the requested tables which showed that the majority, but not all clinical batches were tested for batch release using the original reference reagent, (b) (4). The 10 mg and 100 mg PPQ batches also used this reference reagent. The remaining PPQ and commercial batches all used the new reference reagent, (b) (4). For batch analysis, potency data statistical analysis was resubmitted on 18 November 2019 using (b) (4) to enable comparability of relative potencies measured against different reference standards. This is acceptable.*

*These tables are discussed separately in 3.2.P.8 in relation to the stability studies.*

**CBER comment 7**

In Figure 4 of Section 3.2.P.5.4 you have provided plots of your relative potency results showing the version numbers of the method that was used. Please clarify the following in an amendment to your BLA:

- a. Please explain the annotation regarding markers for TM-0326 ver 0.14 and ver 1.0.
- b. Please add a line to each plot indicating when the new reference standard was introduced for the ELISAs.

*Aimmune clarified that the different markers relate to different versions of the test methods and provided new figures with legends and with added lines noting the lot of reference standard used. This information together with the response to comment 6 was used in review of the information provided in this section.*

**CBER comment 8**

In your analysis of comparability of analytical methods (part 2.1 of Section 3.2.P.5.4), you state that the relative potency method change is category 2 ((b) (4)), but produces equivalent test results). You have not included an assessment of how the recent reference standard change affected the ELISA results or any other results.

*Since batch release results were reanalyzed using a (b) (4) for the old reference standard, this comment has been addressed sufficiently.*

IR#38 dated 8 November 2019

Response received 26 November 2019

**CBER comment 5**

In module 3.2.P.5.4, table 20, you state that a method bridging study was performed that showed comparability between version 5 and version 6 of the protein content assay method TM-066. Please provide the report for this study.

*Aimmune provided this report. In summary, the report demonstrates similarity between the two versions of the method and (b) (4) with version 6.*

Deficiencies in this section were all resolved satisfactorily.

**3.2.P.6 Reference Standards or Materials**

Refer to section 3.2.S.5.

**3.2.P.7 Container Closure System**

Capsules were reviewed under section 3.2.P.4. Defer to DMPQ for review of sachets and blisters.

### 3.2.P.8 Stability

#### 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The sponsor proposes a shelf life of (b) (4) months at 2 - 8°C for commercial product in both sachets and capsules. The proposal is based on primary registration stability data to (b) (4) months at 2 – 8°C and (b) (4) relative humidity (RH). The stability studies employed a (b) (4) approach. All stability studies were performed on select sets of blisters to capture the full range of capsule sizes. Sachets were stored in (b) (4) in the stability chambers, no secondary packaging was used.

Additional stability studies were also conducted on the (b) (4) sachet (b) (4) manufactured from the (b) (4) foil laminate which planned for commercial production. These were performed at 2-8°C and (b) (4) RH. on (b) (4) and at (b) (4) RH on a (b) (4).

Stability studies were also initiated on commercial batches of drug product across all doses at 2-8°C, (b) (4) RH, (b) (4) RH and (b) (4) RH. Data and analysis to (b) (4) months was received on 18 December 2019 and compared with data from the primary registration studies and the development sachet lot.

Multiple deficiencies were identified in the analysis of stability studies. These were addressed in several IRs to the sponsor (see comments in summary section below). The results, analysis and conclusions described in this section are based upon the information provided in response to these IRs.

It is unclear where each stability study was performed, and no information has been provided in the submission regarding shipping of stability samples. See comments and Aimmune's response in summary section.

Information provided as a follow up to the May 2, 2019 telecon provided the time elapsed between manufacture of the batch and start of the stability studies, which was up to (b) (4) months. This information has been included in the summary tables below. The duration between manufacture and receipt of drug product at the distributor for commercial product is projected to be (b) (4) months with a maximum anticipated duration of (b) (4) months.

#### Primary registration studies

The primary registration stability studies were performed on a total of (b) (4) lots at 5°C ± 3°C (b) (4). This comprised (b) (4) lots of drug product packaged in blisters (b) (4) lots of 0.5 mg, (b) (4) each of 1, 10, 20 and 100 mg doses) and (b) (4) lots of drug product packaged in sachets (300 mg doses). The lots used for these studies were the same formulation as commercial product, but they were manufactured at (b) (4) scale using the phase 3 manufacturing process. The capsules and blisters used for these studies were of the same materials as the commercial product, however the (b) (4) in the blisters were larger. The sachets for the primary registration studies were manufactured from a different (b) (4) and were (b) (4) than commercial sachets. However, Aimmune provided data to (b) (4) months from (b) (4) lots of sachets using the new sachets (see details in commercial stability section below and responses to comments in the summary of this section). Table 44 shows the tests performed at each timepoint and Table 45 summarizes the primary registration studies to date.

*Table 44. Stability Protocol for primary registration stability studies*

(b) (4)

*Table 45. Summary of primary registration stability studies*

(b) (4)

Lot (b) (4) (0.5 mg) failed microbiological tests at 12 months due to a blister packaging issue. The packaging issue was resolved for subsequent batches and this lot was removed from the stability studies.

### Commercial stability studies

The stability studies on product manufactured using the commercial process were performed at  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ , (b) (4)

The tests performed at each time point are shown in Table 46. Additional samples are stored for (b) (4) time points, but not sampled unless required. In addition, to test the effect of the change in sachet (b) (4) on stability, (b) (4) development (b) (4) of product was included that uses the new sachet.

Several revisions were made to the methods between the primary registration studies and the commercial stability studies. The revisions were minor for (b) (4), but as discussed above, the revisions to the ELISA were major, including the new reference standard that was introduced in June 2018 prior to commencing commercial stability studies (discussed above).

*Table 46. Stability Protocol for commercial stability studies*

(b) (4)

The studies were performed initially on (b) (4) PPQ lots of drug product (b) (4) lots of 0.5 mg, (b) (4) each of 1, 10, 20 mg doses, (b) (4) lots of 100 mg doses and (b) (4) lots of 300 mg doses). An additional (b) (4) lots (b) (4) of 0.5 mg, (b) (4) lots of 20 mg, (b) (4) of 100 mg and (b) (4) of 300 mg were subsequently added, bringing the total to (b) (4) lots (Table 47). The details of the development (b) (4) for the commercial sachets (b) (4) are also included here.





(b) (4)

### Stability study results

Aimmune performed trends analysis (b) (4) on quantitative data from the registration stability studies according to ICH Q1E guidelines for evaluation of stability data. In response to an IR request they also performed trends analysis on 18 months of data from the development sachet (b) (4) and 12 months of data from the commercial stability study. These data were also considered during review of the stability data with the acknowledgement that the trends from incomplete studies may show more variability due to the lower number of data points available. The 95% confidence intervals calculated for each batch and for each test were used to provide estimates of the most conservative shelf life for data generated from each of the studies. All OOS were confined to the 0.5 mg dose, and for commercial batches, this was only at (b) (4). The sponsor notes that the OOS may be related to (b) (4)

(b) (4), which in response to an IR, Aimmune acknowledged must be filed as a prior approval supplement (See comment and Aimmune's response in summary section). Due to the change in sachets, the data from the development and commercial lots is more appropriate to determine sachet shelf life than the primary registration studies.

### Appearance

No changes were noted in the appearance during either stability study. These data support a 24-month shelf life.

### Deliverable mass

Results remained within specifications (b) (4) for both studies. These data support a 24-month shelf life.

### Relative potency

Trends in the registration stability results over (b) (4) months from samples stored at 5°C were analyzed by (b) (4). Since the reference standard changed during the stability studies a (b) (4) was used on the data generated with the old reference standard to ensure comparability to data generated with the new reference standard across all time points (adjusted data set). For 0.5 mg, the new reference standard was introduced for 24- (b) (4)-month time points, for all other doses, the new reference standard was used for only the (b) (4)-month time point. The ELISA method for primary registration stability studies was TM-0129 and was not changed throughout the study. All commercial stability studies use TM-0326 with the new reference standard, so no correction factor is required.

The adjusted data is the most appropriate data set to use for determining shelf life since it would better represent the commercial reference standard that will be used going forwards. However, the (b) (4)

(b) (4) for the reference standard is not as robust as it should be, so the unadjusted data should also be considered when determining shelf life. The trends for Ara h1 and Ara h2 were relatively flat for both adjusted and unadjusted data at all doses. For Ara h 6, the slopes for each differed dependent on batch and dose and not in the same direction. The trends graphs of the adjusted and unadjusted data show that the 95% confidence intervals are within specifications to (b) (4) months for Ara h 1 and Ara h 2, however the 95% confidence intervals of Ara h 6 cross the acceptance criteria between 24 (b) (4) months in both adjusted and unadjusted data sets suggesting that Ara h 6 is only stable to 24 months. These data support a 24-month shelf life for all capsules at 2-8°C.

The sachet development (b) (4) showed only minimal upward trends for all allergens to 18 months at 2- 8°C using the adjusted relative potency data and was similar to the primary registration stability study results. However, there is considerable variability in results at (b) (4), which could be due to assay variability, or because (b) (4) is not recommended as a storage temperature based on these data. Due to the lack of real-time data on the commercial sachets, these data can only support an 18-month shelf life for commercial sachets at 2-8°C.

All relative potency results for commercial stability lots stored at 5°C (b) (4) were within specifications up to 12 months. At (b) (4)

(b) (4) Comparison of the clinical, sachet development (b) (4) and commercial trends at 12 months revealed that all allergens in the commercial batches and the sachet development (b) (4) show minimal trends, this means that the Ara h 6 is more stable in commercial batches, while the Ara h 1 and Ara h 2 trends are similar between clinical and commercial batches. These data to 12 months show similar trends to the primary registration study for capsules and the development (b) (4) for sachets and suggest that a 24-month shelf life for capsules and an 18-month shelf life for sachets are appropriate.

Due to the major change in the assay reference standard, it is critical that the data from these commercial stability studies are monitored further and specifications and requests for extensions to expiry dates should be re-evaluated based on any new data post approval.

#### □ Protein integrity

As discussed above, HPLC analysis (b) (4) Trends analysis of results from the primary registration stability studies at 5°C showed that the confidence intervals of the 0.5 mg doses would not cross the lower limit of the specifications (b) (4) of Ara h 2 until (b) (4) months (b) (4) analysis) or later (b) (4) analysis) or (b) (4) Ara h 6 until (b) (4) months (b) (4) analysis) or after (b) (4) months (b) (4) analysis). (b) (4). Based on these results, the estimated shelf life is at least (b) (4) months. Similar results were obtained from the registration stability studies at (b) (4). Overall, protein integrity results suggest that the most conservative shelf life estimate is (b) (4) months. These data support a 24-month shelf life for capsules at 2-8°C.

The confidence interval for Ara h 6 (b) (4) the upper acceptance limit at 18 months for sachet development (b) (4) stored at 5°C. A similar trend is observed at (b) (4), though it is not quite intersecting the upper limit at 18 months. The Ara h 2 (b) (4) results showed minimal variation over time, but since it is calculated from the Ara h 6 (b) (4), there was a slight trend towards a

decrease in the (b) (4). Due to the lack of real-time data on the commercial sachet, these data can only support an 18-month shelf life at 2-8°C for commercial sachets.

For commercial lots stored at 5°C (b) (4) all stability measurements of (b) (4) Ara h2, (b) (4) Ara h 6, and (b) (4) were within specifications up to 12 months. At (b) (4)

. Due to the tightening of specifications during the course of review of this submission, some lots had initial stability results that were close to the upper acceptance limit for (b) (4) Ara h 2 (20 mg lot (b) (4), 300 mg lot (b) (4)) or (b) (4) (0.5 mg lot (b) (4)) and for these lots despite only minimal trends, the 95% confidence interval was outside the acceptance limits at all time points. For the purposes of setting limits, these lots were considered stable to 24 months. In the future it is unlikely that lots will be at the outer limits of acceptance criteria due to better source material batch selection procedures and tighter (b) (4) specifications.

For capsules, Ara h 2 and Ara h 6 trends were stable to 12 months, but (b) (4) showed variable trends depending on the individual capsule batch. The trends were not consistent in any one direction and Aimmune suggested that this could be due to assay variability. Aimmune provided graphs showing extrapolation of the trend for each batch to 24 months and showed that based on current results no trends crossed the acceptance limits by 24 months. Further data points will increase the certainty on this. For sachets, Ara h 2 was stable, but Ara h 6 showed a similar upward trend to the development (b) (4) although the confidence intervals were not intersecting the acceptance limit at 12 months. Similar to the development lots, a slight downward trend in (b) (4) was observed. These data to 12 months show similar trends to the primary registration study for capsules and the development (b) (4) for sachets and suggest that a 24-month shelf life for capsules and an 18-month shelf life for sachets are appropriate.

#### □ Total protein content assay

Analysis of (b) (4) months of data from the registration stability studies showed that slope data from all doses could be (b) (4). The estimated change at (b) (4) months is (b) (4) of label claim at (b) (4) of label claim at (b) (4). Due to higher relative levels of excipients, there is greater variability in the lower doses (0.5 and 1.0 mg).

The total protein assay was optimized for (b) (4), and validated for commercial stability studies. Using the revised assay, overall variability is (b) (4)


(b) (4)

All total protein content results for commercial stability lots stored at 5°C (b) (4) were within specifications up to 12 months and at (b) (4). Although average data from six samples were within specifications, some individual samples from two 0.5 mg lots were below specification because of a low signal to noise ratio at these doses. The overall results from the two 0.5 mg and one 1


mg batch were also very variable, though don't appear to show a consistent trend. This is also most likely also due to the low signal to noise ratio of the assay at these doses and is similar to the results for the primary registration study. All other doses showed minimal changes over time. Additional data will provide a better picture of the trends. For sachets, similar to the development study, slight decreases in trends were observed over time.

These data to 12 months show similar trends to the primary registration study for capsules and the development <sup>(b) (4)</sup> for sachets and suggest that a 24-month shelf life for capsules and an 18-month shelf life for sachets are appropriate.


□ (b) (4)



□ (b) (4)




□ (b) (4)



**Additional supporting studies**

(b) (4)



(b) (4)

### 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The sponsor commits to continuing the stability studies on commercial drug product batches according to the protocol above (Table 46) and will provide the updated stability data following the ICH guidelines Q1A and Q5C.

For future commercial batches of drug product, Aimmune commits to place on stability at 5°C (b) (4)

The frequency of initiating stability studies for the capsules is acceptable. However, since the 300 mg sachet is a (b) (4) of sachets should be placed on stability each year. (See CMC agreement at the end of this memo).

#### Overall Reviewer's Assessment of Section 3.2.P.8:

We agree with the 24-month shelf life proposed for capsules based on analysis of (b) (4) months of data from registration stability studies and 12 months of data from PPQ batches according to ICH Q1E.

We do not agree with the proposed (b) (4)-month shelf life for the sachets. The sachet (b) (4) were changed between clinical and commercial batches and the available stability data on sachets from PPQ batches does not demonstrate the same trends as for clinical sachets. Only 18 months of stability have currently been demonstrated. The shelf life of commercial sachets should be set at 18 months. Aimmune may submit further data from the ongoing studies with early commercial and PPQ batches to extend this shelf life.

#### IR#1 dated 14 March 2019

##### CBER comment 14

Section 3.2.P.8.1 should be limited to a summary of your stability studies including your conclusions from the stability studies and how you established your expiration dates. Please revise section 3.2.P.8.1 to provide this summary. Please provide the detailed analysis and graphical representations of your stability data in section 3.2.P.8.3.

*Aimmune provided updated drug product stability sections with a short summary section, an extensive analysis section and separate tables in amendment 14 received 13 May 2019. This is acceptable.*

**CBER comment 15**

Please describe how the drug product sachets are stored for stability studies and whether any secondary packaging is used.

*Sachets are stored in (b) (4) at approximately (b) (4) sachets per (b) (4) with no secondary packaging. This is acceptable.*

IR#24 dated 9 September 2019

Response received 8 October 2019

**CBER comment 6**

We note that you replaced your original primary reference standard with a new primary reference standard. Please provide tables showing which batch of reference standard was used for batch release and each time point of stability studies for drug substance and drug product produced for phase 3 and commercial production. Please also state which are primary or secondary reference standards.

*These data were provided. Two reference standards have been used to date. The original clinical reference standard was replaced with lot (b) (4) in June 2018 just before the introduction of TM-0326. The reference standard changed during the stability studies. For 0.5 mg, the new reference standard was introduced for 24- and (b) (4)-month time points, for all other doses, the new reference standard was used for only the (b) (4)-month time point. Consequently, the relative potency stability data produced using the original reference standard were reanalyzed using an adjusted relative potency value to enable comparability with batches analyzed using the new primary reference lot (b) (4). See Module 3.2.S.5 for details of the (b) (4) used.*

IR#31 dated 13 October 2019

Response received 18 November 2019

**CBER comment 1**

Please provide details of all procedures for shipping, tracking and handling of samples for testing including samples for in-process, batch release, and stability testing. This should include, but is not limited to:

- a. Shipping of samples from manufacturers or packagers to all test locations and stability storage locations.
- b. Shipping of samples from stability storage locations to testing locations.
- c. Internal handling, storage, transfer and tracking of samples (e.g. at CoreRx or (b) (4))

*Aimmune provided this information and clarifications were provided in a teleconference on 19 November 2019. A follow up submission received on 5 December 2019 provided a flow chart with additional clarifications. All shipping and storage are at (b) (4) either in temperature monitored vehicles or in validated shippers with temperature control and tracking. The temperature charts are reviewed upon receipt of the shipment at each location. This is acceptable.*

CBER comment 2

Please state the storage location, including company and street address for each stability study.

*Aimmune stated that samples for registration stability studies were stored at CoreRx and samples for commercial stability studies (PPQ batches) were stored at (b) (4). In a telecon on 19 November 2019 we requested clarification regarding whether there is an FEI number for the (b) (4) site. Aimmune clarified that this (b) (4) address is the address of the stability storage facility on the main (b) (4), which spans (b) (4) postal addresses. Since this is all the same company there is only one FEI number and only the main (b) (4) campus address was included in the manufacturer's list. This is acceptable.*

CBER comment 3

We note that during your stability studies for (b) (4) drug product, you substituted an unmatched reference standard to measure potency at 24 months for 0.5 mg doses and (b) (4) months for all other doses and the (b) (4). Due to this change it is hard to interpret the analysis that you provided. Whenever possible, reference standards should not be changed while a study is ongoing. When changing the reference standard is unavoidable, the new reference standard must be comparable to the old one. Matching reference standards requires bridging studies to demonstrate similarity between the two references. Only after proving similarity, should you use the new reference. Please reanalyze your trend data by: 1) Omitting the points that used the new reference; and 2) If possible, employing a conversion factor that takes into account the calculated differences between the two reference standards. Please state the shelf life that each analysis will support.

*A complete reanalysis of relative potency stability data was provided. Once outliers were removed, the adjusted and unadjusted data were compared. This submission contained all the results of the statistical tests, but they did not provide the trends graphs to show the 95% confidence intervals of the data relative to the acceptance criteria. See comments in IR#43 below for review of this data.*

CBER comment 9

In Section 3.11 of Module 3.2.P.8.3 (Data Analyses), you state that due to the (b) (4)

(b) (4) We remind you that any changes to the (b) (4) must be submitted as a Prior Approval Supplement to your approved application.

*Aimmune confirmed that any (b) (4) changes would be submitted as a prior approval supplement.*

CBER comment 13

We note that the 300 mg sachet lots (b) (4) that are used for the commercial stability studies were produced before PPQ of the sachet filling process. Please explain the rationale for this and describe any differences in the manufacturing process between these lots and the PPQ lots.



*This was done for expediency to start stability studies in a timely manner. With the exception of the level of testing, these batches were manufactured the same as the subsequent PPQ batches. One additional PPQ sachet batch was subsequently added to the stability studies as discussed during the pre-BLA meeting. This is acceptable.*

CBER comment 14

In Table 5 of Module 3.2.P.8.1, you state that equivalent test methods may be used if (b) (4). Please note that if you intend to (b) (4), a prior approval supplement may be required to your approved application.

*This was not acceptable, CBER guidance regarding this is available. See comment 12 of IR#48 below for resolution.*

CBER comment 15

In your drug product stability data tables in Module 3.2.P.8.3 (Tables), you refer to INC 19-00180, INC 19-00187 and INC 19-00191. Please summarize each incident, the results of any investigation and whether these incidents affected stability results and conclusions.

*INC 19-00181 and 19-00191 related to individual protein content results (out of (b) (4) being out of specification. However, this did not amount to an OOS result because only the (b) (4) is reported. Investigations were initiated to acknowledge this issue. This is acceptable. INC 19-00187 was initiated because ELISA testing was performed for the stability program beyond the (b) (4)-day time frame outlined in the SOP due to changes to the protocol. The testing was completed by 35 days. This is acceptable.*

CBER comment 16

Please analyze your stability data for the sachets separately from the capsules and do not (b) (4) data or analyses from the different packaging types.

*Aimmune agreed and provided the statistical analysis in their response, but no trending graphs. See IR#43 below for comment and resolution.*

CBER comment 17

Please confirm that Table 32 Module 3.2.P.8.3 (Tables) shows data for a 0.5 mg dose packaged in blisters.

*Aimmune confirmed this. This is acceptable.*

CBER comment 18

Tables 32, 33, 36, 37, 43, 44 and 45 in Module 3.2.P.8.3 (Tables) have two results for the protein integrity tests, which are not fully explained in the text referred to in Module 3.2.P.8.3, Section 3.11. Please provide an explanation including why these samples were retested when the initial results appear to be within specifications.

*An OOS in one sample led the investigator to believe there was an issue with the (b) (4) of all samples run on one day was, so all samples were (b) (4) but similar results were obtained*

with all lots except the OOS, ruling out a general (b) (4) issue. Both results were reported. This is acceptable.

CBER comment 19

In Section 2.1.7 of Module 3.2.P.8.3 (Data Analyses), you state in Table 4 that the (b) (4) for 0.5 – 100 mg capsules is (b) (4), but you state in the text that it is (b) (4). Please clarify.

Aimmune clarified that (b) (4) is the correct value. This is acceptable.

CBER comment 20

In Figure 22 of Module 3.2.P.8.3 (Data Analyses), you show graphs of trends of (b) (4) and state you have used a (b) (4) analysis. However, you have not stated which type of (b) (4) analyses of those listed in Table 4 are represented in Figure 22. Please provide similar figures showing the analysis of the different packaging configurations separately.

Aimmune provided the requested graphs of data from the registration stability studies and an updated table showing the tests used for determining (b) (4)

This is acceptable.

CBER comment 21

In Figure 56 of Module 3.2.P.8.3 (Data Analyses) you have provided (b) (4) comparing release and (b) (4)-month data for (b) (4) of a 100 mg dose. Please overlay the release and (b) (4)-month (b) (4) for each temperature. In addition, please provide similar overlaid (b) (4) for a batch of 0.5 mg and its corresponding (b) (4) batch to demonstrate across the range.

(b) (4) were provided and appear similar. This is acceptable.

CBER comment 22

Please analyze the available data for your commercial stability study and demonstrate that the calculated trends over time are similar between the registration and commercial studies.

Aimmune provided updated stability data tables to 12 months for (b) (4) commercial lots and to 6 months for a further (b) (4) commercial lots. They statistically compared the trends from commercial stability lots with data to 12 months with the primary registration studies to (b) (4) months. No trending graphs were supplied. See IR#43 below for comment and resolution.

CBER comment 23

You provided stability data from (b) (4) development lots of sachets manufactured using the commercial sachets. Please provide a trend analysis and conclusion from this study to date and compare with data from the primary registration studies. In addition, please state which reference standard applies to which time point.

Aimmune provided a trend analysis of the (b) (4) available to 18 months. Due to the (b) (4), there was greater variability in the trends and confidence intervals. Both the primary registration and development sachet stability studies show that the (b) (4) of Ara h 6 increases, with a consequent decrease in the (b) (4). They also show a decrease in protein content over time and increases in LOD over time. Primary registration lots support a shelf life of (b) (4) months. Based on confidence intervals for Ara h 6 (b) (4), data from the development (b) (4) with the new sachets support a shelf life of only 18 months. Data from the commercial stability study with the new sachets shows similar a similar trend and are within specifications at 12 months. Taken together, these data support a shelf life for sachets of 18 months.

**CBER comment 24**

You have provided ELISA results for (b) (4) studies (b) (4)

(b) (4)

**CBER comment 25**

Please provide data on the protein content of samples after (b) (4)

Aimmune performed an additional study (b) (4)

This is acceptable.

IR#43 dated 25 November 2019

Response received 9 December 2019

**CBER comment 1**

Please provide graphs showing your trends analyses for the following data sets:

- a. Adjusted relative potency (Tables 2 – 7) for registration stability studies
- b. Protein integrity (Tables 8 – 11) for registration stability studies
- c. Assay (Tables 8 – 11) for registration stability studies
- d. All tests within the commercial scale stability study plotted so that the graphs are easily comparable to those from the registration studies

**CBER comment 2.**

Please state the acceptance criteria used for each trend analysis.

Aimmune provided all the requested graphs for the primary registration study plotted to 24 months. In a telecon we confirmed with Aimmune's statisticians that the analysis did include the (b) (4)-month time point, but it was just not shown in the graphs since the proposed shelf life is 24 months. In addition, Aimmune provided trends graphs and updated stability results tables to 18 months for development sachet batches and to 12 months for the (b) (4) commercial batches.

Stability results tables to 6 months were provided for the (b) (4) additional PPQ batches placed on stability. All this data was taken into consideration when assessing acceptable shelf life for each dose configuration. The approach used was that described in ICH Q1E where 95% confidence intervals are calculated for the mean curve. (b) (4)

(b) (4)

(b) (4)

(b) (4)

*Sachets:*

The sachet (b) (4) were changed between the primary registration study and the commercial product. While the primary registration studies for sachets at 2- 8°C support a (b) (4) month shelf life, the results from the (b) (4) development (b) (4) available using the commercial sachet only support an 18-month shelf life based on the 95% confidence interval intersecting the upper acceptance limit for (b) (4) at 18 months (See response to IR#31 comment 23 above). The 12 months of data from the commercial stability study show a similar trend for (b) (4) for Ara h 6, although at 12 months they are not yet intersecting the upper limit. Similar to the capsules, the data from sachet stability studies at (b) (4) would only support a much shorter shelf life.

*Conclusion: 18-month shelf life for sachets at 2 – 8°C*

IR#48 dated 20 December 2019

Response received 6 January 2020.

CBER comment 12

In your response to comment 14 (of IR#31), you state that you plan to follow CDER's guidance on post approval changes regarding the type of supplement to file for a change in (b) (4) as the 2017 draft guidance for changes to an approved application for certain biological products does not address post-approval changes in (b) (4). We do not agree with your plan as the CDER guidance you reference is only applicable to CDER drug products approved under an NDA or ANDA. Please note the 2017 draft guidance you reference discusses post-approval changes in (b) (4) in the Facilities section of the Table located in the Appendix (pg. 37). If any change

you plan is not listed, please contact CBER for guidance prior to implementation and submission.

*Aimmune acknowledged this comment, agreed to follow the recommended guidance document and stated that they will contact CBER for discussion prior to initiating or submitting any changes that are not in the guidance. This is acceptable.*

**CBER comment 14**

It is unclear what you are showing in figures 8 and 9. Please provide a brief description and legend for each of these figures.

*Aimmune provided updated graphs with legends and clarified that the graphs are overlays of the (b) (4) for the (b) (4) initial commercial lots in capsules with trend lines extrapolated to 24 months. These graphs were provided as part of the summary of comparability analysis between the clinical and commercial stability data and were included to show that the directionality of the trend lines is not consistent between doses or batches and as such, the data could not be pooled. This suggests that the extrapolated trends may be more indicative of analytical variability than future changes to the drug product. In the registration stability study once additional months of data were collected, the slopes of the trends decreased.*

**CBER comment 30**

In this IR and in IRs 24 and 31 you provided updated stability data and graphs. Based on your stability data, we agree with your proposal for a 24-month expiry date for all doses in capsules. Your sachets changed since the registration stability studies. In IR#31 you provided stability data to 18 months from (b) (4) development (b) (4) using the new sachets and in IRs 31 and 43 you provided stability data to 12 months for commercial batches using the new sachets. Since we do not have real-time data beyond 18 months and because the 95% confidence interval for Ara h (b) (4) is outside the acceptance criteria at 18 months in your development (b) (4) please set your expiry date for the drug product in sachets at 18 months. If you wish to extend this expiry date based on real time data, please submit it as a PAS.

*Aimmune agreed to establish a shelf-life of 24 months for all dosage strengths in capsules and a shelf life of 18 months for sachets. They stated that they plan to (b) (4) This is acceptable.*

Stability studies were reviewed, all deficiencies were resolved and a shelf-life of 24 months for capsules and 18 months for sachets was agreed with Aimmune. Aimmune will continue the ongoing stability studies on commercial batches and the sachet development (b) (4) and any shelf life extension request will be submitted as a PAS.

For future commercial batches of drug product, Aimmune agreed to place on stability at 5°C (b) (4)

### 3.2.A APPENDICES

#### 3.2.A.1 Facilities and Equipment

Defer to DMPQ reviewer.

#### 3.2.A.2 Adventitious Agents Safety Evaluation

The sponsor states that none of the materials in AR101 drug product contain products of animal origin or animal-derived products.

The (b) (4) used in the manufacture of the sachet foil laminate material, which is in direct contact with the drug product, is derived from the (b) (4) sources. However, these (b) (4) sources comply with Commission Decision 2000/418/EC, Commission Decision 2001/2/EC, and Commission Directive 2000/6/EC regarding the use and inactivation of materials presenting risks with respect to TSE.

Microbial content and (b) (4) are controlled for in the (b) (4) drug product specifications and no OOS have been reported up to (b) (4) months for these tests during stability studies.

Several pages were missing from the product regulatory data sheets from (b) (4) for magnesium stearate and from (b) (4) for pre-gelatinized maize starch. See comment in summary section below.

#### ❑ Viral Clearance Studies

Because the AR101 drug substance is not derived from cell lines of human or animal origin, and the drug substance/drug product manufacturing processes do not pose a risk for inadvertent viral contamination, viral clearance studies for the AR101 are not applicable and were not performed. This is acceptable.

#### Overall Reviewer's Assessment of Section 3.2.A.2:

IR#38 dated 8 November 2019

CBER comment 2

It appears that several pages are missing from the product regulatory data sheets from (b) (4) that you submitted in Module 3.2.A.2. Please supply the complete documents.

*These were provided in the submission dated 26 November 2019 and are acceptable.*

The deficiency was resolved satisfactorily.

#### 3.2.A.3 Novel Excipients

This section is not applicable – no novel excipients.

#### 3.2.R Regional Information (USA)

#### ❑ Executed Batch Records

The sponsor provided executed batch records for stability studies for the following doses produced at (b) (4) scale for registration stability studies, and at commercial scale: (b) (4) 0.5 mg batches, (b) (4) each of 1.0 mg, 10 mg and 20 mg and (b) (4) lots each of 100 mg and 300 mg that were and the same for batches. The batch records provided are for powder blending and capsule or sachet filling at CoreRx and blistering at (b) (4).

These batches are produced for stability studies and not for commercial distribution. No records were provided regarding packaging into secondary containers. Executed batch records for all PPQ lots were reviewed during the inspection of CoreRx and were found to be acceptable.

*Table 48. Executed batch records provided including lot number history*

(b) (4)

A separate (b) (4) lot number for the capsules (bulk lots (b) (4) ) was not provided for the registration stability studies. According to the batch records provided, the lot was produced, (b) (4) was tested according to protocol, and the bulk was packaged into sachets the next day.

No current master batch records were provided. See comment in summary section below.

**□ Method Validation Package**


A methods validation package has been provided that provides links to all the relevant method development and validation documents. These are reviewed elsewhere. The sponsor also provided brief descriptions of the antibodies used for the relative potency assay.

(b) (4)

section 3.2.S.4.2 for review of ELISA methods, reagents, replacement procedures and validations.

❑ **Comparability Protocols**

(b) (4)



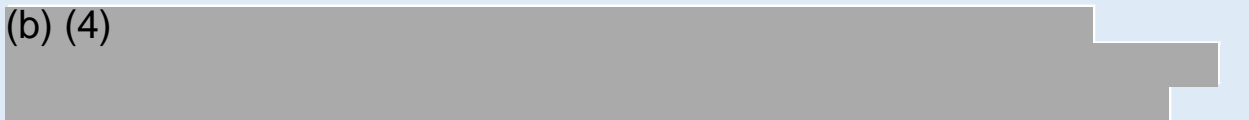
❑ **Excipient Certificates of analysis**

CoAs were provided for (b) (4) lots each of colloidal silicon dioxide and microcrystalline cellulose and (b) (4) lots each of maize starch and magnesium stearate. The procedures associated with testing and accepting lots of excipients were reviewed in section 3.2.P.4.1 of this review including the 14 March 2019 IR regarding clarifications on these CoAs. All deficiencies were resolved acceptably.

**Overall Reviewer's Assessment of 3.2.R**

Several deficiencies were identified and communicated to the sponsor. The date of the IR is followed by the CBER comment with a summary in italics of the Aimmune's response and the reviewer's assessment.

(b) (4)



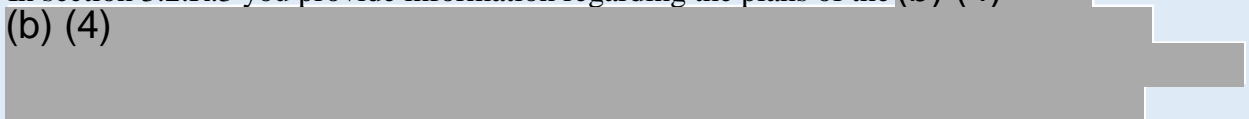
, so was not approved under this BLA and will be submitted as a PAS. All other deficiencies were resolved satisfactorily.

IR#1 dated 14 March 2019

Comment 16

In section 3.2.R.3 you provide information regarding the plans of the (b) (4)

(b) (4)



Therefore, this information should be provided in the BLA. We require the following information to complete the review of your application:

- a. Please state the size and number of all batches of commercial (b) (4) drug product you have available at each dose prior to the (b) (4) manufacturing.



- b. Please state when you anticipate manufacturing and releasing the first batches of (b) (4) drug product produced using the new manufacturing process for (b) (4)

- c. We note that you have provided a list of tests for the enhanced testing that you plan to perform to compare (b) (4). Please provide a detailed description for each test (other than those validated methods already used for release and stability testing).

*In the submission received 5 April 2019, Aimmune stated that once (b) (4)*

*(b) (4). The comparability protocol is insufficiently described, and CBE-30 is not an appropriate mechanism for this change in (b) (4). An IR requesting additional information was sent to the sponsor on 14 August 2019 (See IR#20 below).*

IR#10 dated 26 June 2019

Response received 9 July 2019

CBER comment 1

Please provide master batch records for each process involved in commercial manufacture of drug product. Please include master batch records for each dose for blending and encapsulation.

*There were several updates from the batch records of the PPQ batches to the current commercial batch records, but the updates were minor and most clarified the procedures and provided additional checks or information. All were acceptable.*

IR #20 dated 14 August 2019

Response received 12 September 2019

Comment 4

We reviewed your responses to question 16 of the CBER IR dated April 05, 2019 and the information regarding your comparability protocol that you provided in section 3.2.R of the BLA. We note that you planned to manufacture (b) (4)

, please submit the comparability protocol for review post approval. We do not agree that a CBE 30 is appropriate for this change. Additionally, we do not agree with your comparability protocol as submitted in section 3.2.R of

the BLA and have included the following comments for your consideration while preparing the comparability protocol. Please note that these comments are not all-inclusive; we may have additional comments after reviewing your submitted protocol. You may wish to request a telecon for discussion of your comparability protocol prior to submission as a future regulatory supplement.

(b) (4)

*On 12 September 2019, Aimmune responded that they will submit a revised comparability protocol for review as a post-approval supplement to the BLA prior to performing any additional studies, and they will take the above points into consideration when designing the protocol. This is acceptable.*

- b. You plan to use AR101 reference standard for side-by-side comparison of (b) (4) . Please confirm that this reference standard is your already established reference standard from a (b) (4) lot that was (b) (4) and please state the lot number of the reference standard that will be used in the comparability protocol. Please state whether in future you will manufacture reference standard from (b) (4) . If you plan to do so, please submit a reference standard replacement protocol using the (b) (4) for prior approval.

*On 12 September 2019, Aimmune responded that for the comparability testing, they plan to use an established reference standard that was manufactured from (b) (4) . They will confirm the lot number in the comparability protocol when the new version is submitted. If a reference standard needs to be prepared from (b) (4) , then the sponsor will submit a reference standard replacement protocol prior to its qualification. This is acceptable.*

The comparability protocol will be submitted as a PAS and was not approved under this BLA. All other deficiencies in this section were resolved satisfactorily.

## Other eCTD Modules

### Module 1

#### A. Environmental Assessment or Claim of Categorical Exclusion

Aimmune states that this product qualifies for a claim of categorical exclusion from the requirement to prepare an environmental analysis, per 21 CFR § 25.31(c). Defer to DMPQ for review.

#### B. Labeling Review

##### Full Prescribing Information (PI):

I provided input to the review of CMC information in the prescribing information.

##### Carton and Container Label:

I provided input to the review of CMC information on carton and container labels.

### Modules 4 and 5

#### Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

No animal studies were performed in the development of this product and the primary clinical endpoints do not require any assays.

### **Aimmune agreements**

Aimmune confirmed that they agree to these agreements in their submission dated 27 January 2020.

1. Aimmune agrees to perform (b) (4) testing of (b) (4) batch of (b) (4) each calendar year for the next (b) (4) years as described in amendment 56 dated 18 November 2019. Aimmune will analyze the data along with the (b) (4) previous lots and submit a report including data from all (b) (4) lots as product correspondence.
2. Aimmune agrees to collect data on a minimum of (b) (4) lots tested by TM-0326 with the new reference standard lot (b) (4) acceptance criteria for (b) (4), as described in amendment 71, received by CBER on 6 January 2020. Aimmune will report the data and any proposed changes to acceptance criteria based on this re-evaluation as a supplement to the license application.
3. Aimmune agrees to collect data on a minimum of (b) (4) lots using (b) (4) to re-evaluate the (b) (4) acceptance criteria for (b) (4) as described in amendments 71 and 74 received by CBER on 6 January 2020 and 15 January 2020. Aimmune will report the data and any proposed changes to acceptance criteria based on this re-evaluation as a supplement to the license application.
4. Aimmune agrees to re-evaluate the (b) (4) results using only the data from commercial lots once a minimum of (b) (4) have been collected for each dose as stated in amendment 71 received by CBER on 6 January 2020. Aimmune will report the data and any proposed changes to acceptance criteria based on this re-evaluation as a supplement to the license application.
5. Aimmune agrees to collect data on a minimum of (b) (4) of drug product manufactured using the commercial process and tested for (b) (4) by TM-0326 using the new reference standard lot (b) (4). Aimmune will re-evaluate the drug product acceptance criteria for each of these assays as described in amendments 57 and 71, received by CBER on 18 November 2019 and 6 January 2019, respectively. Aimmune will report the data and any proposed changes to acceptance criteria based on this re-evaluation as a supplement to the license application.
6. Aimmune agrees to place (b) (4) of 300 mg sachets on stability each year at long term storage conditions of 5°C±3°C and to test them according to the stability protocol described in table 2 of 3.2.P.8.2 of the original submission.
7. Aimmune agrees to put the next (b) (4) lots of qualified reference standard on stability as described in table 12 of module 3.2.S.5 of the original submission.
8. Aimmune agrees to contact CBER to discuss its plans for post-approval reference standard qualification and comparability studies. These plans will include how new reference standards will be tested to determine (b) (4) for each new batch of reference standard. After the discussion, Aimmune will submit its plan as a prior approval supplement before testing a new reference standard.

9. Aimmune agrees to submit a plan for CBER approval before (b) (4) and other critical reagents for the (b) (4) assays, either as a product correspondence or as a comparability protocol.