

CBER DMPQ CMC BLA Review Memorandum

BLA STN 125696

PALFORZIA [AR101/Peanut (*Arachis hypogaea*) oral allergen powder]

**Gregory Price/Biologist/DMPQ
Laura Fontan/CSO/DMPQ**



U.S. FOOD & DRUG
ADMINISTRATION

1. BLA#: STN 125696/0

2. APPLICANT NAME AND LICENSE NUMBER:

Aimmune Thereapeutics, Inc.

3. PRODUCT NAME/PRODUCT TYPE:

PALFORZIA (AR101), Oral Peanut (*Arachis hypogaea*) Allergen Powder

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Oral Peanut Allergen Powder contained in capsules (0.5, 1, 10, 20 and 100 mg) or sachets (300 mg). Capsules are not intended for ingestion. The indication is for use as an oral immunotherapy treatment to reduce the incidence and severity of allergic reactions, including anaphylaxis, after accidental exposure to peanut in patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy.

5. REVIEWER RECOMMENDATION

Based on the information provided with this submission approval is recommended.

6. INSPECTIONAL FOLLOW-UP

Aimmune commits to performing formal validation studies for the blister pack (b) (4) CCIT methods to provide additional assurance regarding the performance of the current method. Aimmune expects to complete these validation studies by the end of first quarter 2020.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Gregory Price, Biologist, DMPQ BI	Concur	
Laura Fontan, CSO, DMPQ BI	Concur	
Carolyn Renshaw, Branch Chief, DMPQ BI	Concur	
John A. Eltermann, Jr, Director, DMPQ	Concur	

Review of CTD Module 2.2

Aimmune Therapeutics, Inc. has developed AR101 for patients with peanut (*Arachis hypogaea*) allergy. The proposed indication for AR101 is to reduce the risk of anaphylaxis after accidental exposure to peanut in peanut allergic patients aged 4 through 17 years old. AR101 drug product consists of peanut flour formulated with (b) (4) and is packaged in graduated doses. The AR101 active pharmaceutical ingredient is sourced as raw peanuts and processed into food grade, (b) (4) defatted, roasted peanut flour that contains approximately (b) (4). The peanut flour is received by the manufacturer CoreRx, Inc. (Clearwater, FL) for further processing to produce AR101 as an oral powder in capsules and sachets. Five capsule dosage strengths of 0.5, 1, 10, 20, and 100 mg, and 1 sachet dosage strength of 300 mg are produced. The contents of the capsules and sachets are emptied and mixed with age-appropriate food for administration.

Module 2.3

The information for the overview of drug substance and drug product is located in 3.2.S and 3.2.P review sections.

Module 2.4

Nothing was submitted in this section.

Module 3

3.2.S DRUG SUBSTANCE

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

This section is deferred to the Product Office.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

2.3.S DRUG SUBSTANCE – AR101

AR101 drug substance is an allergen source material derived from raw shelled peanuts (*Arachis hypogaea*). The active ingredient of AR101 are the allergenic peanut proteins, a natural mixture of proteins termed (b) (4). Of the allergenic proteins, (b) (4) are the most clinically important allergens (immunodominant) and are controlled within the drug substance as described in submission Module 3.2.S.4.1.

AR101 drug substance is a (b) (4) (partially defatted peanut flour – (b) (4) fat – light roast).

3.2.S.2.2 Description of Manufacturing Process

There are no additional manufacturing processes performed on the allergen source material in order to generate the AR101 drug substance.

The source material is manufactured by (b) (4) a food and food ingredients manufacturer who does not operate under pharmaceutical good manufacturing practices (GMPs) and is therefore not classified as a drug substance manufacturer. The source material lot selection process is performed by CoreRx, Inc., a GMP contract pharmaceutical manufacturing organization (Module 3.2.S.2.1).

The source material manufacturing process and process controls are described in Module 3.2.S.2.3

□ Manufacturing process steps

Refer to Packaging and Storage of source material in Module 3.2.S.2.1.

□ Batch Numbering, Pooling and Scale Definition

Not Applicable

□ Storage and Shipping

Refer to Packaging and Storage of source material in Module 3.2.S.2.1.

3.2.S.2.3 Control of Materials


ACCEPTANCE OF ALLERGEN SOURCE MATERIAL AS AR101 DRUG SUBSTANCE (CORERX)

Selection of Source Material Lots for Drug Substance

Source material batches are subject to a selection process before undergoing formal testing and release as drug substance into GMP production. The selection process of source material lots for drug substance is provided in a flowsheet in Figure 3 and a sample Certificate of Analysis is in Figure 4 (Submission Section 3.2.S.2.3). Usually, multiple batches of source material are evaluated against the specification provided in Module 3.2.S.4.1.

(b) (4)

(b) (4)



Rework or reprocessing of either the allergen source material or drug substance are not permitted.

☐ **Control of Raw Materials NOT of Biological Origin**

Not Applicable

☐ **Control of Raw Materials of Biological Origin**

Refer to Module 3.2.S.2.3.

☐ **Control of Starting (i.e., Source) Material(s)**

Refer to Module 3.2.S.2.3.

☐ **Generation of the Seed Stock and Expression Construct (e.g., vector and plasmid)**

Not Applicable

☐ **Cell Banking System - Generation, Characterization, and Testing**

Not Applicable

☐ **Master and Working Viral or Bacterial Seeds**

Not Applicable

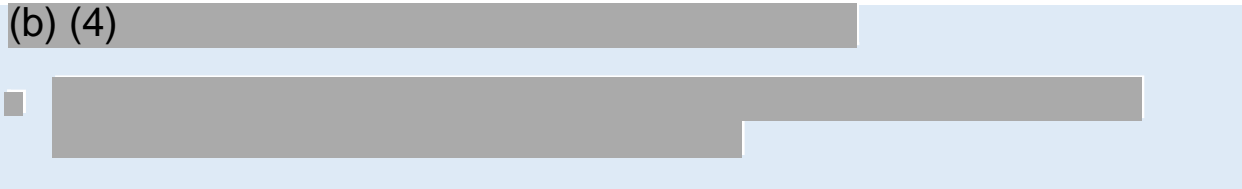
Overall Reviewer's Assessment of Section 3.2.S.2.3:

☐ Acceptable

3.2.S.2.4 Controls of Critical Steps and Intermediates

Submission section contains minimal information and refers to 3.2.S.2.3

(b) (4)

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3.2.S.2.5 Process Validation and/or Evaluation

No Process Validation submitted. Not Applicable

Facility review is in Section 3.2.A.

3.2.S.2.6 Manufacturing Process Development

Manufacturing Process Development is Not applicable

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and Other Characteristics

Defer to Product Office

3.2.S.3.2 Impurities


Defer to Product Office

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)

SPECIFICATIONS (AR101 DRUG SUBSTANCE, CORERX)

(b) (4)

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(b) (4)

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(b) (4)

3.2.P DRUG PRODUCT

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

DOSAGE FORM

AR101 DP is an oral immunotherapy powder that is administered orally following mixing with food. AR101 is available in pull-apart capsules packaged in foil-backed (b) (4) blister

packs and filled into foil-laminate (b) (4) sachets. AR101 is emptied from the capsules or sachets and mixed into food prior to being swallowed.

The dosing regimen for AR101 comprises 3 stages: initial dose escalation, up-dosing, and maintenance.

- Initial dose escalation treatment is given on a single day under a doctor's supervision. Five single doses of 0.5, 1, 1.5, 3, and 6 mg are administered at 20-30 minute intervals as tolerated.
- Up-dosing escalation occurs approximately every 2 weeks with once daily doses of 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg/day.
 - First dose at each dose level is administered under medical supervision using a single dose physician sample.
 - At home administration is comprised of 15 daily doses. Each daily dose is packaged into blister strips presented in paperboard cards to assist in dispensing individual doses. The 300 mg/day sachets are packaged in paperboard cartons containing 15 units.
- Maintenance consists of a once daily dose of 300 mg/day taken at home. The 300 mg sachets are packaged in a paperboard carton containing 30 units representing a 30-day supply.

COMPOSITION

The qualitative and quantitative compositions of AR101 drug product at the individual dose strengths (0.5, 1, 10, 20, 100, and 300 mg) are listed in Tables 2, 3, and 4 below. The proportion

(b) (4) for the lower strengths (0.5 to 20 mg) to achieve (b) (4). The proportion of (b) (4) to manufacture the AR101 powder (b) (4). There are no overages used in the formulations of AR101 drug product capsules or sachets.

Table 2: Qualitative and Quantitative Composition of AR101 Drug Product, 0.5 and 1 mg

Capsule Size		3			
Dosage Strength (Peanut Protein)		0.5 mg		1 mg	
Component	Function	Concentration (b) (4)	Target Weight (mg)	Concentration (b) (4)	Target Weight (mg)
AR101, DS [1]	Drug Substance	(b) (4)			
Partially Pregelatinized Maize Starch	(b) (4)				
(b) (4)					

Microcrystalline Cellulose	(b) (4)	(b) (4)
(b) (4)		
Colloidal Silicon Dioxide	(b) (4)	
(b) (4)		
Magnesium Stearate	(b) (4)	
(b) (4)		
Total Weight		

[1] Actual amount (b) (4) is calculated based upon the Assay (TM-0066 or equivalent) and (b) (4) (TM-0103 or equivalent) of the material to achieve the unit weight listed per capsule. The Master formula values listed in this table assume (b) (4) AR101 drug substance with an (b) (4) Assay value of (b) (4). Range in parenthesis reflects the allowable range based on the potential Assay and (b) (4) values.

[2] (b) (4) of AR101 (b) (4) used to achieve the total weight listed. Allowable range for microcrystalline cellulose is provided in parenthesis.

Table 3: Qualitative and Quantitative Composition of AR101 Drug Product, 10, 20, and 100 mg

Capsule Size		00					
Dose (Peanut Protein)		10 mg		20 mg		100 mg	
Component	Function	Concentration (b) (4)	Target Weight (mg)	Concentration (b) (4)	Target Weight (mg)	Concentration (b) (4)	Target Weight (mg)
AR101 DS [1]	Drug Substance	(b) (4)	(4)	(b) (4)	(4)	(b) (4)	(4)
Partially Pregelatinized Maize Starch (b) (4)	(b) (4)						
Microcrystalline Cellulose (b) (4)	(b) (4)						
Colloidal Silicon Dioxide (b) (4)	(b) (4)						
Magnesium Stearate (b) (4)	(b) (4)						
Total Weight							

[1] Actual amount (b) (4) is calculated based upon the Assay (TM-0066 or equivalent) and (b) (4) (TM-0103 or equivalent) of the material to achieve the unit weight listed per capsule. The Master formula values listed in this table assume (b) (4) AR101 (b) (4) with an (b) (4) Assay value of (b) (4). Range in parenthesis reflects the allowable range based on the potential Assay and (b) (4) values.

[2] (b) (4) of AR101 (b) (4) used to achieve the total weight listed. Allowable range for microcrystalline cellulose is provided in parenthesis.

Table 4: Qualitative and Quantitative Composition of AR101 Drug Product, 300 mg

Sachet Size		2.5 × 3 inch	
Dose (Peanut Protein)		300 mg	
Component	Function	Concentration (b) (4)	Target Weight (mg)
AR101 DS [1]	Drug Substance	(b) (4)	(b) (4)

Microcrystalline Cellulose (b) (4)	(b) (4)	<div>(b) (4)</div>
Colloidal Silicon Dioxide (b) (4)	(b) (4)	
Magnesium Stearate (b) (4)	(b) (4)	
Total Weight		

- [1] Actual amount (b) (4) is calculated based upon the Assay (TM-0066 or equivalent) and (b) (4) (TM-0103 or equivalent) of the material to achieve the unit weight listed per capsule. The Master formula values listed in this table assume (b) (4) AR101 (b) (4) with an (b) (4) Assay value of (b) (4). Range in parenthesis reflects the allowable range based on the potential Assay and (b) (4) values.
- [2] (b) (4) of AR101 (b) (4) used to achieve the total weight listed. Allowable range for microcrystalline cellulose is provided in parenthesis.

CONTAINER CLOSURE

- Blister Packs-the AR101 DP capsules are packaged into (b) (4) blisters with foil-lined backing in combinations of capsule dosage strengths needed to provide the various individual daily doses.
- Sachets-the 300 mg dosage strength consists of a pre-printed 2.5 X 3 inch foil-laminate film.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

We defer to the PO for review of this section.

3.2.P.2.1.2 Excipients

We defer to the PO for review of this section.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

We defer to the PO for review of this section.

3.2.P.2.2.2 Overages

We defer to the PO for review of this section.

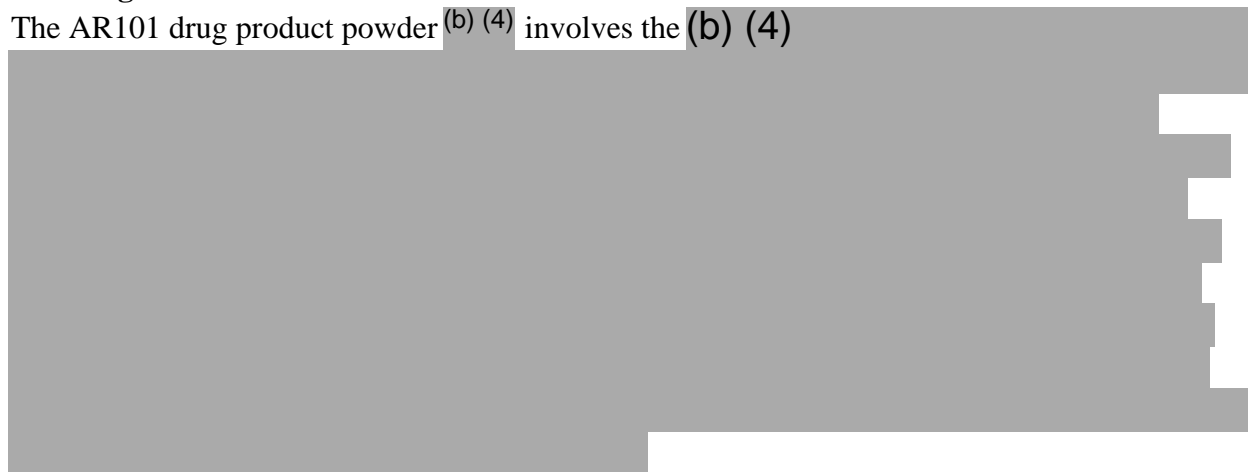
3.2.P.2.2.3 Physicochemical and Biological Properties

We defer to the PO for review of this section.


3.2.P.2.3 Manufacturing Process Development

Blending




The AR101 drug product powder (b) (4) involves the (b) (4)



(b) (4)



(b) (4)



3.2.P.2.4 Container Closure System

The primary container closure system for AR101 drug product consists of either blister strips (initial dose escalation [IDE] card and daily dose packs), individual blisters (physician samples), or sachets. The material components used for primary packaging are described below in Table 1 for the blister strips used in IDE cards and daily dose packs, Table 2 for the individual blisters used for physician samples, and Table 3 for the sachets (Section 3.2.P.2.4 Container Closure System).

Table 1: Summary of the Primary Packaging Components for Blister Strips Used in IDE Cards and Daily Dose Packs

Component	Supplier	Description
Blister base material (b) (4)	(b) (4)	(b) (4)
Lidding (b) (4)	(b) (4)	Push-through blister lidding

(b) (4) .

Table 2: Summary of the Primary Packaging Components for Individual Blisters Used for Physician Samples

Component	Supplier	Description
Blister base material (b) (4)	(b) (4)	(b) (4)
Lidding (b) (4)	(b) (4)	Peel-push blister lidding

(b) (4) .

Table 3: Summary of the Primary Packaging Components for Sachets

Component	Supplier	Description
Sachet foil-laminate (b) (4)	(b) (4)	(b) (4) foil-laminate (b) (4)

(b) (4) .

Blister Packs

Blister packaging was selected as an effective means of allowing combinations of capsules comprising a daily dose to be packaged in a single cavity, making patient dosing both simple and convenient, and reducing the opportunity for dosing errors. The (b) (4) and foil-laminate lidding material closure system are commonly used for packaging of solid oral dosage forms. The AR101 drug product capsules (for commercial distribution and physician samples) are packaged at (b) (4) into clear (b) (4) blister strips with foil-backing.

(b) (4) base was selected for its ability to protect the product from moisture during long-term storage. (b) (4) were performed to determine the moisture (b) (4)

were evaluated and the results from this simulation analysis are summarized below in Table 4 (Section 3.2.P.2.4 Container Closure System).

(b) (4)

Based on the results, a blister with barrier properties equal or greater to (b) (4) is expected to provide adequate protection of the product from (b) (4) uptake during storage at (b) (4) temperature (which represents a worst-case long-term storage condition). To provide additional safety margin, for the AR101 capsule drug product, (b) (4) was selected in part due to its protective barrier properties as the base material. The structure of the (b) (4) blister base film material for commercial use is described in Table 5 below (Section 3.2.P.2.4 Container Closure System).

(b) (4)

This (b) (4) is the same grade that has been used to package all blistered AR101 drug product use in clinical trials.

The blister base material was tested for conformance according to (b) (4) of the blister base material were prepared according to (b) (4) and tested for applicable physicochemical tests (b) (4). The results of the blister base material are presented below in Table 6 (Section 3.2.P.2.4 Container Closure System).

(b) (4)

(b) (4)

The results demonstrate the blister base packaging material meets the (b) (4) requirements for plastic components of containers used to package pharmaceuticals, and it is suitable for its intended use. (b) (4) screening analysis of the blister base film was performed, and any (b) (4) were identified by comparing to a National Institute of Standards and Technology (NIST) spectral library. No (b) (4) were detected above the reporting limit of (b) (4) of the (b) (4) material (the limit of quantitation based on the internal standard (b) (4)). Since AR101 is a solid oral dosage form, (b) (4) would present a minimal risk. Given that no (b) (4) were detected above the reporting limit, the low risk associated with the route of administration, and likelihood of component-dosage form interaction (per (b) (4)) no additional studies were warranted for risks associated with leachables.

Blister Lidding Material

Two different lidding materials are used to seal capsules into the (b) (4) blister base material, to form the primary capsule container closure system: Blister strips for IDE cards and daily dose packs utilize a foil-laminate push-through lidding whereas individual blisters for physician samples utilized a foil-laminate peel-push lidding. Both lidding materials are a foil (b) (4)-laminate film that is (b) (4) to the blister base material during production. The structures of both films are described below in Table 7 (Section 3.2.P.2.4 Container Closure System).

(b) (4)

(b) (4) .

The peel-push lidding material for individual blisters is used because it enables the incorporation of child resistant features. The peel-push lidding has a composite outer layer that must be peeled away before the capsules can be pushed through the (b) (4) foil layer but is otherwise comparable to the push-through lidding used for daily dose packs.

The commercial lidding materials were tested for conformance according to (b) (4) (b) (4) of the foil-laminate were prepared according to (b) (4) and tested for applicable physicochemical tests (b) (4) The results of this testing on the 2 lidding materials are summarized below in Table 8 (Section 3.2.P.2.4 Container Closure System).

(b) (4)

[1] This test was performed in support of (b) (4) Effective

(b) (4)
 (b) (4); NMT, not more than; (b) (4)

The results in Table 8 demonstrate the lidding materials met the (b) (4) requirements for plastic components of containers used to package pharmaceuticals and are suitable for their intended use. (b) (4) analysis of the foil-laminates was performed, and any detectable (b) (4) were identified by comparing to a NIST spectral library. No (b) (4) were detected above the reporting limit of (b) (4) of the (b) (4) material (the limit of quantitation based on the internal standard (b) (4)). This result is consistent with the vendors specified limit of not more than (b) (4). Since AR101 is a solid oral dosage form, (b) (4) would present a minimal risk. Given that no (b) (4) (b) (4) were detected above the reporting limit, the low risk associated with the route of administration, and likelihood of component-dosage form interaction (per (b) (4)) no additional studies were performed for leachables.

Blister Pack (b) (4)

The (b) (4) barrier properties of the commercial blister packs met the performance requirements of (b) (4) (methods (b) (4)). The blister packs can be classified as (b) (4). Results of the studies are provided in Table 9 below (Section 3.2.P.2.4 Container Closure System).

(b) (4)

Both the (b) (4) film and lidding materials used to make the primary capsule container system meet the FDA and EU compliance regulations for food contact. Combined, the lidding and blister base materials provide adequate protection against moisture and are suitable for use and compatible with AR101 drug product.

Sachets

Sachet packaging was selected for the higher volume (300mg) as more patient convenient package while still supplying a reproducible dose. The sachets are made from a (b) (4) foil laminate material that is (b) (4) sides and constitute the primary container closure system for this dosage strength. The foil laminate is composed of (b) (4)

The commercial sachet material was tested for conformance according to (b) (4) and tested for applicable physicochemical tests (b) (4). The results were acceptable and are summarized in Table 11 (3.2.P.2.4). The results demonstrate the sachet foil-laminate material meets the (b) (4) requirements for plastic components of containers used to package pharmaceuticals and is suitable for its intended use.

(b) (4) no additional studies were warranted for risks associated with leachables.

3.2.P.2.5 Microbiological Attributes

MICROBIOLOGICAL ATTRIBUTES (AR101 DRUG PRODUCT, ORAL POWDER)

Quality of AR101 drug product, with regards to microbiological attributes is controlled through drug substance, excipients, manufacturing process, storage conditions, and primary packaging as discussed in Modules 3.2.S.2.3 (source material), 3.2.S.6 (container closure), and 3.2.P.8 (stability data). Testing of drug product for microorganisms is performed according to (b) (4) which are harmonized with the requirements of (b) (4) respectively. The testing is consistent with ICH Q6A and ICH Q6B requirements for non-sterile oral solid dosage products.

(b) (4) FOR AR101 DRUG PRODUCT

AR101 drug product contains low levels of (b) (4). As part of stability protocol (for information only), (b) (4) studies were conducted on lots of AR101 drug product capsule and sachet manufactured by the proposed commercial process and stored at 5°C, (b) (4) relative humidity (RH), and (b) (4). These studies produced results ranging from (b) (4) at the initial and (b) (4) stability time points and are well below the (b) (4) threshold (b) (4) at which microbial growth becomes a concern.

Overall Reviewer's Assessment of Section 3.2.P.2.5:

- ☐ The information supplied for microbiological attributes appears adequate.

3.2.P.2.6 Compatibility

We defer to the PO for review of this section.

3.2.P.3 Manufacture**3.2.P.3.1 Manufacturer(s)****Table 1: AR101 Drug Product Manufacturing and Testing Sites**

Facility Information	Responsibility
CoreRx, Inc. 14205 Myerlake Circle Clearwater, Florida 33760 USA FEI Number: 3007209985 DUNS Number: 780516717 and 080580013	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)
(b) (4)	Manufacturing (blister packaging of capsules, secondary packaging, and labeling of blistered capsules and sachets)
Aimmune Therapeutics, Inc. [1] 8000 Marina Boulevard, Suite 300 Brisbane, California 94005 USA FEI Number: NA DUNS Number: 057562771	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))

[1] Site does not have a FEI Number.

[2] Laboratory performs the indicated testing under contract with CoreRx, Inc.

[3] Site complies with provisions of ISO 17025 “General Requirements for the Competence of Testing and Calibration Laboratories.”

DUNS, Data Universal Numbering System; FEI, FDA Establishment Identifier; NA, not applicable.

3.2.P.3.2 Batch Formula

We defer to the PO for review of this section.

3.2.P.3.3 Description of Manufacturing Process

The commercial manufacture of AR101 drug product involves (b) (4) operations which are listed in Table 1 below (Section 3.2.P.3.3.-Description of Manufacturing Process and Process Controls).


(b) (4)

(b) (4)

(b) (4)

14 pages determined to be not releasable: (b)(4)

(b) (4)



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

- ☐ The information provided for the manufacturing process is acceptable and complete. No additional information required.


3.2.P.3.4 Controls of Critical Steps and Intermediates

Control of Critical Steps for AR101 Powder (b) (4)


AR101 powder (b) (4) is the (b) (4) process intermediate (b) (4). The critical process parameters associated with the production of AR101 powder (b) (4) are summarized in Table 1 below (Section 3.2.P.3.4-Control of Critical Steps and Intermediates).

(b) (4)

(b) (4)



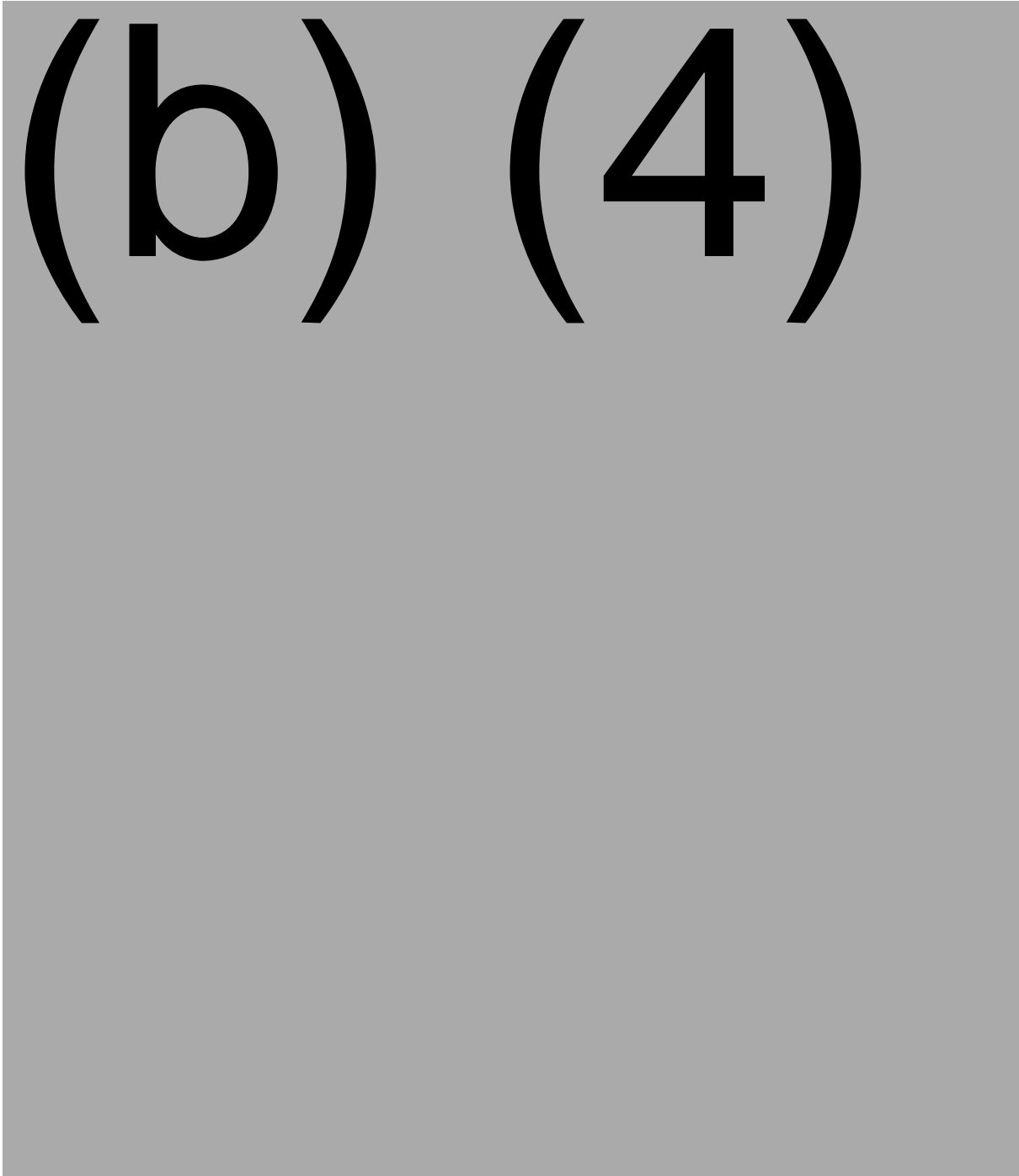
(b) (4)

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Control of Critical Steps for AR101 Capsule Drug Product

The critical process parameters and IPTs associated with the production of the AR101 capsule drug product are summarized below in Tables 4 and 5, respectively (Section 3.2.P.3.4-Control of Critical Steps and Intermediates).

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

Control of Critical Steps for AR101 Blister Drug Product

The critical process parameters for the blister drug product are summarized in Table 13 below for blisters strips packaged for initial dose escalation (IDE) and for daily dose packs used for in-home up-dosing. It was determined that (b) (4)

(b) (4) These parameters were developed for each (b) (4) used in the blister forming operation.

6 pages determined to be not releasable: (b)(4)

(b) (4)

Control of Critical Steps for AR101 Sachet Drug Product



During AR101 manufacturing process development for drug product sachets, critical process parameters and In Process Controls were identified. These limits are summarized below.

AR101 Sachet Drug Product – Critical Process Parameters

(b) (4)

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

(b) (4)



Overall Reviewer's Assessment of Section 3.2.P.3.4:

The information provided for the (b) (4), hold time, capsule and sachet filling, and blister packaging is adequate. Sachet (b) (4) test method qualification was not available during the inspection conducted in June 2019. The firm could not provide rationale for the adequacy of the test method or the use of a (b) (4) used for the positive control. As a response to the 483 item, the firm will qualify the testing method and supply rationale to support the adequacy of the sachet (b) (4) test. (b) (7)(E)

□

3.2.P.3.5 Process Validation and/or Evaluation

Process Validation of Powder (b) (4), Encapsulation, and Sachet Filling

For the manufacture of AR101 drug product at CoreRx (blend, encapsulation, and/or primary packaging of sachets), validation activities were performed under separate protocols for each dosage strength within each unit operation in accordance to the AR101 drug product manufacturing PPQ Master Plan. The AR101 drug product PPQ lot genealogy and list of batch records used are summarized in Table 2 below (3.2.P.3.5- Process and/or Evaluation-AR101 Drug Product).

(b) (4)

28 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.5:

- The PPQ results for powder (b) (4) and encapsulation were all within acceptance criteria. The deviations that occurred were minor and adequately resolved. In addition, these deviations had no impact to the safety and quality of the product. The results provided in the submission are acceptable.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

Not Applicable

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

ANALYTICAL PROCEDURES FOR EXCIPIENTS

The excipients microcrystalline cellulose (MCC), partially pregelatinized maize starch, colloidal silicon dioxide, and magnesium stearate used in the manufacture of AR101 capsules and sachets are (b) (4) compendial materials.

These excipients are tested in full compliance in accordance with the current version of the (b) (4). The analytical procedures are described in the monographs. Therefore, the analytical procedures are not described here.

In addition to testing in accordance with the monographs, these excipients are tested and controlled by the manufacturers for functionally-related characteristics that are relevant physical properties. These excipients are controlled for (b) (4). The quality attributes and acceptance criteria for these physical properties testing that are performed by the excipient manufacturers are reported on their respective certificates of analysis.

ANALYTICAL PROCEDURES FOR CAPSULES

Capsules upon receipt are visually inspected against purchasing and receiving specification and component specification. Capsules are sampled and visually inspected at the AR101 drug product manufacturing site for defects according to acceptable quality levels and sample sizes as defined in ANSI/ASQ Z1.4-2008. For critical, major, and minor defects, the acceptable quality levels are (b) (4) respectively. (b) (4) of capsule (b) (4) are measured with a (b) (4).

Capsules are tested for chemical, physical, and microbiological attributes by the manufacturer of the capsules. Drug Master Files were filed by the capsule shell manufacturers for further information.

VALIDATION OF ANALYTICAL PROCEDURES (AR101 DRUG PRODUCT, ORAL POWDER)

The excipients microcrystalline cellulose (MCC), partially pregelatinized maize starch, colloidal silicon dioxide, and magnesium stearate used in the manufacture of AR101 capsules and sachets are (b) (4) compendial materials, and they are tested in accordance to the (b) (4) monographs. There are no additional analytical procedures beyond the requirements of compendial testing ((b) (4)) used for testing the lots of excipients for release to manufacture AR101 drug product.

For release, the incoming capsule shells are visually inspected for appearance, defects, and verification of labeling information and manufacturer's certificate of analysis. Capsule (b) (4). As these are simple methods, no validation of these methods is required.

3.2.P.4.4 Justification of Specifications

CoreRx maintains the excipients microcrystalline cellulose (MCC), partially pregelatinized maize starch, colloidal silicon dioxide, magnesium stearate, and capsules are tested in accordance with the specifications set for each material to ensure quality and safety of the materials used in AR101 drug product. A representative certificate of analysis, including the

testing by AR101 drug product manufacturer and by the excipient were provided in Section 3.2.R.1.

The above excipients and capsules are (b) (4) compendial materials and are tested in accordance to the (b) (4) monographs and released against the specifications in these monographs. The excipients also meet the (b) (4) requirements for (b) (4). As a part of the overall risk assessment for (b) (4) lots each of the excipients MCC, partially pregelatinized maize starch, colloidal silicon dioxide, and magnesium stearate were tested for (b) (4)

Capsules are tested for (b) (4) attributes by the manufacturer of the capsules. The capsules for AR101 drug product meet the (b) (4) requirements for (b) (4). Conformance with the (b) (4) requirements is certified by the manufacturers.

3.2.P.4.5 Excipients of Human or Animal Origin

Aimmune confirmed that all excipients, including hydroxypropyl methylcellulose (HPMC) capsules, in AR101 drug product are not produced from materials of human or animal origin. The HPMC capsules are produced from a (b) (4) source. The excipients magnesium stearate, starch, colloidal silicon dioxide, and microcrystalline cellulose are produced from a (b) (4) source or derived from synthetic materials.

3.2.P.4.6 Novel Excipient

N/A

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

- ☐ The information provided in this section is acceptable. All materials are (b) (4) compendial materials, and they are tested in accordance to the (b) (4). No further inquiries required.

3.2.P.5 Control of Drug Product

We defer to the PO for this review.

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

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

We defer to the PO for review of these sections.

3.2.P.5.4 Batch Analyses

We defer to the PO for review of this section.

3.2.P.5.5 Characterization of Impurities

We defer to the PO for review of this section

3.2.P.6 Reference Standards or Materials

We defer to the PO for review of this section

3.2.P.7 Container Closure System

AR101 drug product is available in either capsules enclosed in blister strips or sachets. The capsules are made from hydroxypropyl methylcellulose (HPMC) and are color coded and sized 00 or 03 according to dosage. The capsules are not meant to be swallowed but are used to hold the defined amount of AR101 and upon use the capsule is pulled apart and the DP is poured into food. The primary container for the capsules are blister strips manufactured using a (b) (4) base material and (b) (4) Push Through lidding. The blister strip is also packaged in a paperboard card which provided access to each of the individual doses on the blister strip.

Blister strips are manufactured in either 8-count or 7-count strips. The 7-count and 8-count blister strips are manufactured using (b) (4) base material and (b) (4) Push Through lidding material. For a given dose level, one 7-count and one 8-count blister strip are packaged in a paperboard card with child-resistance features to make a daily dose pack that is used by patients for dosing at home over 2 weeks (15 doses in total).

The individual blisters (physician samples), are manufactured using (b) (4) base material and (b) (4) Peel Push lidding material. (b) (4) . Note the individual blisters may contain more than 1 capsule. For example, the 3 mg dose contains 3 × 1 mg capsules.

Blister Base Material

(b) (4) manufactures, tests, and releases the blister base material. (b) (4) versions of the same base material, differing only in (b) (4) , are used for the 7-count, 8-count, and individual blister strips (b) (4) width) and IDE blister strips (b) (4) width), respectively. (b) (4) performs the blister packaging of AR101 drug product, see Module 3.2.P.3.1 and Module 3.2.P.3.3 for additional information. (b) (4) receives the (b) (4) blister base materials and tests them for product conformance. The (b) (4) incoming specifications for the blister base material are listed in Table 7 (b) (4) web width) and Table 8 (b) (4) web width) below (Section 3.2.P.7-Container Closure System).

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

(b) (4)

Representative (b) (4) specification release forms and representative certificates of analysis of the (b) (4) blister base materials from (b) (4) were provided with this submission.

Blister Pack Lidding

The push-through (for IDE and 2-week daily dose packs) and peel-push (for individual blisters) lidding materials are manufactured, tested, and released by (b) (4) receives (b) (4) types of these lidding materials and tests them for product conformance. (b) (4) versions of the

push-through lidding, differing (b) (4), are used to manufacture the blister strips that go into the daily dose packs (b) (4) width) and the IDE blister strip that goes into the IDE card (b) (4) width). The peel-push lidding material (b) (4) width) is used to manufacture the individual blisters provided as physician samples. The (b) (4) incoming specifications for the lidding materials are listed in Tables 9, 10, and 11 below (Section 3.2.P.7-*Container Closure System*).

(b) (4)

(b) (4)

Representative (b) (4) specification release forms and representative certificates of analysis from (b) (4) for each lidding material were provided in the submission.

Blister Pack Secondary Packaging

IDE blister strips with push-through lidding are packaged into paperboard cards to assist in dispensing individual doses in a clinical setting. The individual blisters for physician samples are packaged into 12 or 18 count cartons depending on the dose level. Seven-count/8-count

blister strips are packaged into paperboard cards (daily dose packs) to assist in dispensing individual doses and provide child resistant features for product used by the patient in the home.

Blister Pack CCIT Method at (b) (4)

The blister strips CCIT method is a (b) (4) test. The method is summarized in the (b) (4) standard operation procedure (b) (4). The test parameters are summarized in the blister packaging batch records. The blister strips CCIT test is implemented as an in-process check for the blister packaging process. The in-process test is performed (b) (4) during blister packaging. Representative test results from the blister packaging machine performance qualification studies are summarized in Table 5 below (Obtained from *Response to FDA Information Request #1 (FDA Email Correspondence dated 14 March 2019; eCTD 0009)*).

Table 5: Blisters CCIT Results

Lot	(b) (4)
Blister configuration	
Number of samples tested	
Results	

(b) (4) testing is performed to demonstrate adequate sealing of the blister strips. In table 5 above, representative blister packs were tested for the various lots with no (b) (4) observed. This is an in-process test which demonstrates adequate sealing throughout the process. At present, sealed blister strips are also being used in stability studies and data has been compiled up to (b) (4) months. All commercial stability samples have passed acceptance criteria for potency, capsule integrity, (b) (4), microbial limits and (b) (4). No concerns noted with blister pack CCIT.

PRIMARY PACKAGING – SACHET

AR101 drug product, 300 mg, is filled into sachets made from a (b) (4) foil-laminate film. The foil-laminate is manufactured, tested, and released by (b) (4). The supplier information for the foil-laminate used to make the sachet are provided in the submission Section 3.2.P.7, Table 12. The (b) (4) foil-laminate is received and tested for conformance at CoreRx. The proposed CoreRx incoming specification for the general attributes of the foil-laminate used for physician and maintenance dose strengths is listed in Section 3.2.P.7, Table 14. (b) (4)

(b) (4) feature to aid in opening the sealed packet during administration. The ink used to print the label graphics for the sachets are separated from the product by the impermeable (b) (4) foil layer and are not expected to come into contact with the product.

A representative certificate of analysis (COA) of the foil-laminate from (b) (4) is provided Submission Section 3.2.P.7, Attachment 34. The proposed final artwork is included in Module Section 3.2.P.7, 1.4.1.1.

SECONDARY PACKAGING – SACHET

The sachets are packaged in a paperboard carton. The 2-week up-dosing carton and physician sample carton each contain 15 units and the maintenance carton contains 30 units.

Overall Reviewer's Assessment of Section 3.2.P.7:

- ❑ The submission adequately explained the sachets. Container closure for sachets is adequately described in Module 3.2.P.3.4. The submission adequately explained the blister packs and lidding. CCIT performed at (b) (4) adequately demonstrates blister pack integrity. No further inquiries.

3.2.P.8 Stability

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

The proposed commercial shelf-life for AR101 drug products is 24 months at the refrigerated storage condition (2 to 8°C). This is based on primary (registration) stability study data with completed (b) (4) months testing after storage at 2 to 8°C and (b) (4) relative humidity (RH).

The AR101 drug product stability studies included long term stability studies with the (b) (4) primary (registration) lots and (b) (4) commercial-scale lots, both conducted at 2 to 8°C (b) (4) RH. In addition, supportive studies were conducted with the (b) (4) commercial-scale lots at the accelerated storage condition (b) (4) and (b) (4) 0.5 mg commercial-scale lots at the intermediate storage condition (b) (4) development studies with the 300 mg sachet, a (b) (4) study, and a (b) (4) study using select drug product dosage strengths. A description and discussions on the (b) (4) approach, the analytical methods and specifications, and the data analysis approaches used for the stability studies are presented in Module 3.2.P.8.3 along with the stability data tables, plots, and conclusions from each study.

The drug product (AR101) stability program included studies for capsules of different strengths (0.5, 1, 10, 20, and 100 mg) and sachets (300 mg). For AR101 capsules, these strengths are combined into appropriate blister packaging dose configurations to achieve the different dose levels. The stability studies were conducted in compliance with ICH Guidance for Industry Q1A(R2) “Stability Testing of New Drug Substances and Products”.

AR101 drug product's quality attributes tested include the potency, protein integrity, protein content, (b) (4), and microbiological properties. The dosage strengths studied only differed in the concentration of the drug substance and/or main (b) (4) so a (b) (4) approach was used.

Stability testing results review for AR101 drug product quality attributes other than microbial properties (b) (4) testing results, are deferred to the product office.

Primary Lots

Testing for microbiological limits and (b) (4) for the Phase 3 Drug Product capsule and sachet lots was required at the following timepoints: time 0, 3, 6, 12, 15, 18, 24, and (b) (4) months. Additional testing for microbial limits and (b) (4) was performed on certain lots and timepoints. See Module 3.2.P.8.3, Section 2.3.5, Table 9 for a complete record of all testing and results.

The results for all microbiological limits (b) (4) testing remained within specification for (b) (4) months storage at both the 2 to 8°C and the (b) (4) RH storage conditions. The only confirmed OOS results were observed were for lot (b) (4). The (b) (4) levels for lot (b) (4) were above specification at the 2 to 8°C condition due to a packaging issue which was subsequently corrected. This lot was removed from the stability study after the investigation concluded, and lot (b) (4) was therefore not considered a primary stability lot. A detailed discussion of lot (b) (4) out of specification results observed is presented in Module 3.2.P.8.3, Section 2.4.

Stability data at the 2 to 8°C condition, (b) (4) RH condition, and Data comparisons of 2 to 8°C and (b) (4) RH conditions are summarized in Module 3.2.P.8.3, Section 2.1, Section 2.2 and Section 2.3, respectively.

Commercial Lots

Testing for microbiological properties for the commercial lots is required at the following timepoints: time 0, 1, 3, 6, 9, 12, 18, 24, (b) (4) months. Any microbial growth is required to be speciated if found.

(b) (4) commercial scale lots have been placed on stability. Nine months data are available for (b) (4) commercial scale lots placed on stability in August 2018 while 3 months data are available for the additional (b) (4) lots placed on stability in February 2019.

For microbial limits and (b) (4) remained well within the specification limits of not more than (b) (4), respectively. Similar to the primary stability data, growth has been detected on several occasions on (b) (4). There was no observable trend with either different storage conditions or different dosage strengths. For the commercial stability lots, the identified organisms in most cases have been of the (b) (4) group. (b) (4) and the members of (b) (4) group are considered non-pathogenic and their counts observed were well below the infectious dose of pathogenic (b) (4). Refer to Module 3.2.P.8.3, Section 3.8.

(b) (4) testing is performed in support of microbial safety but is currently being monitored for information only with no established acceptance criteria. This testing was performed for (b) (4) commercial stability lot for the 2 to 8°C, (b) (4) RH, (b) (4) RH and (b) (4) RH storage conditions. The highest (b) (4) result was seen for the (b) (4) RH storage condition of (b) (4)

The values remained well below accepted threshold values supporting microbial growth. The (b) (4) levels in the AR101 drug product at all conditions remained well below levels suggested to support growth of microorganisms as described by (b) (4) which are (b) (4) for most organisms. No significant trend was observed across dosage strength and across all storage conditions.

Development Studies conducted for 300 mg Sachet in (b) (4) foil-laminate sachets remained within product specifications over the course of the study. (b) (4) evaluated at (b) (4) RH for (b) (4) months, while the (b) (4) evaluated at (b) (4) storage conditions (2 to 8°C, (b) (4) RH) for (b) (4) months in an on-going study (Section 6). The microbiological data from these 2 studies support the suitability of the foil laminate proposed for sachets and demonstrate product stability at accelerated conditions.

Microbial properties were not tested in the (b) (4) Studies or (b) (4) Study.

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

REGISTRATION STABILITY BATCHES

AR101 drug product stability study data to (b) (4) months are available for the 1, 10, 20, and 100 mg capsules from registration (primary) stability lots. These stability studies are complete. Stability data to 24 months are available for the 0.5 mg capsules and 300 mg sachets from registration (primary) lots. Aimmune commits to continue the long-term registration stability studies of drug product batches (0.5 mg capsules and 300 mg in sachets) up to (b) (4) months.

COMMERCIAL SCALE STABILITY BATCHES

Stability studies for (b) (4) commercial scale stability lots are ongoing. Aimmune commits to continue the stability studies of these drug product batches manufactured and placed on stability, which use the proposed commercial manufacturing and packaging processes.

Aimmune placed on stability (b) (4) additional commercial lots in 1Q2019 using the same stability protocol up to (b) (4) months.

ANNUAL COMMITMENT

For future commercial batches of AR101 drug product based on the guidelines provided in ICH Guidelines Q1A and Q5C, Aimmune commits to place on stability (b) (4)

The dosage strengths will continue to be placed on stability following the same dosage strength (b) (4) of

(b) (4)

strengths the following year).

All dosage strengths will be placed on stability at the long-term storage condition of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ according to the protocol in Table 2 below (Section 3.2.P.8.2-Postapproval Stability Protocol and Stability Commitment).

(b) (4)

The primary packaging container closure systems for AR101 drug product packaged in blisters and sachet configurations will be used for stability setup of all post-approval drug product lots. For consistency between all stability studies and with current commercial-scale stability studies, capsules for the 0.5 to 100 mg dosage strengths will be set (b) (4) using the commercial blister cavity configurations shown in Table 3 below (Section 3.2.P.8.2-Postapproval Stability Protocol and Stability Commitment).

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

(b) (4)

For any given capsule dosage strength, the blister cavity listed in Table 3 above for that dosage strength represents the worst case in terms of the susceptibility of the capsule to environmental conditions such as ambient moisture. Therefore, the stability of a given capsule in the blister cavity listed in Table 3 is representative of the stability of that capsule in all other blister cavities in which it is packaged.

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

- Shelf-life stability data demonstrate product integrity up to at least 24 months and (b) (4) months for some of the doses. The current shelf-life is 24 months at 2 to 8°C, which is justified based on the current stability data. Aimimmune has committed to placing product on hold annually. The data presented here is acceptable.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Facilities

CoreRx

The CoreRx facility consists of (b) (4) buildings with manufacturing suites, QC laboratories, and warehouses. There is a dedicated AR101 commercial manufacturing suite, a clinical manufacturing suite, development laboratories, and a warehouse located in the (b) (4) building. The warehouse is used primarily for the storage of raw materials (primarily excipients and packaging materials) used for the manufacture of product. The testing laboratory for raw materials and products is located in a different building on the CoreRx site (b) (4).

AR101 drug product commercial manufacture is performed in Building (b) (4) Area (b) (4). Area (b) (4) is a dedicated suite for the commercial manufacture of AR101 and occupies approximately (b) (4) of the approximately (b) (4) of available space in (b) (4). Area (b) (4) can only be accessed from the materials/equipment corridor (Area (b) (4)) and the personnel entry/egress corridor (Area (b) (4)). Area

(b) (4) is serviced by a dedicated heating, ventilation, air conditioning (HVAC) system, (b) (4) which controls temperature and humidity in the commercial manufacturing suite.

The cGMP manufacturing facilities in (b) (4) are designed to ensure the following:

- Buildings and facilities are of adequate size to facilitate the various manufacturing activities carried out therein. The process rooms are maintained at ISO Class (b) (4) cleanroom per ISO 14644-1:2015 standards: Cleanrooms and associated controlled environments, Part 1 - Classification of air cleanliness by particle concentration.
- The AR101 manufacturing suite is equipped with a HVAC system, which includes high efficiency particulate air (HEPA)-filtered supply air to clean rooms. A (b) (4) airlock design is used to maintain air pressure differential between the process rooms and the airlock to the non-good manufacturing practice (GMP) corridor. (b) (4) studies and ongoing monitoring ensure that a positive pressure cascade with a minimum pressure differential of (b) (4) is maintained from the airlock to the processing rooms and from the airlock to the non-GMP corridor.
- Flow of materials, equipment, and personnel were carefully considered to prevent contamination. Material and equipment utilize a dedicated pass-through corridor when entering the AR101 commercial suite. This corridor is separate from the entrances and exits utilized for personnel flow. An (b) (4) step is required for material entering and existing the AR101 suite and processing room to ensure cleanliness of the room and prevent allergens exposure outside the commercial manufacturing suite.
- An environmental monitoring (EM) program is established. There are EM standard operating procedures, established action limits for monitoring viable microbial count and non-viable particulate count.
- Manufacturing and laboratory personnel are trained to gown/de-gown upon entry and exit into the AR101 commercial manufacturing area. A full coverall gown, hair net, shoe covers, and gloves are required when entering the manufacturing suite.
- Facilities, critical utilities, equipment, and processes are qualified in the AR101 manufacturing suite.
- Coolers for the storage of (b) (4) drug product are qualified.
- Cleaning validation is performed for all manufacturing equipment to demonstrate the effectiveness of the established cleaning procedures.

- Warehouse is qualified with mapping for temperature and humidity uniformity.

A detailed layout of the commercial AR101 drug product manufacturing suite (Area ^{(b) (4)} is presented below (Taken from Facilities and Equipment 3.2.A.1).

(b) (4)

(b) (4)

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

(b) (4) and warehouse (Area (b) (4)) at the back entrance. In addition, the air flows and environmental conditions in the AR101 commercial manufacturing suite are controlled by a dedicated HVAC system.

There are 5 major equipment/utility systems which support the AR101 commercial manufacturing suite and the manufacturing operations performed there:

1. Building management system
2. HVAC system
3. Purified Water System
4. (b) (4) Air System
5. Coolers (2-8°C)

1. Building Management System (BMS)

The BMS is a computer and programmable logic controller (PLC) based system that monitors and records data and provides alarms for selected facility environmental conditions (temperatures, relative humidities and differential pressures). In addition, the BMS provides operational data for the purified water system, the compressed air system, the coolers, and the current operational status for the HVAC system. The BMS monitors the areas/equipment and associated attributes as shown in Table 2 below.

Table 2: Building Management System Inputs

Area/Equipment	Inputs
Warehouse	(b) (4)
Clinical Suite	
AR101 Commercial Suite	
Purified Water System	
Compressed Air System	
Door Interlocks	
Coolers	

There are room status indicators on the BMS monitor located in the AR101 commercial manufacturing suite to show the processing rooms status. A green-light indicator indicates the monitored criteria of the processing room are within acceptable limits. The status of each alarms is also shown on the BMS monitor. Simultaneously, the alarm will also trigger a red-light indicator and an audio buzzer at the HMI terminal located inside the manufacturing suite.

2. HVAC System

The (b) (4) facility uses independent HVAC air handling unit for each manufacturing suite (ie, AR101 commercial manufacturing suite, clinical suite, and future suite) as well as separate systems for warehouse and sampling rooms. The Air Handling Unit (b) (4) is designed to control and maintain temperature and dehumidification within the AR101 commercial

manufacturing suite to predetermined set points. Dehumidification is controlled by a (b) (4). Temperature is maintained by a thermostat mounted in the area of the building served by the HVAC unit and is only adjustable through a secure (b) (4) accessible with an authorized user name and password. The HVAC system is equipped with a humidifier to assist with maintaining the specified Relative Humidity (RH) of (b) (4).

(b) (4) is equipped with a HEPA filter (b) (4) with efficiency not less than (b) (4) percent when tested in accordance with (b) (4).

HEPA filtration and a local speed controller. This post HEPA air filtration/purification system is designed to remove (b) (4) particles and to ensure cleanliness.

The AR101 (b) (4) powder (b) (4) are contained by a differential pressure cascade maintained between processing areas. The building design principle behind the differential pressure cascade is to keep the peanut allergen contained within the rooms while at the same time preventing the ingress of outside contaminants from the warehouse and other common areas of the building. This principle is achieved by (b) (4) air flow induced by the differential pressure cascade. The pressure differential direction is designed to have the highest pressure at the cleanroom next to the uncontrolled corridor and the room pressure cascades down to each processing rooms (ie, (b) (4) room). The intent of this airflow design is to contain the powder (b) (4) within the process room and prevent particles or contaminants from entering the AR101 commercial manufacturing suite from the corridor.

3. Purified Water

The purified water (PW) System is a (b) (4) water purification system manufactured by (b) (4). The PW system uses (b) (4) to produce and convey purified water (See Figure 10 below for schematic).

(b) (4)

The predominant piping of the PW loop is (b) (4) in the system. This prevent entrapment of foreign materials and the possibility of bacterial growth and contamination. The produced purified water is used for (b) (4). The PW system has (b) (4) monitoring of (b) (4).

The PW is designed to meet the definition of purified water according to (b) (4) and to meet the criteria listed in Table 3 below. The PW is also compliant with the water quality guidance in (b) (4).

(b) (4)

There are (b) (4) PW drops in the CoreRx (b) (4) facility. They are in the (b) (4)

The purified water system functionality was verified over a period of (b) (4) days during system performance qualification.

The continuous monitoring program (CMP) of the purified water system is designed to ensure the PW system continues to produce PW consistently meeting the established acceptance criteria. The CMP monitors water for (b) (4) based on a set schedule for each point of use (POU).

4. (b) (4) System for Producing Compressed Air

The (b) (4) is used to produce and provide clean, compressed air to various POU in the (b) (4) facility. The air produced by the (b) (4) system is used to (b) (4) for some equipment. The system is equipped with a redundant compressor and is designed for a minimum supply pressure of (b) (4) (pneumatic usage) at each point of use.

The system is comprised of (b) (4)

The compressors are equipped with (b) (4)

is also provided. The front panel contains the (b) (4) control module with the start/stop button and an emergency stop button. The electric cabinet containing fuses, transformers, etc., is located behind this panel.

The system provides clean, compressed air to various points of use in the facility. The use points in the AR101 commercial facility are located in (b) (4). The (b) (4) system was qualified over (b) (4) consecutive business days through (b) (4) sampling for air purity at all use points according to ISO 8573-1:2010 (Compressed Air Contaminants and Purity Classes). Air purity specifications in (b) (4) are based upon risk and/or use of the compressed air system.

Figure 11 below shows the layout of the (b) (4) system components. (b) (4)

which is connected to the piping out to POU ports.

(b) (4)

The compressed air system has been classified as indirect product contact during qualification. Indirect contact testing is performed on a (b) (4) basis for the (b) (4) year and (b) (4) thereafter with a classification of (b) (4). The compressed air system has been qualified and it met criteria listed in Table 4 below.

(b) (4)

5. Coolers

(b) (4) /drug product coolers are installed in the (b) (4) facility to store AR101 (b) (4) drug product (capsules and sachets) 2 to 8°C. These cooler systems (b) (4).

Each cooler is an (b) (4) were qualified and temperature mapping was performed to ensure the consistency of storage condition within the cooler. The cooler is maintained between 2 to 8°C.

6. Environmental Monitoring

The effectiveness of the facility's cleaning program and the HVAC filtration system are assessed through environmental monitoring of the following items within the manufacturing area.

- (b) (4) [REDACTED]

Environmental monitoring and testing aspects of the AR101 commercial manufacturing suite are summarized below.

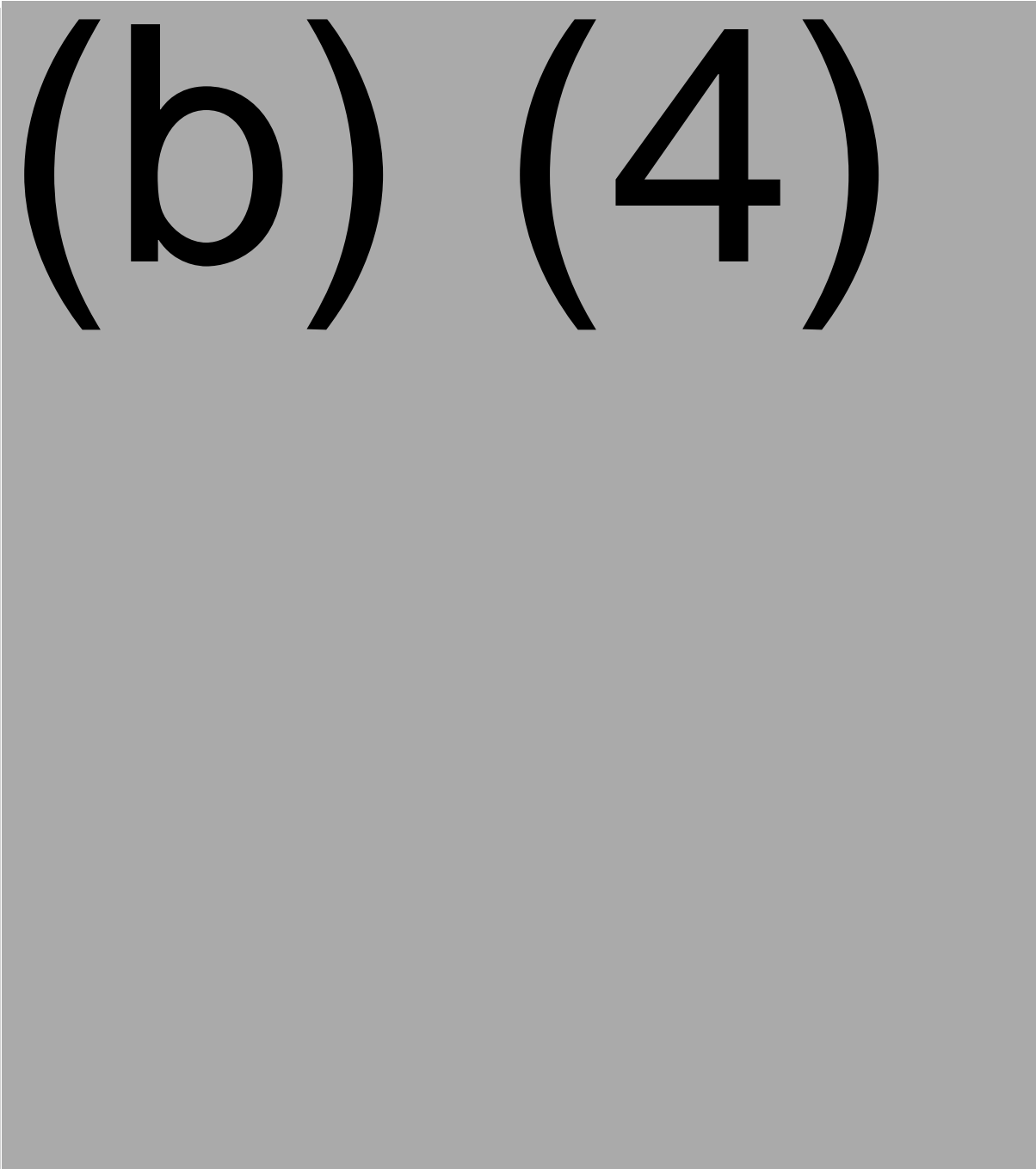
- (b) (4) [REDACTED]

(b) (4)

(b) (4)
(b) (4) is a contract manufacturing firm that specializes in primary and secondary packaging of AR101 capsules in blister strips and secondary packaging of AR101 sachets. The (b) (4) facility contains manufacturing suites, warehouses, and refrigerated storage facilities. The (b) (4) floor plan was submitted in section 3.2.A.1 *Facilities and Equipment* and the suite dedicated to AR101 manufacturing highlighted (Suite (b) (4)). The suite has a (b) (4) which is designed to contain the allergen within the blistering room and to prevent conveyance of material from common areas into the blistering room. The secondary packaging room are in areas (b) (4)

(b) (4) currently processes (b) (4) products, AR101, (b) (4) product. Both manufacturing areas of the (b) (4) are completely separated from the AR101 blistering area.

To prevent potential cross-contamination, the air flows and environmental conditions in the AR101 primary packaging suite (Suite (b) (4)) are controlled by a (b) (4) HVAC system. The AR101 drug product is contained in Suite (b) (4) (primary packaging) by a differential pressure cascade maintained between the packaging room and the vestibules as illustrated in Figure 13 below (3.2.A.1 *Facilities and Equipment*).



The building design principle behind the differential pressure cascade is to keep the allergen contained within the rooms while at the same time preventing the ingress of outside contaminants from the warehouse and other packaging areas of the building. This principle is achieved by (b) (4) air flow induced by the differential pressure cascade as illustrated in Figure 13 above.

The cGMP packaging facilities is designed to ensure the following:

- Buildings and facilities are of adequate size to facilitate different packaging processes.
- The controlled areas have a dedicated HVAC system, which includes HEPA-filtered supply air to the (b) (4) rooms. A pressure cascade design is setup to maintain air pressure differential between the (b) (4) rooms and the (b) (4). There is ongoing monitoring to ensure that a pressure cascade is maintained from the (b) (4).
- Material, equipment, and personnel flows Figure 14 are standardized with dedicated gowning area to the primary packaging room to prevent cross contamination.
- An EM program is established.
- Manufacturing and laboratory personnel are trained and qualified to gown/de-gown upon entry and exit into the manufacturing area. A lab coat cover, hair net, and shoe covers are required when entering the manufacturing suite.
- Facility and equipment qualifications and process validations are conducted per (b) (4) established procedures.

(b) (4) **Supporting Utility Equipment**

Two major equipment/utility systems support the AR101 commercial packaging facility and its operation

- HVAC
- Cooler

HVAC system

There are multiple HVAC systems used to control temperature, airflow within the control area and the primary packaging room (Suite (b) (4) has its own dedicated HVAC system. The HVAC system is fitted with a HEPA filter (b) (4) rated with efficiency of (b) (4) percent. The environment of the manufacturing area is monitored per approved work instruction for (b) (4) samples. The (b) (4) sampling is performed (b) (4) and the (b) (4) sampling is performed (b) (4) in the packaging rooms.

Coolers

Cooler (b) (4) is used for the storage of (b) (4) and packaged products. The cooler was qualified and temperature mapping was performed to ensure the consistency of storage condition within the cooler. The cooler is maintained between 2 to 8°C.


MANUFACTURING EQUIPMENT

CoreRx

The following equipment are dedicated for the AR101 commercial manufacturing process.

- (b) (4)

(b) (4)



EQUIPMENT CLEANING

The risk of potential product cross contamination has been minimized because the AR101 commercial manufacturing suite at CoreRx (b) (4) is a product-dedicated suite with dedicated manufacturing equipment.

However, the AR101 product line includes 6 dosage strengths: 0.5, 1, 10, 20, 100, and 300 mg and (b) (4) of the 6 dosage strengths (0.5, 1, 10, 20, and 100 mg) share common equipment for both blending and encapsulation. The primary risk of using common equipment among different dosage strengths is associated with potential carryover of drug substance from 1 dosage strength to a different dosage strength. Such carryover could result in an unacceptable change in the concentration of that dosage strength, especially in the case where production of a lower dosage strength immediately follows production of a higher dosage strength. The 300 mg dosage strength is manufactured as a sachet which uses the 100 mg powder (b) (4) and has its own dedicated sachet filling equipment. The 100 mg powder (b) (4) formulation and the 100 mg capsules have the highest drug substance content and, therefore, represent the greatest cleaning

challenge for the equipment that is shared among dosage strengths. Although the AR101 commercial manufacturing equipment at CoreRx are dedicated to AR101 manufacturing and there is low risk in cross-contamination with other drug products, the Maximum Allowable Carry-Over (MACO or MAC) of protein residues during change-over between dosage strengths was used to calculate the acceptance criteria of potential protein levels after cleaning. The equation used in the MACO calculation is summarized below.

(b) (4)

Based on the calculation, (b) (4)

The equipment cleaning procedure is established and validated for each piece of manufacturing equipment.

The manufacturing equipment is separated into different major equipment groups as follows:

- (b) (4)

Each major equipment group has undergone a soiling step by running a (b) (4) -scale production batch for the cleaning validation. The soiled equipment was held in a dirty state for no less than (b) (4) then cleaned and tested.

The cleaning agent was selected based on the product characteristics. In order to remove the (b) (4) residue, which is (b) (4) products) were selected for equipment cleaning based on earlier development studies.

(b) (4) of equipment cleaning samples were made to ensure removal of residual cleaning agents. Microbiological purity was also verified as part of the cleaning validation. In addition to visual inspection, (b) (4) on selected equipment surfaces were verified to be acceptable using a commercially available (b) (4)

(b) (4) . Table 7 below shows the acceptance criteria employed for the cleaning validation studies.

(b) (4)

(b) (4)


(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)



(b) (4)

Reviewer Comments


The cleaning validation of the (b) (4) is adequate.

EQUIPMENT QUALIFICATIONS

CoreRx

Equipment qualifications for CoreRx were reviewed as part of the Pre-License Inspection conducted from June 10-14, 2019. No issues were noted for the blending, encapsulation, and sachet filling equipment qualifications. Refer to the EIR for this information.

(b) (4)



(b) (4)

PQ runs for all tested and representative blister pack presentations met the predefined acceptance criteria. No further inquiries regarding the blister pack manufacturing OQ/PQ.

Overall Reviewer's Assessment of Section 3.2.A.1:

- The information provided here was adequate and demonstrated that product contact equipment is effectively cleaned and sanitized following the cleaning SOPs. Only the (b) (4) had any detectable bioburden following cleaning of the (b) (4) due to the inability to properly dry it. To circumvent this issue CoreRx decided to (b) (4). This proved and effective corrective action as no issues with bioburden were observed following the (b) (4) CV. A cleaning continuous process verification program is in effect to monitor the state of validation for all processing equipment. No further inquiries needed.

3.2.A.2 Adventitious Agents Safety Evaluation

An overview of the testing and control strategy for adventitious agents in AR101 drug product including bacteria, fungi, mycotoxins (b) (4)

agents is summarized in Table 1 below.

Table 1: Overview of Control Strategy for Adventitious Agents in AR101 Drug Product

Stage of Manufacturing Process		Controls	Module
Materials certified by the suppliers to be either free of animal components or to comply with the (b) (4)	Allergen Source Material	(b) (4)	3.2.S.2.3
	Drug Substance	(b) (4)	3.2.S.4.1 3.2.S.4.2
	Drug Product	Bioburden (b) (4)	3.2.P.5.1 3.2.P.5.2

(b) (4)

All materials used in the manufacture of AR101 DP are either (b) (4) materials. No animal-derived products are contained in AR101 DP. The (b) (4) used in the manufacture of the sachet foil laminate material, which is in direct contact with the DP, 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.

❑ Viral Clearance Studies

N/A

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

- ❑ The information provided in this section is adequate, no further inquiries.

3.2.R Regional Information (USA)

❑ Executed Batch Records

Executed batch records for all PPQ Lots of AR101 were provided in this submission.

❑ Method Validation Package

Method validation Package was provided with this submission with links to the validation documents and reports in the appropriate Drug Substance (3.2.S.) and Drug Product (3.2.P.) sections.

Overall Reviewer's Assessment of Combination Products Section:

- ❑ The information presented here is adequate, no further inquiries..

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

AR101 peanut (*Arachis hypogea*) allergen qualifies for a claim of categorical exclusion from the requirement to prepare an environmental analysis, per 21 CFR § 25.31(c), as the drug substance occurs naturally in the environment and does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental analysis.