



MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: STN 125592/0

From: Joyce Rockwell, Consumer Safety Officer, Manufacturing Review Branch 1(MRB1), Division of Manufacturing and Product Quality (DMPQ)

Through: Carolyn Renshaw, Chief, Manufacturing Review Branch 1(MRB1), Division of Manufacturing and Product Quality (DMPQ)

Subject: Review of Biologics License Application submitted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Product: House Dust Mite Allergen Extract

Route of Administration: Oral lyophilized tablet for sublingual use

Action Due Date: February 8, 2017

Recommended Action: Approval Memo

Chronology of Events

February 9, 2016	Receipt by CBER DCC
March 29, 2016	Filing Meeting
July 20, 2016	Mid-Cycle Meeting
July 25, 2016	Teleconference (DMPQ)
July 29, 2016	Amendment 125592/0/15 (Response to 7/25/16 Teleconference)
August 2, 2016	Information Request (IR)
September 14, 2016	Amendment 125592/0/22 (Response to 8/2/16 IR)
October 3 – 7, 2016	Pre-License Inspection (PLI)
December 12, 2016	Amendment 125592/0/39 (Update to 8/2/16 IR, Item #13)
December 16, 2016	Amendment 125592/0/42 (Response: Item #1, PLI closeout)
January 5, 2017	Amendment 125592/0/46 (Response: Item #2, PLI closeout)
February 8, 2017	Action Due Date

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Inspectional Consideration

The following is an inspectional consideration request. CBER understands that the recommendation may or may not be taken (based on risk and available resources), and is not requesting documentation to be submitted as evidence of completion. Two inspectional considerations have been identified for this BLA based on:

- (b) (4)

Review Narrative

1. Background

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., submitted a Biologics License Application (BLA) for marketing a house dust mites (HDM) allergen extract formulated as a sublingual tablet (Merck Identification Code: MK-8237).

The proposed indication for use of the HDM tablet is: An allergen extract indicated as immunotherapy for the treatment of house dust mite-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* IgE antibodies. The HDM tablet is indicated for use in adults 18 through 65 years of age.

The allergenic product described in this application was approved in August 2015 in all 11 EU countries under the trade name ACARIZAX for use in adults 18 – 65 years of age. In September 2015, Japan approved MITICURE (ACARIZAX equivalent) for use in adults 12 years of age and above.

ALK's Alutard SQ product (also containing a HDM extract drug substance) has been on the market in following countries (since): China (2004), Czech Republic (1992), Denmark (1984), Finland (1991), Germany (1990), Hong Kong (2010), Iceland (1999), Netherlands (1996), Poland (1995), Slovakia (1992), Sweden (1990), and Switzerland (1985). In the 2000 to 2013 time period, 232,813 treatments have been reported for Alutard SQ. During this time period, there were no reports or indications that the active substance had direct effects on organ systems other than the immune system. Alutard SQ has not been reviewed by FDA.

The HDM tablet contains two drug substances, each of which consists of a (b) (4) extracted from two cultivated house dust mite species, *Dermatophagoides farinae* (*Der far*) and *Dermatophagoides pteronyssinus* (*Der pte*). The drug substances (DSs) (b) (4)

The HDN tablet is a non-sterile sublingual orally disintegrating tablet, lyophilized, white to off-white, and debossed. Each HDN tablet consists of a strength and unit value of 12 SQ-HDM units. During clinical development, the term development units (DU) were used. 12 DU is equal to 12 SQ-HDM. (Note: SQ is a method for standardization on biological potency, major allergen content, and complexity of the allergen extract.) The tablet also includes two inactive ingredients: gelatin (sourced from fish skin) and mannitol. The gelatin and mannitol meet the compendia requirements of the current USP/NF.

Information Request (Response to July 25, 2016 teleconference in Amendment 125592/0/15): provided clarification and additional information for Module 2.4 of BLA, which is been incorporated in the Background section above. FDA Assessment: Merck's response was found satisfactory.

2. Overview of the Manufacturing Process

(b) (4)

(b) (4)

(b) (4)

The drug product is manufactured by Catalent, located in Blagrove, Swindon, United Kingdom. This site manufactures approved drug products for the US and European markets. Catalent manufactures the HDM drug product (b) (4)

(b) (4)

In addition, Catalent performs primary packaging and release testing of the HDM tablet. The manufacturing and testing sites involved with the HDM tablet are:

Table 1

Manufacturing/ Testing activities	Inspection/ Waiver Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4)				
Source Material Manufacturing and release testing of the <i>Der far</i> and <i>Der pte</i> source materials.	Inspection: No	No	YES	(b) (4)
(b) (4)				
<u>Drug Substance:</u> manufacturing, testing, and release <u>Drug Product:</u> Testing (water content, identity, potency, and (b) (4)) and stability testing	Inspection: YES	YES	YES	(b) (4) (b) (4) Team Bio inspection classified as OAI: (b) (4) CBER/DMPQ PLI: (b) (4)
Catalent Pharma Solutions Limited Frankland Road Blagrove, Swindon, Wiltshire, SN5 8RU United Kingdom				
DP Manufacture and primary packaging of tablets, and testing (appearance, disintegration, microbiological	Inspection: Waived	YES	YES	FEI: 3003812585

examination)				
(b) (4)				
Optional facility for microbiological testing	Inspection: Waived	Yes	YES	(b) (4)
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.				
(b) (4)				
Secondary packaging (DP)	Inspection: No	No	YES	(b) (4)
(b) (4)				
Storage (DP)	Inspection: No	No	YES	(b) (4)

3. Source Material (SM) Manufacture – (b) (4)

The SM manufacturing process consists of the following steps: (b) (4)

(b) (4)

Information Request (Q#1, Response in Amendment 125592/0/22):

We note that following the (b) (4)

Please provide data to support this hold time.

FDA Assessment: Results from a holding time study were provided on the (b) (4)

(b) (4)

(b) (4)

4. Drug Substance (DS) Manufacture – (b) (4)
(DS also referred to as MK- 8237 DS)

The DS is an allergen extract derived from cultivated HDM: *Der far* and *Der pte*. The source materials (SMs) for the DS consist of (b) (4)

[Redacted]

[Redacted]

(b) (4)

(b) (4)

Information Request (Q#13, Response in Amendment 125592/0/22 and 125592/0/39): Please indicate if any deviations occurred during the process validation of the drug substance or drug product. If so, please provide a summary of the deviation, assignable root cause, and corrective actions.

FDA Assessment: *Catalent's response is acceptable. Process related and non-process related deviations occurred during the manufacture of the Der far and Der pte DS PPQ batches.*

Der far DS PPQ process related deviations (b) (4)

Der far DS PPQ non-process related deviations (b) (4)

Der pte DS PPQ process related deviations (b) (4)

(b) (4)

Der pte DS PPQ non-process related deviation (b) (4)

[Redacted]

The investigations, root cause, corrective actions, and conclusions for the Der far and Der pte DS PPQ deviations appear adequate.

8. Container Closure System - DS - (b) (4)

[Redacted]

(b) (4)

[Redacted]

[Redacted]

(b) (4)

Information Request (Q#4, Response in Amendment 125592/0/22):

The container closure system used for the drug substance consists of an

(b) (4)

- .
- a. Please confirm that the same container closure system is used for storing the in-process material (b) (4). If not, please provide detail information for the container closure system used for storing the (b) (4) material.
 - b. Please clarify if the container (b) (4) are single use or re-used. If re-used, please provide a cleaning validation summary for the container (b) (4), including if any preliminary cleaning of the containers (b) (4) is performed at Catalent Pharma Solutions prior to returning to (b) (4).
 - c. Please indicate if the (b) (4) containers (b) (4) are supplied as “ready-to-use” from your vendor. If yes, please indicate how the containers and stoppers are assessed for cleanliness prior to use. If no, please indicate how the containers and stoppers are prepared for use.

FDA Assessment: (b) (4) response is acceptable. The container closure system used for the DS is used for storing the (b) (4). The containers (b) (4) are single-use, (b) (4) washer, and stored in a manner to protect against contamination. Prior to use, the containers (b) (4).

9. Water Systems – DS - (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

**Information Request (Q#5, Response in Amendment 125592/0/22):
The Drug Substance manufacturing process includes (b) (4)**

We note that in Section 2.3.S., Table 19 indicates the (b) (4) are only performed at the release of the DS.

The DS manufacturing flowchart does not indicate when the (b) (4) is performed. Please clarify if any in-process (b) (4) is performed. If not performed, please provide a justification and risk assessment for not (b) (4) during production.

FDA Assessment: (b) (4) response is acceptable. (b) (4) is not classified as an in-process test and was not indicated on the DS Manufacturing Process flowchart. (b) (4) is performed routinely as follows:

(b) (4)

(b) (4) is routinely (b) (4) as part of their continued process verification (CPV) according to their protocol to (b) (4) in order to obtain real time data on the manufacturing process. (b) (4) results obtained under the CPV were evaluated during the pre-license inspection and is summarized below:

The following diagram indicates the testing intervals according to the CPV Protocol PRO37531.

(b) (4)



16. Drug Product (DP) Manufacture – Catalent

16.1 Overview: The Merck MK-8237 house dust mite (HDM) tablet is non-sterile oral lyophilized for sublingual use. The tablet is designed to rapidly disintegrate in the mouth. Each unit is a freeze-dried, white to off-white, debossed, solid preparation referred to as a tablet. The HDM tablet is packaged in an all-aluminum blister card, with one tablet per cavity, and 10 tablets per blister.

The HDM tablet is manufactured using the (b) (4)



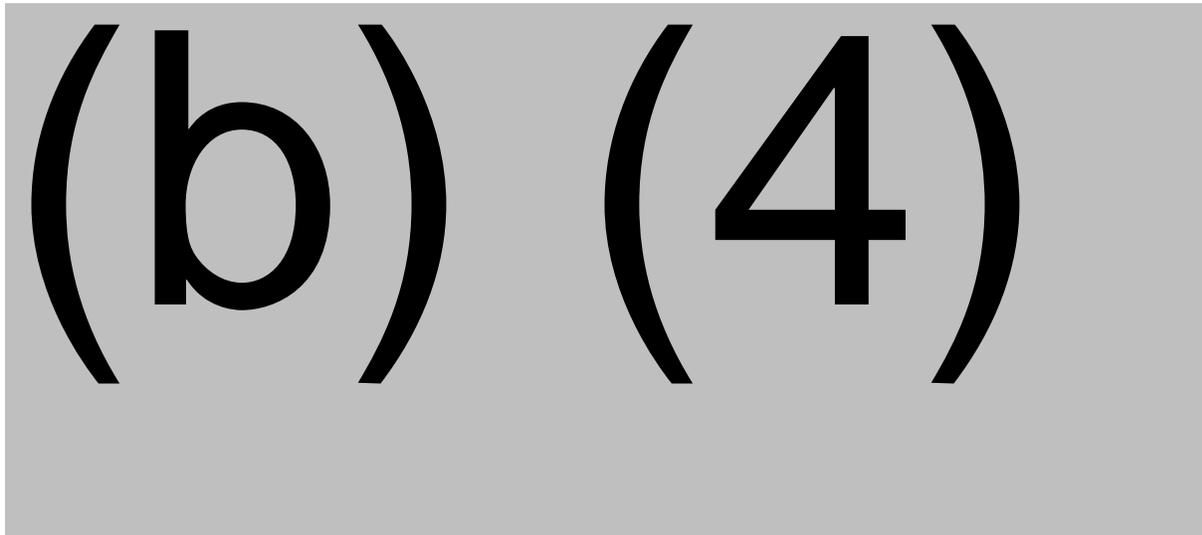
The knowledge and prior experience was leveraged during the development of the HDM tablet.

The HDM manufacturing facility is a multi-use facility. The (b) (4) building is on (b) (4)



The rooms used for manufacturing the DP are controlled not classified (CNC) areas. The rooms are designed but not validated to (b) (4) standard. Precautions are taken to reduce or prevent contamination and cross contamination during the dosing and freeze drying processes on Line (b) (4). Tables 18 and 19 list the Line (b) (4) rooms and other areas in proximity to Line (b) (4) activities.

Table 18 Line (b) (4) Rooms in the (b) (4) Manufacturing Area for HDM DP



(b) (4)

(b) (4)

[Redacted]

Information Request (Q#6, Response in Amendment 125592/0/22): Please describe the receipt and acceptance process for the in-coming drug substance upon receipt at Catalent Pharma, including if any (b) (4) is performed.

FDA Assessment: *Catalent's response is acceptable. Upon receipt of the DS, documentation checks are performed using the drug substance CoA, the transport vehicle temperature log, and the timed temperature movement log of the DS from the transport vehicle to the (b) (4). Incoming acceptance testing consists of (b) (4)*

The CoA contains the results of the (b) (4) testing performed on the DS (b) (4).

(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

The blisters cards are (b) (4) [Redacted] The (b) (4) [Redacted] are packaged into shipping cartons for subsequent secondary packaging. The bulk blister cartons are transported by ground, air and/or sea from Catalent to Merck Sharp & Dohme Corp (b) (4) [Redacted] for secondary packaging. The temperature is monitored during shipment for all modes of transportation.

(b) (4)



19. Process Validation – DP - Catalent

A prospective process validation of the manufacturing process at the commercial (b) (4) batch size on Catalent Production Line (b) (4) was performed, with the following batches.



All three consecutive batches (ID (b) (4)) met the validation acceptance criteria including all release, in-process testing, and extended validation testing requirements. In addition, the following hold times were verified as having no negative impact on product quality:

(b) (4)

Information Request (Q#13, Response in Amendment 125592/0/22):
Please indicate if any deviations occurred during the process validation of the drug substance or drug product. If so, please provide a summary of the deviation, assignable root cause, and corrective actions.

FDA Assessment: *Catalent’s response is acceptable. Six process related deviations occurred during the manufacture of the DP PPQ batches. Three deviations involved a single batch, one deviation involved two batches, and two deviations involved three batches. The deviations included a calculation error and master batch record documentation, yield percentages, labeling text and artwork, environmental monitoring, and a sampling error. The investigations, root causes, corrective actions, and conclusions appear adequate.*

20. Release Specifications– DP - Catalent

Table 23 (Copied from BLA section 3.2.P.5.1)

Test Parameter	Acceptance Criteria	Analytical Procedure
Appearance	White to off-white circular freeze-dried units with a debossed pentagon detail on base	Visual examination
Disintegration	≤ 10 seconds	(b) (4)
Water content	(b) (4)	
Total allergenic activity, Potency		
Major allergen content Der p 1, Potency		
Major allergen content Der f 1, Potency		
Major allergen content Der 2, Potency; identity		
(b) (4)		
Microbiological Examination		
(b) (4)		
Microbiological Examination		
(b) (4)		
Test for Specified Microorganisms	(b) (4)	

a: Stated amount equals 12 DU
 b: Testing only performed at release

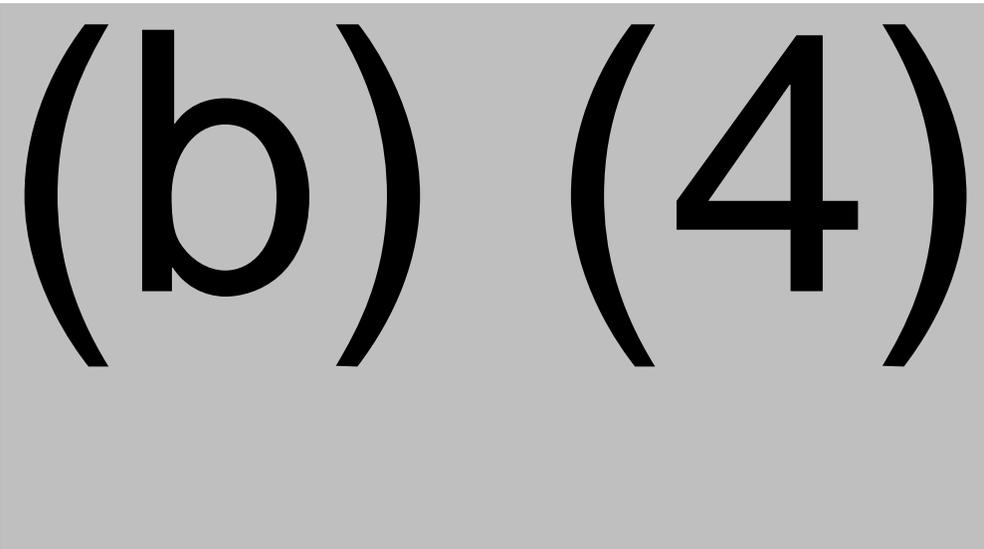
21. Container Closure System / Packaging– DP - Catalent

The HDM tablet is packaged in an all-aluminum blister. The blister material consists of a (b) (4) blister material, (b) (4) paper/foil laminate lidding foil. Each blister card consists of one tablet per cavity with 10 tablets per blister card.

The blister film is supplied by (b) (4) and the lidding foil is supplied by (b) (4). Each batch of film and foil is supplied with a Certificate of Analysis. Surfaces (b) (4) in contact with the product meet all Code of Federal Regulations (CFR) and European Union (EU) requirements for food contact packaging. Tables 24, 25, and 26 provide technical information regarding the packaging materials.

Table 24 (Copied from BLA section 3.2.P.7)

Packaging Material	Composition
Blister film	The blister film consists of a (b) (4) (b) (4)
Lidding foil	The lidding foil is a paper foil laminate as follows: (b) (4) (b) (4)



(b) (4)

Information Request (Q#8, Response in Amendment 125592/0/22): The container closure system for the Drug Product, i.e., House Dust Mites (HDM) tablet is an all-aluminum blister card sealed with a paper/foil laminate lidding foil. An in-process check includes a (b) (4)

. Your response should address the following:

- a. Operator training / qualification for performing the (b) (4)
- b. Design of the blister card including the (b) (4)
- c. Validation summary for (b) (4)

FDA Assessment: Catalent provided a detailed response which was found acceptable and is summarized below.

a. Training is performed by certified operators, and includes training on the SOP, on the job training, and demonstration. The trainee is deemed competent based on ability to answer questions and practical demonstration of the task.

b. (b) (4)

c. During the manufacture of the validation batches, the (b) (4) of the blisters were monitored as part of the in-process checks. (b) (4)

Information Request (Q#9, Response in Amendment 125592/0/22): Please provide validation data for the (b) (4) test method used to detect defects in the seal integrity of the all-aluminum blister cards. Please address the following items in your response:

- a. Please clarify if your package has adequate (b) (4) characteristics to test using the (b) (4) method.
- b. Please clarify if the (b) (4) is standardized. In addition, please clarify if a (b) (4). If so, to what (b) (4)
- c. Please indicate the amount of (b) (4) an operator would be able to visually recognize.
- d. Please clarify if you are using a positive control ((b) (4)). In addition, please clarify if you challenged the procedure to determine what (b) (4) operators can visually recognize.
- e. Please clarify if you challenge the method regularly to confirm its ability to detect defects.

FDA Assessment: *Catalent provided a detailed response which was found acceptable and is summarized below.*

The (b) (4) is used as an in-process manufacturing control test to confirm the performance of the sealing operation. The method is used in conjunction with a (b) (4) test which is used for 100% inspection of the base film (b) (4)

a. The actual blister pocket (b) (4) is estimated to be between a maximum and minimum (b) (4) values of (b) (4). An adequate (b) (4) the test conditions which allows the (b) (4)

b. The (b) (4) is visible by the naked eye, (b) (4), and consists of (b) (4)

d. Studies have been completed to challenge the detection threshold on the blister pack format. These studies showed that (b) (4)

e. A positive control was included in the (b) (4) equipment calibration, and is included with the routine calibration of the (b) (4) equipment.

22. Water Systems – DP - Catalent

There is (b) (4) Purified Water (PW) (b) (4) that provides water for use during the production of the HDM Drug Product (DP), for preparing excipients for the DP solution, and for cleaning and rinsing of equipment. The PW meets (b) (4) requirements. (b) (4) also supplies PW for (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

23. Heating, Ventilation, and Air Conditioning – DP - Catalent

The manufacturing areas of the (b) (4) building used to manufacture the MK-8237 Drug Product (DP) are supplied by (b) (4) HVAC systems, for Line (b) (4)

(b) (4)

Since the HDM DP is an allergenic extract, precautions are in place to assure that the product is contained within the manufacturing areas used for the DP dosing and freeze drying. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The HVAC systems are monitored by a building monitoring system for pressure, temperature, and humidity. (b) (4)

The HVAC systems supplying air to the HDM DP production area were qualified in accordance with GMP and industry standards. The validations for HVAC (b) (4), HVAC (b) (4),

and HVAC (b) (4) consisted of Installation Qualification (IQ) and Operational Qualification (OQ). The IQ was performed in December 2009 and the OQ was performed in April/May 2009.

The OQ measured temperature, humidity, differential pressure, and air change rates (b) (4)

[Redacted]

All justifications and/or corrective actions were scientifically sound.

Routine environmental monitoring is performed using a validated Environmental Monitoring Systems (EMS) installed on Line (b) (4). Digital displays on the EMS instruments are used to monitor and record air-temperature, relative humidity, and differential pressure. The system is computer-controlled and is designed to measure and log data from the sensors automatically. If the measured value from any sensor is outside pre-defined upper/lower alarm limits, then a visible alarm appears on the Enunciator Panel and an audible alarm will sound simultaneously. The limits are defined by the use of the room or area. In addition, temperature and humidity values are recorded in the batch records for each lot for steps where the parameter is critical.

24. Equipment Description and Qualification – DP - Catalent

Information Request (Q#10, Response in Amendment 125592/0/22): Please provide a summary report for operational and performance qualifications for the following equipment:

(b) (4)

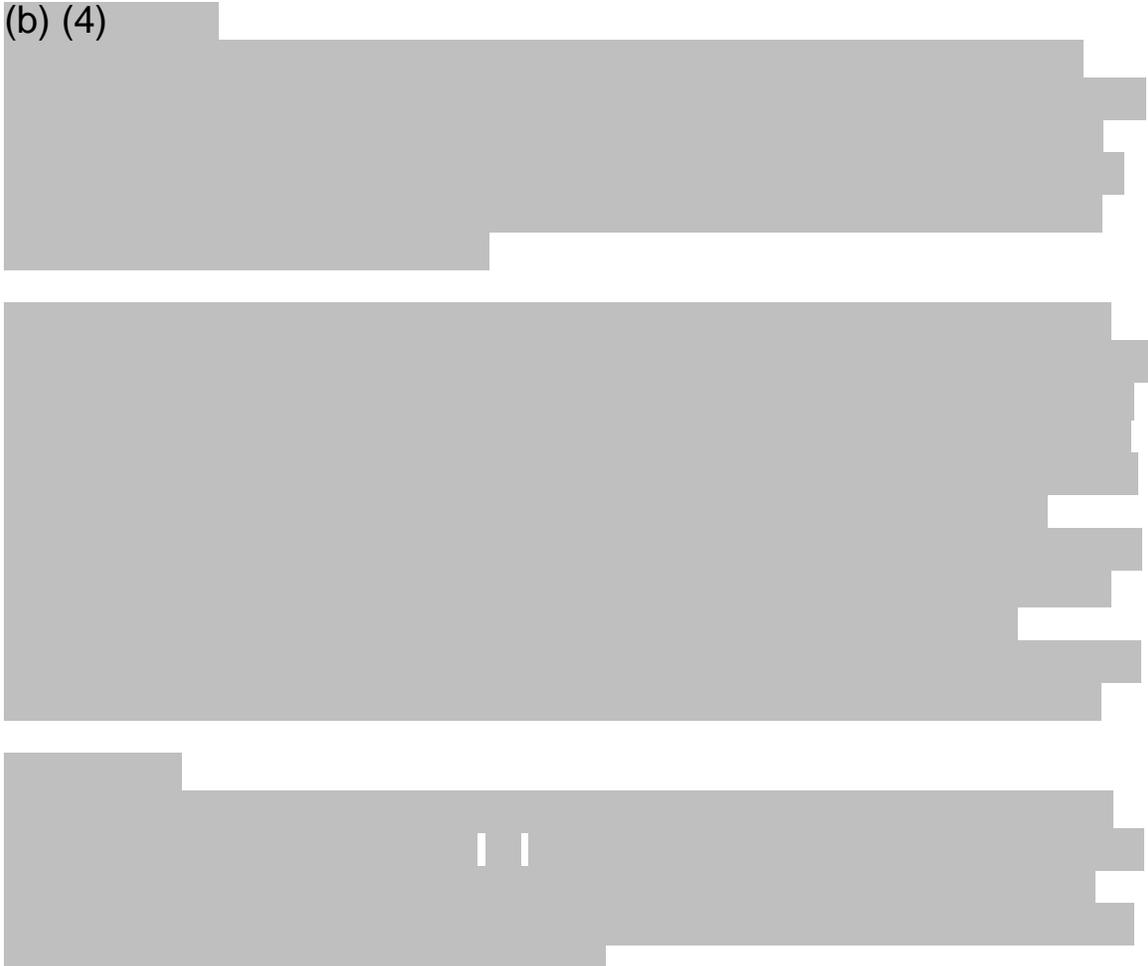
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FDA Assessment: *Catalent's response was found acceptable and is summarized in the corresponding equipment section below.*

(b) (4)

[Redacted]

(b) (4)



Information Request (Q#11, Response in Amendment 125592/0/22): Catalent Production Line ^{(b) (4)} includes ^{(b) (4)} freeze driers (b) (4) Please indicate if the ^{(b) (4)} freeze driers are of similar design and operating principle.

FDA Assessment: *Calatent's response was found acceptable. ^{(b) (4)} freeze dryers were manufactured by the same vendor. The major system mechanical components and automation systems are identical. ^{(b) (4)} freeze dryers use the same equipment and processes for chamber vacuum control, shelf temperature control, and condenser cooling.*

Information Request (Q#12, Response in Amendment 125592/0/22): In Section 3.2.A.1.6, Table 2 lists the Production Line ^{(b) (4)} freezer drier operational qualification acceptance criteria and results for Freeze Drier (b) (4). Please provide the product temperature and ramp rates for each phase of the lyophilization cycle.

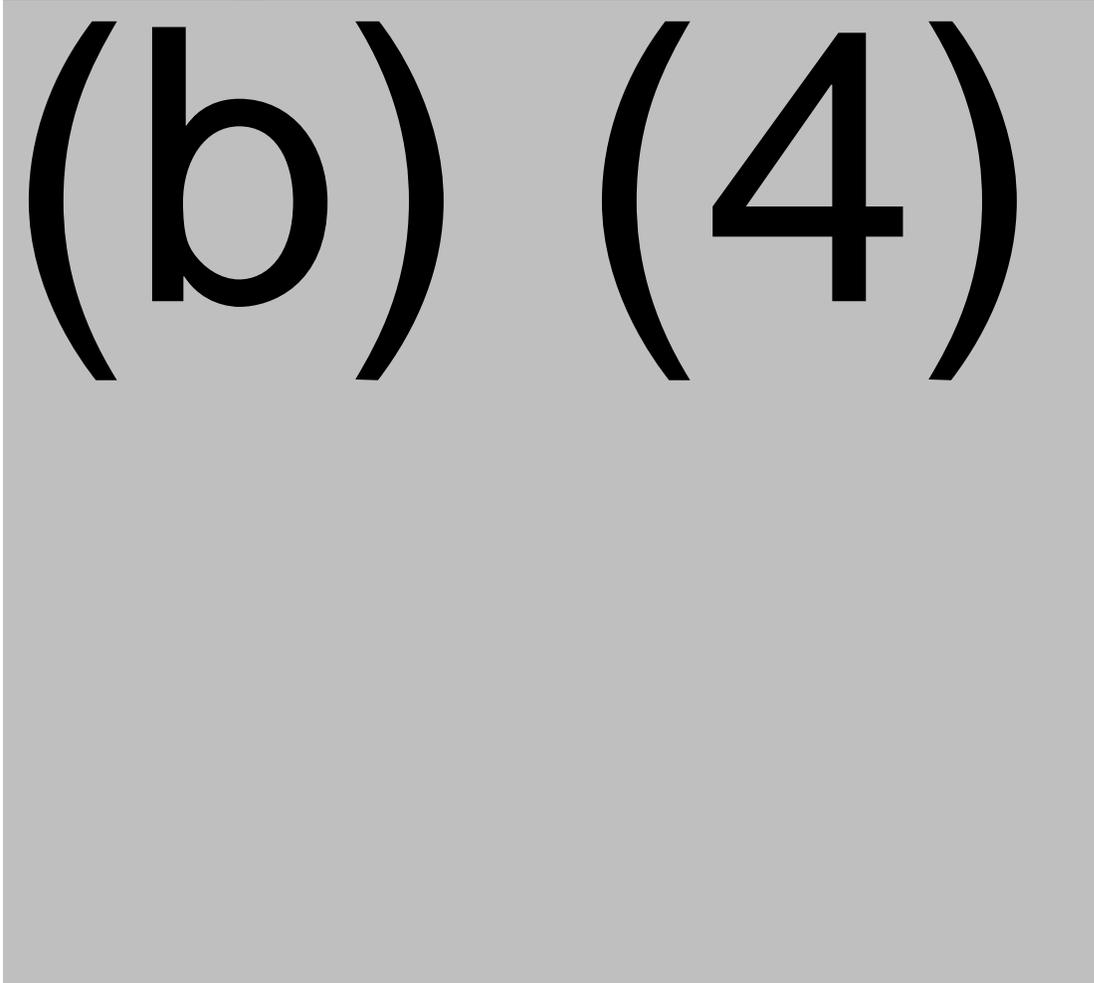
FDA Assessment: *Catalent's response was found acceptable. Freeze drying is performed on (b) (4) using a pre-programmed, validated lyophilization cycle. The cycle parameters are:*

(b) (4)

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(b) (4) freeze dryers were fully qualified prior to use for the HDM DP manufacturing process.

Table 30 Line (b) (4) Freeze Dryer OQ Acceptance Criteria and Test Results



25. Microbiological Examination – DP - Catalent

The (b) (4) DP solution are susceptible to microbiological growth. In order to reduce and/or keep the bioburden level low during the manufacturing process, several control strategies were evaluated during pilot scale process development studies and validated at commercial scale on Line (b) (4), including the DP 2 process change (b) (4) of the DP solution (Note: DP2 process change is described in Section 16.2 Development Change, of this memo).

Information Request (Q#7, Response in Amendment 125592/0/22): You state in Section 3.2.P.2.5 (Microbiological Attributes) that several steps have been introduced to ensure the microbiological quality of the (b) (4) freeze-dried DP during the manufacturing process. Please provide validation data to support the following process parameters used to reduce or slow potential microbial proliferation:

- (b) (4)

(b) (4)

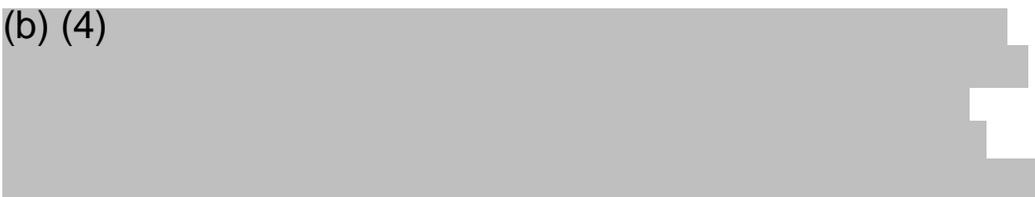
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FDA Assessment: *Catalent provided a detailed response including data which is summarized below.*

(b) (4)

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(b) (4)

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(b) (4)

Release testing includes microbial enumeration tests (b) (4)

Microbiological Examination is performed by (b) (4)

Table 31 Acceptance Criteria for Microbiological Examination

(Copied from BLA section 3.2.P.5.6)

(b) (4)

In addition, testing for specified microorganisms is performed at release and during stability testing. (b) (4)

(b) (4)

The tests for specified microorganisms are performed in accordance with the methods described in (b) (4)

Table 32 Acceptance Criteria for Specified Microorganisms

(Copied from BLA section 3.2.P.5.6)

(b) (4)

All (b) (4) batches of HDM tablet at release and during stability testing met the acceptance criteria for microbial enumeration and specified microorganisms.

26. Contamination / Cross-Contamination Prevention – DP - Catalent

The (b) (4) facility is a multi-product facility. Manufacturing occurs on a campaign basis, and various controls and measures are in place to prevent contamination, cross-contamination, and mix-ups, such as:

- Only one active ingredient and strength at a time is allowed per room at any one time
- Only one lot may be processed in a given room at any one time
- Transportation of raw materials and active ingredients between rooms is strictly controlled
- Signage is used to clearly identify the activity/product being manufactured
- Controlling the movement of personnel and single use or disposable gowning
- Efforts to reduce possible contamination such as use of closed systems and minimize exposure of the product to the environment

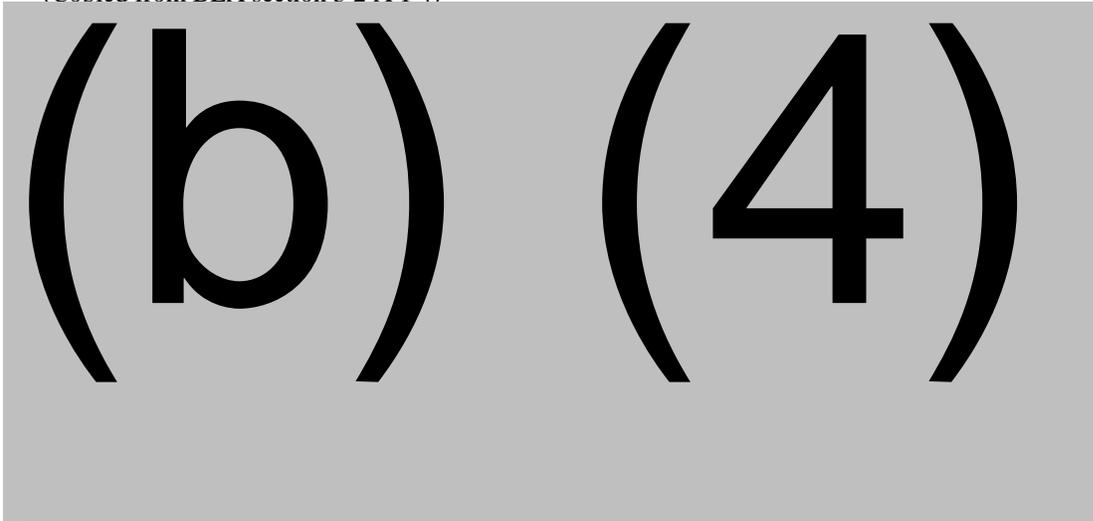
26.1 Equipment:

Dedicated equipment used in the manufacture of the DP consists of the (b) (4)



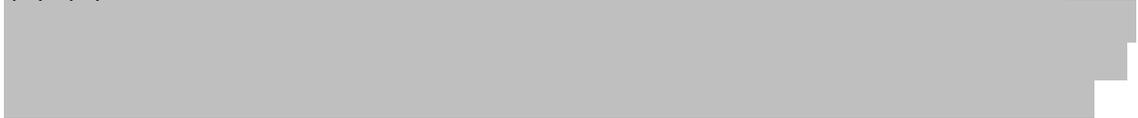
Table 33 Multi-Use Equipment Used for Production of HDM on Line (b) (4)

(Copied from BLA section 3.2.A.1.4)

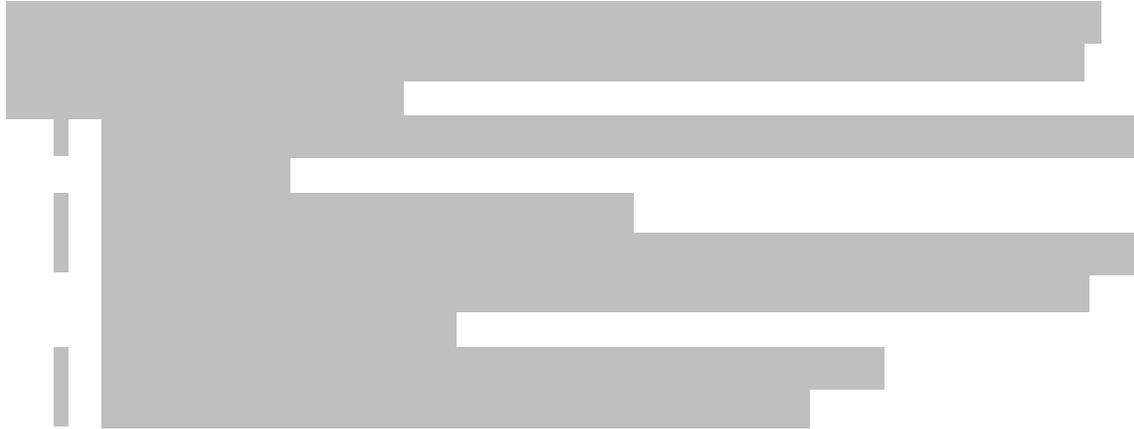


26.2 Cleaning of Product-Contact Equipment:

(b) (4)



(b) (4)

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26.3 Cleaning of Non Product-Contact Equipment:

(b) (4)

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(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

26.4 Cleaning Validation:

Catalent's cleaning studies included assessing product contact equipment for carryover using the hardest to clean reference product and cleaning/sanitizing agents. Product contact equipment used on Line (b) (4) for the HDM DP includes the (b) (4) [Redacted]. Contamination / cross-contamination from the product contact equipment could potential be distributed throughout a subsequent batch(es) processed on Line (b) (4), if cleaning of the equipment is insufficient, or compounded by mechanical design of the production line equipment, due to re-circulation of solutions and line stoppages.

(b) (4) [Redacted]

(b) (4)

(b) (4)

27. Computer Systems – DP - Catalent

Computers and microprocessors are used in MK-8237 DP manufacturing process. The following equipment is controlled by programmable logic controllers (PLCs):

(b) (4)

The installation qualification (IQ) and operational qualification (OQ) of the computer systems were performed in accordance with cGMP and applicable industry standards including cGAMP. The computer systems are 21 CFR Part 11 compliant.

The PQ of Line ^{(b) (4)} consisted of the manufacture of 3 commercial scale (b) (4) placebo batches (b) (4). For this PQ, only (b) (4) was available for use. The PQ of (b) (4) was performed separately using a placebo load (Load (b) (4)). The PQ of the control system met all acceptance criteria outlined in the protocol.

Changes to the computer systems are performed under a change control using a “life cycle approach” as defined in cGAMP.

28. Shipping Validation – DP - Catalent

Blister cards are temporarily placed in (b) (4) bulk shipment to the site of secondary packaging. The HDM tablets were tested in two simulated shipping studies, (b) (4) standards. These studies simulated shipment of product by air, sea, and ground that demonstrated both the bulk (primary) and secondary packaging components adequately protect the product and primary package from physical damage.

The HDM tablets are classified (b) (4) tablets as a Category 1 product which means the product is labelled for storage at room temperature and can be transported under ambient conditions. No additional temperature controls are required when temperature exposure is

expected to be between (b) (4) for a maximum of (b) (4). Protective measures are taken when product is expected to be exposed to temperatures that exceed this range during shipping. Temperature excursions during shipment are supported by the accelerated stability data in Stability Study 1.

Bulk blister cards are transported from the DP manufacturing site to the secondary packaging site by ground, air and/or sea.

Finished goods are transported from the secondary packaging site to the distribution centers in a temperature-controlled truck.

Temperature monitoring during shipment is performed for all modes of transportation.

29. Environmental Assessment

Merck has requested a categorical exclusion from the preparation of an environmental assessment for House Dust Mite Extract (b) (4) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. Such exclusion is provided in 21 CFR 25.31(c) for an action on a Biologics License Application if the substance occurs naturally in the environment, when approval of the application does not significantly alter the concentration or distribution of the substance, its metabolites or degradation products in the environment. Extraordinary circumstances as referred to in 21 CFR 25.21 does not apply. The requested categorical exclusion is acceptable.