DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CDER/OPQ/OPMA/Division of Pharmaceutical Manufacturing Assessment VI 10903 New Hampshire Avenue; White Oak Building 51, Room 2269 Silver Spring, MD 20993 E-mail: opmablainspection483responses@fda.hhs.gov	07/09/2026-07/17/2026
	FEI NUMBER 3002809620

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Yusuke Ishii, VP and Head of Yaizu Technology Center	
FIRM NAME Astellas Pharma Inc.	STREET ADDRESS 180 OZUMI
CITY, STATE, ZIP CODE, COUNTRY YAIZU-SHI, SHIZUOKA JP 4250072	TYPE ESTABLISHMENT INSPECTED Drug Product Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM, WE OBSERVED:

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed. Specifically:

A. Smoke Studies, First Air & Aseptic Setup

i. The smoke studies for the aseptic filling line are deficient in that you failed to evaluate airflow patterns during pre-production (b) (4) aseptic setup operations, including critical installation steps for the sterile stopper bowl, (b) (4), stopper chute, and associated accessories and tools.

ii. Prior to drug product (DP) fill of (b) (4) batch # (b) (4) I observed that the operator placed (b) (4) and using non-sterile (b) (4), blocking first air over the exposed direct product-contact surfaces of sterilized (b) (4).

iii. The indirect-product-contact parts, such as stoppering station parts, have never been removed from the (b) (4) for cleaning and sterilization, prior to each DP fill operation.

iv. During (b) (4) setup of (b) (4) batch # (b) (4), I (CK) observed that the operator bent into the (b) (4), with his upper body obstructing first-air over the exposed indirect product-contact surfaces of the stopper bowl (b) (4).

v. Your smoke study (In operation – dynamic condition No. 20) revealed that operators performed interventions using non-sterile (b) (4), making contact with the sterilized stopper chute and obstructing first air over the indirect product-contact surface of stopper bowl.

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	DOAN N. SINGH -S Digitally signed by DOAN N. SINGH -S Date: 2026.07.20 11:51:27 -07'00' Charles Y. Kuo -S Digitally signed by Charles Y. Kuo -S Date: 2026.07.20 15:02:14 -04'00'	Doan N. Singh, PharmD, MS-RAQA, Regulatory Specialist Charles Kuo, Ph.D., Pharmaceutical Scientist	July 20, 2026

vi. Your smoke study clip (In operation – dynamic condition No. 11) revealed that the operator ripped and punched the tool pouches, which may introduce particles into the open product vials in close vicinity.

B. (b) (4) Operations & Alarm Bypassing

i. On 10 July 2026 during aseptic filling operations of (b) (4) DP, (b) (4) were observed remaining on the (b) (4) throughout the production run. The firm had not adequately evaluated the potential impact of the persistent (b) (4) on aseptic processing, fill accuracy, or product quality.

ii. Alarms generated during aseptic filling operations in (b) (4) used in the production of (b) (4) DP were bypassed without documented evaluation or justification. For example, the 'vial fell' alarm occurred more than 26 times during the observed manufacturing operation. The operator bypassed each alarm without documenting the alarm, the assessment performed to verify the condition did not exist, or the justification for continuing manufacturing. In addition, your firm lacked written procedures defining the evaluation and documentation required before bypassing these alarms.

C. (b) (4) Integrity

During aseptic manufacturing operations, one (b) (4) exhibited visible marks on the product contact (b) (4) side, and several (b) (4) had marks on the (b) (4) side. There is no assurance you have evaluated the observed condition or documented that (b) (4) integrity and decontamination efficacy remain acceptable for the aseptic process. Without routine maintenance, including dirt and stain removal and thorough cleaning, such marks may obscure visual identification of physical defects and particulates and interfere with decontamination effectiveness, presenting a risk to the sterility assurance of drug product manufactured within the (b) (4) environment.

D. Personnel Qualification & Media Fill Simulation

Aseptic processing validation is deficient in that your personnel qualification procedure for interventions, SOP-AST-28969 'SOP for Education and Qualification of (b) (4) Intervention in Building No. (b) (4) fails to consider the complexity and microbial risk of individual interventions. For example, an operator who successfully performs vial removal during media fill is considered qualified for (b) (4) setup, an intervention that is much more complex and carries higher risk of product contamination than vial removal. The intervention list documented

in WI-AST-17881 'SOP for Validation of Process Simulation in Building No.(b) (4) does not specify the frequency or counts of individual interventions that may occur during routine and non-routine commercial manufacturing operations. Media fill simulations are expected to reflect the types, frequency, and counts of interventions performed during actual commercial production in order to adequately evaluate the contamination risk associated with those operations.

E. (b) (4) Biological Indicator Placement

Placement of biological indicators (BIs) during (b) (4) decontamination qualification is not scientifically justified. BIs were positioned (b) (4) in open spaces and (b) (4) with direct air exposure, which do not represent worst-case conditions for (b) (4) penetration.

F. Cleaning & Disinfection Deficiencies

i. The cleaning and disinfection process and procedure for the Grade C room which surrounds the (b) (4) does not ensure effective removal of contamination. The procedure fails to specify: minimum contact (wet dwell) time for the disinfectant/cleaning solution to achieve effective disinfection; sequence or order for cleaning room surfaces and equipment, maximum number of surface passes or area cleaned before replacing wipes; wipe saturation requirements to ensure adequate disinfectant application; and a consistent wiping or mopping technique or direction. During observation of (b) (4) cleaning operations, operators did not clean underneath movable equipment with visible dirt observed on equipment wheels, and an operator stepped onto a freshly mopped floor surface, potentially recontaminating the cleaned area.

ii. On 9 July 2026, dirt and debris were observed on shelving surfaces in gowning rooms (b) (4), (b) (4) prior to entry into the Grade C manufacturing area. These areas were not maintained in a clean and orderly condition suitable for a controlled manufacturing environment.

G. Disinfectant Efficacy Study

No assurance your cleaning disinfectant study tested all materials that would potentially have microbial growth, such as the tape used on the floor in your Grade C room and the glue residue from your adhesive floor roller.

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OBSERVATION 2

Your environmental monitoring program for the drug product manufacturing facility is deficient and does not provide adequate assurance that the manufacturing environment is maintained in a state of control. Specifically:

A. Environmental Monitoring

i. Sampled EM plates can be held in Grade C areas under (b) (4) conditions for up to (b) (4) before being collected by QC personnel for further processing and incubation. Your current SOP does not define a maximum permissible storage duration for sampled EM plates held under (b) (4) conditions prior to incubation, nor has your firm generated or referenced scientific data to demonstrate that extended holding under these conditions does not adversely impact microbial recovery.

ii. Isokinetic sampling probes for non-viable particulate (NVP) monitoring are not positioned within 1 foot (30 cm) of critical areas such as the (b) (4) system inside the (b) (4) during aseptic filling operations to accurately represent air quality.

iii. No EM has been conducted throughout the DP manufacturing area during EMPQ or routine EM program to evaluate the potential for microbial contamination of high-traffic surfaces, including but not limited to floors, telephones, control panels, and door handles. There is no assurance that the environment is maintained in a state of microbial control.

iv. The maximum allowable personnel in Grade C area across multiple rooms were established as (b) (4) people. However, the conclusion of (b) (4) people was determined by media fill and EM data, which was not based on the comprehensive data from EMPQ.

v. EM plates in the QC laboratory were observed to be incubated within a (b) (4) enclosure. No validation study or supporting data was provided to demonstrate that adequate air accessibility is maintained within the enclosure, nor that microbial growth promotion within the enclosure is equivalent to incubation without the enclosure.

B. Mold Control & Disinfectant Limitations

i. Your firm's EM protocol, SOP-AST-28473 ver 9.0 'SOP for Environmental Management for Sterile Manufacturing Area,' specifies that deviation and microbial identification of mold recovery are only initiated when the same mold species is recovered more than (b) (4) CFU or when the result exceeds the established action limit. Moreover, you use (b) (4) disinfectants for routine facility cleaning that cannot effectively eliminate mold. Unidentified

and unaddressed mold contamination can eventually ingress into the product stream, compromise product quality and patient safety.

ii. Adhesive rollers for hair and debris removal from the floor in the gowning area were repeatedly used until visually soiled or no longer adhesive. A degraded or overused adhesive roller may fail to capture and retain particulates and microorganisms and risks spreading microbial contamination across floor surfaces rather than removing them.

C. EM (b) (4) & Filling Station Sampling

i. During the post-operation (b) (4) monitoring by operator, only (b) (4) samples were taken, which do not represent the entire surface area used during the aseptic filling operation. Furthermore, the sampling of (b) (4) was not performed with a (b) (4) (b) (4) on the contact plate with sufficient time and contact. Only a light and quick contact was made between the contact plates and the (b) (4).

ii. During the aseptic filling operations, (b) (4) was used (b) (4) However, you did not sample (b) (4) during environmental monitoring following filling activities.

iii. For the post-operation EM sampling of filling station, only one contact plate sample (b) (4) (b) (4) was taken. This location does not represent all high-risk locations among the filling area. EM samples were not collected for the stoppering station (e.g., parts located on top of exposed vials and contacts with stoppers). Only one contact plate sample was taken (b) (4) on the flat surface, a location that does not represent the contamination risk at the stoppering station.

OBSERVATION 3

Your visual inspection program is deficient and does not provide adequate assurance that drug products are accurately examined for visible defects. Specifically:

A. Visual Inspection SOP

The visual inspection (VI) SOP, 02MN03001 'SOP for Defect Limit in Visual Inspection for Injectables,' classifies (b) (4) and fibers as intrinsic particles without considering potential extrinsic origins of these particles, such as equipment, wipes, or gowns outside the

Grade A (b) (4) boundary. The firm's VI SOP specifies that the detection of intrinsic particles in (b) (4) vials does not require the initiation of a deviation, regardless of particle size, material, or number of units with intrinsic particles. Unexpected presence or levels of intrinsic particles can indicate equipment or facility malfunction and/or degradation of product quality and safety, both of which warrant a formal investigation and product impact assessment. Your VI defect kit used for personnel training and certification does not represent the true defects in your products. For example, your VI kit does not include white fibers or metal particles which have been found in (b) (4) batches intended for commercial distribution. The VI defect training/certification kit is accessible to all inspection team members and not secured and controlled by supervisor or manager.

B. Visual Inspection Controls

i. Inspection lighting was not adequately controlled for (b) (4) visual inspection operations. Operators used (b) (4) (b) (4) lighting; however, objective controls for the (b) (4) were not established. For example:

- Light output (e.g., illuminance/lux) was not measured or monitored to ensure consistent lighting conditions during inspection.
- Batteries were replaced only when operators perceived the light to be dim or after the (b) (4) ceased functioning. Battery replacement frequency ranged from less than one day to two days, resulting in potentially variable and uncontrolled illumination during inspection operations.
- (b) (4) were not consistently identified with unique equipment identification numbers, preventing traceability of the inspection equipment used.
- Lighting conditions were not qualified or validated to ensure consistent and reliable detection of visible defects.

ii. During observation of (b) (4) visual inspection operations, operators used (b) (4) as the sole background for inspection of (b) (4) vials. Standardized inspection backgrounds (e.g., black and white backgrounds) were not used. The firm provided a comparative study evaluating operator detection performance using (b) (4) background versus black and white backgrounds; however, the study is inadequate as it was not documented whether the defects represented worst-case or most difficult-to-detect defects relevant to actual production, or whether defect-spiked vials were replaced or randomized

between background conditions. Without this documentation, the study cannot be considered a meaningful demonstration that use of (b) (4) as an inspection background ensures consistent and reliable detection of visible defects.

OBSERVATION 4

Your equipment maintenance, calibration, and utility systems are not adequately controlled to ensure reliable performance and do not provide objective evidence that equipment operates within established parameters. Specifically:

A. (b) (4) System Monitoring

i. (b) (4) system monitoring procedures are inadequate in that the return loop is sampled (b) (4) Although use points are sampled (b) (4) (b) (4), the sampling frequency at the return loop, which represents the worst-case location of the (b) (4) distribution system, is insufficient to detect microbiological contamination trends and provide adequate assurance that the system remains in a state of microbial control.

ii. Your firm failed to adequately investigate and respond to rouging identified on the (b) (4) of (b) (4) Tank T-7001 during routine maintenance. Your firm reviewed the photographic documentation of the rouging on the (b) (4) provided by the contractor and concluded that no further action was required. No surface analysis was conducted to characterize the extent or nature of the rouging. No CAPA was initiated, and no formal risk assessment was documented to support the conclusion of no risk to product quality or patient safety. No cleaning or routine replacement schedule for the (b) (4) has been established.

B. Scale Calibration

i. The equipment calibration program is inadequate because the in-process vial fill weight scale is not calibrated over the range of its intended use. The lowest calibration standard used is (b) (4) (b) (4) although the average weight of filled drug product vials is approximately (b) (4) As a result, the firm lacks objective evidence that the scale provides accurate measurements at the weights routinely used to verify fill volume.

ii. Weight calibration records for WIRA-101 and 102 documented only 'no error' with a zero without recording the actual measured weight displayed on the scale. Records lack objective

evidence demonstrating the quantitative performance of the scale and do not permit independent verification that the scale met acceptable calibration criteria.

C. (b) (4) Maintenance

Your firm's (b) (4) maintenance procedure does not ensure timely response to maintenance alarms. On 16 July 2026, (b) (4) No. 2 displayed a '(b) (4)' alarm at (b) (4) replacement interval). Your engineering technician stated that such alarms are routinely deferred until the (b) (4) inspection based on a personal belief that there is no product impact, without documented evaluation or justification to support this practice.

OBSERVATION 5

Your facilities and buildings are not maintained in a clean and orderly condition and do not provide adequate protection against contamination, pest activity, or deterioration of the controlled manufacturing environment. Specifically:

A. Pest Control

i. Your firm has not established an adequate pest control program for Building (b) Pest control measures were absent around the building perimeter, roof walkway, and access points leading into Building (b) Although pest control was observed on one side of the building, demonstrating your firm's awareness of the need for monitoring and control, no scientific justification or risk assessment was provided to support the absence of pest control measures in the remaining areas of the building exterior.

ii. Your firm's pest control program failed to prevent recurrent pest infestations in the controlled manufacturing areas, as evidenced by small insect recoveries on multiple occasions in the vicinity of the (b) (4) located in the Grade C manufacturing room and gowning room during summer months.

B. Floors and surfaces

i. The floor in the Grade C room surrounding the aseptic processing (b) (4) contained multiple long cracks. The damaged floor surfaces were not maintained in a condition that permitted adequate cleaning and maintenance of the controlled environment.

ii. Damaged flooring in the gowning room and preparation room was observed to have been repaired using adhesive tape-type patches, and demarcation lines were similarly constructed of adhesive tape, with several observed to be peeled off or worn away at the corners. These temporary repairs do not represent a cleanable, durable surface suitable for a controlled manufacturing environment.

iii. During the inspection of Room (b) (4), a shelf used to store and place the (b) (4) (b) (4) spray bottle was observed to exhibit visible signs of rusting. The presence of rust on the surface within a controlled manufacturing environment (b) (4) represents a deterioration of facility integrity that may compromise the cleanliness and contamination control status of the area. Your firm has not demonstrated that adequate facility maintenance and inspection programs are in place to identify and remediate such conditions in a timely manner, nor has your firm evaluated the potential impact of this deteriorated surface on the microbial and particulate contamination risk to drug substance (DS) and drug product (DP) manufacturing operations accessed through this (b) (4)

OBSERVATION 6

Your quality oversight program is deficient in that material controls, deviation classification, and record-keeping practices do not ensure compliance with established procedures and specifications. Specifically:

A. Quality Oversight

i. There is no quality oversight for issuance and review of calibration records for the compounding vessel scale and the drug substance bag scale. The calibration forms are printed, completed, reviewed, and approved by the production department. In addition, the final approval signature of the calibration documents is missing from two out of three calibration records.

ii. You failed to follow the procedure for deviation classification. For example, deviations NC-31662, NC-31302, NC-30039 were initiated as minor or major deviations for EM and VI excursions. However, based on your SOPs, those three incidents all pose potential product recall prior to investigation and should fall into the critical category for initial classification of a deviation initiation.

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B. Active Pharmaceutical Ingredient (API) Material Controls

Your firm does not have adequate controls to ensure API materials are not used beyond the allowable (b) (4) period. For example, (b) (4) (manufactured (b) (4) (b) (4) was observed on hold status pending retesting; however, your inventory system documents only the retest date and not the original manufacturing date.

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	DOAN N. SINGH -S Digitally signed by DOAN N. SINGH -S Date: 2026.07.20 11:59:28 -07'00' Charles Y. Kuo -S Digitally signed by Charles Y. Kuo -S Date: 2026.07.20 15:09:19 -04'00'	Doan N. Singh, PharmD, MS-RAQA, Regulatory Specialist Charles Kuo, Ph.D., Pharmaceutical Scientist	July 20, 2026