Eli Lilly and Company
Indianapolis Parenteral Manufacturing Operations
FEI number: 1819470
Response to Observations related to US FDA Inspection February-March 2021

Date: 06 April 2021

Division of Pharmaceutical Quality Operations III (DPQO3)

Attn: Art Czabaniuk, Program Division Director
CC: Nicholas Lyons, Director of Compliance Branch

Attached for your review is Eli Lilly and Company's formal response to the FDA Form 483 issued at the conclusion of FDA's CGMP inspection of the Indianapolis Parenteral Manufacturing Site (IPM) and the Product Research and Development division (PR&D) (FEI number 1819470). The inspection was conducted at Indianapolis Parenteral Manufacturing from February 18– March 5, 2021, and March 16, 2021.

We take the observations very seriously. As detailed in our response, we have implemented or are implementing actions to resolve any concerns regarding this inspection on aggressive timelines. We thank the investigators for the discussions we had during the course of the inspection as the feedback contributes to enhancing our operational excellence. Please contact Ms. Ainhoa Nieto, Senior Director, Quality, Indianapolis Parenteral Manufacturing at (b) (6) or by email (b) (6) with any questions related to the content of this correspondence or if we may be of further assistance.

Sincerely,

ELI LILLY AND COMPANY

(b) (6)

Ainhoa Nieto
Senior Director, Quality
Indianapolis Parenteral Manufacturing

CC:
Ms. Ann Connery, Vice President, Quality, Drug Product Operations- Americas and Asia
Mr. Kenneth Whitehead, Vice President, Indianapolis Parenteral Operations

Contents

Introduction

Lilly Indianapolis Parenteral Manufacturing (IPM) and Product Research and Development (PR&D) have well-established Quality Management Systems (QMS) that integrate cGMP requirements and guarantee supply of quality medicine. Lilly IPM and PR&D are committed to design and implement systems, processes, and execution across the entirety of our operations to ensure safety, efficacy, and quality of our products.

We take the observations reported by the agency very seriously. Lilly IPM and PR&D assessed potential impact related to the observations reported by the agency and extended the assessment to include all processes and products, as applicable.

We are confident that none of the issues raised in the Agency's observations impact the quality of our products, and we are committed to actively enhancing our systems, processes, and operational execution as part of our existing culture of excellence and ongoing continuous improvement efforts. Where appropriate, and as discussed in our responses below, we are implementing comprehensive action plans on aggressive timelines.

Lilly IPM has engaged and commits to retain qualified external consulting services to provide expertise, oversight, and independent assessment in support of the actions we are taking. This includes, but is not limited to, enhancements to our aseptic processing controls, environmental monitoring and aseptic simulation program, deviation management program and visual inspection program.

Observation Response Summary

For ease of reference, we have reproduced the text of each observation on FDA's Form 483 issued at the close of the inspection on March 16, 2021 and included our detailed responses to each observation following the text of the observation.

Each observation response consists of an introduction, a summary of the action plan and detailed responses to each of the observation sections.

Following the detailed responses, please find an action plan "executive summary" that includes all the actions to which we commit.

A summary of attached documents is provided at the end of this response.

As discussed in more detail below, we will act with urgency to address the observations and we have taken or will take all the necessary actions set forth to address the observations, maintain compliance and drive continuous improvements across all operations at the Lilly IPM site and in PR&D, as applicable.

OBSERVATION 1

Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas.

A. *Personnel Monitoring*
   1. *Scientific rational could not be provided for holding aseptic personnel to Grade B specifications ((b) (4) NMT(b) (4) CFU, chest NMT (b) (4) CFU) during personnel monitoring even though they are performing interventions inside que the Grade A area. This was noted in 100% of the batches reviewed. Grade A specifications are only used for set-up and high-risk interventions (task-related – (b) (4) CFU, task-related forearms (b) (4) CFU) In the table below the interventions are categorized as either (b) (4) or (b) (4) '. (b) (4) interventions (b) (4) (b) (4) of the RABs (b) (4) while (b) (4) interventions can be performed using the RAB (b) (4) A critical (b) (4) intervention would be an intervention which required monitoring (b) (4) . Some examples include:*

Batch	Date	Personnel	Intervention category	Type
D349899 Etesevimab	12/7/20	(b) (6)	260, 113X, 117X	(b) (4) interventions
	12/8/20		113X	(b) (4) intervention
	12/8/20		273, 274	Both (b) (4) and (b) (4) interventions
D340792 Bamlanivimab	12/3/20		610X, 113X	Both (b) (4) and (b) (4) interventions
	12/3/20		274 (2x), 126	(b) (4) Interventions
	12/3/20		271 (2x), 274	Both (b) (4) and (b) (4) interventions
	12/3-4/20		274, 280	(b) (4) interventions
D065359 Glucagon FINJ 1mg 1mL	4/5-6/20		125 (5X), 130 (3X), 126 (4X), 117X (2X), 116X, 251 (4X), 271 (33X), 260, 128, 256, 258, 270	Both (b) (4) and (b) (4) interventions
	4/5-6/20		611X (2X), 271 (4X), 251, 603X, 272, 260, 259, 609X, 125 (6X), 418X (5X), 419X, 611X (2X)	(b) (4) and (b) (4) interventions
	4/5/2020		113X, 115X, 125, 271	(b) (4) and (b) (4) interventions

Batch	Date	Personnel	Intervention category	Type
	4/5/2020	(b) (6)	514X, 418X	(b) (4) interventions
	4/5/2020		271 (3X), 250	(b) (4) interventions
	4/5/2020		125 (2X), 603X, 258, 271 (29X), 126, 251	(b) (4) and (b) (4) interventions
	4/6/2020		126 (3X), 125(3X), 117X, 418X, 412X, 526X (3X)	(b) (4) and (b) (4) interventions
	4/6/2020		133, 262	(b) (4) and Critical (b) (4) interventions
D299479 Bamlanivimab	8/26- 27/20		113X, 271 (2X), 272	(b) (4) and (b) (4) interventions
	8/26/2020		254, 271 (2X), 272, 123	Critical (b) (4) (b) (4) and (b) (4)
	8/27/2020		126, 280 (2X), 272,274	(b) (4) interventions
	8/27/2020		274 (2X), 253X	(b) (4) interventions
D321280 Etesevimab	10/10-11/20		119X, 272 (9X)	(b) (4) interventions
	10/11/2020		254, 271	Critical (b) (4) and (b) (4) interventions
	10/11/2020		113X (2X)	(b) (4) interventions
	10/11/2020		113X (2X)	(b) (4) interventions
D336907 Bamlanivimab	11/19/2020		113X	(b) (4) interventions
	11/19 - 20/20		113X, (b) (4) (2X)	(b) (4) intervention
	11/19 - 20/20		250, 251, (b) (4) (b) (4)	(b) (4) and (b) (4) interventions
	11/19 - 20/20		260, 280, 162, 262	(b) (4) and Critical (b) (4) interventions
	11/20/2020		(b) (4) (5X), 113X (2X)	(b) (4) interventions

In addition, EM personnel are held to grade B specifications even though they need to breach the Aseptic Grade A area in order to perform EM activities. Management stated they consider environmental monitoring not as an intervention but as an aseptic manipulation.

Holding personnel who breach the aseptic grade A area to Grade B specifications resulted in inadequate trending of personnel monitoring data. The following aseptic personnel who performed activities in the Grade A area had a result of 1 CFU during personnel monitoring. These counts were not trended as the results were held to Grade B specifications:

- *Environmental monitoring of aseptic personnel* (b) (6) *) received 1 CFU on* (b) (4) (b) (4) *at 19:48.* (b) (6) *was performing EM activities during the aseptic filling of D259974, CT974601, LY3303560, 600mg/50mL vial. The 1 CFU was not trended.*
- *Environmental monitoring of aseptic personnel*(b) (6) *) received 1 CFU on*(b) (4) (b) (4)*at 10:50.* (b) (6) *was performing EM activities during the aseptic filling of D336908, VL791002, LY3819253, 700mg/20mL vial. The 1 CFU was not trended.*
- *Environmental monitoring of aseptic personnel* (b) (6) *) received 1 CFU on* (b) (4)*,* (b) (4) *at 9:28.* (b) (6) *was performing EM activities during the aseptic filling of D349901, VL795002, LY3832479, INJ 700mg/20mL vial. The 1 CFU was not trended.*
- *Environmental monitoring of aseptic personnel* (b) (6) *) received 1 CFU on*(b) (4)*,* (b) (4) *at 9:20.*(b) (6) *was performing EM activities during the aseptic filling of D350585, CT20601, LY3074828, INJ 15mL vial. The 1 CFU was not trended.*

2. *Monitoring is not taking place after critical interventions as required by 1698-FORM-19-005.*
   - *Operator* (b) (6) *was supposed to be monitored for* (b) (4) *and forearms upon completion of intervention*(b) (4) *–* (b) (4) *Assembly – Front during the execution of batch D065359 (Glucagon) on 4/6/20.*
   - *Operator*(b) (6) *was supposed to be monitored for* (b) (4) *and forearms upon completion of intervention*(b) (6) *–* (b) (4) *assembly during the execution of batch D321280 (Etesevimab) on 10/11/20.*
   - *Operator* (b) (6) *was supposed to be monitored for* (b) (4) *and forearms upon each of the following interventions:*(b) (4) *–* (b) (4) *assembly – Back and* (b) (4) (b) (4) *Assembly – Front during the execution of batch D336907 (Bamlanivimab) on 11/19/20.*
   - *Operator* (b) (6) *was supposed to be monitored for* (b) (4) *and forearms upon completion of intervention* (b) (4) *assembly during the execution of batch D299479 (Bamlanivimab) on 8/26/20. Only* (b) (4) *were tested.*

   The above monitoring did not take place. No deviations were written.

3. *Personnel monitoring is not always performed after the aseptic connection.*

4. *Scientific justification was not provided for personnel monitoring during aseptic filling. Per your Aseptic Personnel Monitoring for Parenteral Products Operations procedure personnel who do not perform set-up or critical interventions are monitored* (b) (4) *during each batch filling operation. During a shift, aseptic operators gown and de-gown multiple*

times within a day and on the same shift without additional personnel monitoring. When they are monitored is not based on the activities they perform. Aseptic personnel can perform various interventions and environmental monitoring with the Grade A area.

B. *The following discrepancies were noted during the qualification of the aseptic B103 vial filling line:*

1. *The* (b) (4) *alarm delay (between Grade B to Grade D transition) and the* (b) (4) *alarm time delay (between Grade B to Grade C gown room/airlock) for pressure differentials are not based on scientific rational. The firm had only two DP alarms in the last year in the B103 aseptic vial filling area.*

2. *Scientific justification for the position of the permanent non-viable monitors in the critical adjacent grade A areas was not provided. The permanent non-viable monitors are not positioned near operator activity. Instead the NVP monitors are positioned approximately* (b) (4) *where activity takes place. Indianapolis Parenteral Manufacturing Environmental Monitoring – Rationale for the cNVPM Probe Locations states "*(b) (4) *" There is no data to support an acceptable level of non-viable particulates are being generated from personnel/activities which takes place in the critical adjacent area.*

3. *Non-viable monitoring at working level is performed* (b) (4) *with a portable monitor in the critical adjacent grade A area. PEM-218 Vial Filling and* (b) (4) *, Syringe Filling, formulation Manufacturing and Equipment Preparation, dated 2020, states Vial Filling and* (b) (4) *area will be monitored for total particulate air during operation* (b) (4) *for NMT* (b) (4) *. During review of the last dynamic annual monitoring, it was confirmed that although a batch was running in the closed RABS unit, there was no activity (i.e. set-up or interventions) taking place in the critical adjacent grade A area where the monitoring was taking place.*

Response to Observation 1

Introduction

IPM has established a comprehensive Environmental Monitoring (EM) program that effectively monitors environmental conditions in aseptic processing areas. Our EM program provides assurance that the classified manufacturing environments are suitable for aseptic manufacturing. As one of many interrelated elements of the overall site sterility assurance strategy, an objective of the EM program is to measure and provide meaningful data that comprehensively assesses the quality of the aseptic processing environments.

The IPM site EM program is designed to holistically assess particulate and microbiological control of manufacturing spaces (including Grade A RABS and associated Grade A critical adjacent zones) through a combination of

- (b) (4)
- (b) (4) ,
- (b) (4) , and
- (b) (4)

Lilly IPM filling lines are designed to prevent and minimize microbial contamination. Sampling locations are established based on (b) (4) (b) (4) results. The design of the fill line(s) and approach to sample site selection ensures that the routine EM program is representative of manufacturing activities and/or locations that represent the highest likelihood and risk of potential contamination. In addition, sampling frequencies are established to ensure monitoring takes place on all production shifts, enabling a holistic assessment of the processing environments that encompasses all phases of production (e.g., set-up, filling, equipment changeover). We have developed and implemented a science and risk-based approach to establishing sampling frequencies that balances the need to generate data supporting our ongoing state of control against the potentially adverse effects of over-sampling to the microbiological and particulate load of Grade A environments.

Specific to the B103 Vial Filling operations, we utilize a Restricted Access Barrier System (RABS) to provide an enclosed environment designed and qualified to reduce the risk of contamination to product, components, and product-contact surfaces. The B103 Vial Filling RABS is a (b) (4) system designed to aseptically fill, stopper, (b) (4) (where applicable), and seal a range of vial sizes. The RABS is designed to separate the operator from the Grade A environment (and product) through use of (b) (4) equipped with integrated (b) (4) for performing aseptic activities. The RABS systems maintain a continuous, unidirectional, downward flow of HEPA-filtered air to protect the filling line equipment and product including during interventions. In addition, the RABS is supported by (b) (4) (b) (4) hoods that provide a Grade A classified environment immediately adjacent to the filling operations (critical adjacent zones). A holistic EM strategy has been established for the B103 Vial Filling Line to assess particulate and microbiological control throughout manufacturing. For the duration of the filling process, continuous non-viable particulate monitoring is performed within the RABS as well as for the

Grade A air supply provided by the critical adjacent (b) (4) hoods. Passive microbiological air sampling (settling plates) is (b) (4) throughout the filling operation, and active microbiological air sampling is performed (b) (4) of filling. All samples are evaluated against Grade A limits.

Lilly IPM employs a modified Hazards Analysis and Critical Control Points (HACCP) approach which is outlined in procedure 001-007248, *Strategy for Managing Aseptic Interventions and Aseptic Manipulations at the IPM Site.* We selected this HACCP-based approach to analyze the risk associated with aseptic interventions and manipulations since it provides a structured method for applying scientific principles to analyze, evaluate, prevent, and control potential risks and is well suited to identify risks associated with microbial hazards. These formalized risk assessment documents provide the rationale for a criticality rating of high, medium, or low risk for each Grade A intervention and manipulation based on the following risk factors:

(b) (4)

The term *aseptic manipulation* is used to describe activities performed in the Grade A areas that are an *inherent* part of the manufacturing process while the term *aseptic intervention* is used to describe process-related activities performed in the Grade A areas that are *corrective* in nature. Addition of (b) (4) (b) (4) and environmental monitoring sampling are examples of aseptic manipulations. Removing a downed vial or unjamming a stopper are examples of aseptic interventions. Personnel monitoring is performed of aseptic operator (b) (4) and gown as determined by procedure and is associated with specific Grade A interventions and manipulations based on criticality. These are held to Grade A limits and are evaluated as part of batch release. Finally, microbiological surface samples within the Grade A RABS are performed at the (b) (4), including sampling of RABS (b) (4) and critical direct and indirect product-contact surfaces (e.g., (b) (4)).

Lilly IPM performed a three-year review (January 2018 – February 2021) of the routine EM program and the associated viable and non-viable (total particulate) data to provide documented evidence of sustained microbial and particulate performance for all IPM classified facilities. This review was conducted, documented, and approved in (b) (4) report, "*Indianapolis Parenteral Manufacturing 3-Year Environmental Monitoring Evaluation"* (Appendix A). The assessment concluded that the training, gowning, sanitization, and aseptic practices, in conjunction with area engineering controls and facility design, were effective in maintaining an expected level of microbial and particulate control for all manufacturing environments and aseptic personnel. Specifically, the Grade A manufacturing environment maintained low recovery rates throughout the duration of the timeframe assessed. Furthermore, both recovery rate and magnitude of total actions demonstrated a general downward trend. The data review strongly supports the effectiveness of our EM Program and demonstrates that our existing procedures and practices consistently maintain a state of control in our classified areas.

Lilly IPM continuously monitors and evaluates its EM program for improvement opportunities and holistically assesses its performance on an ongoing basis. Prior to this inspection, the site was already in the process of implementing EM program improvements such as the requirement for personnel monitoring

upon each exit from the aseptic area as documented in Work Plan Item TR40131149. These in-process environmental monitoring enhancements as well as additional program improvement commitments are detailed in the responses below.

Actions

1. All Grade A open (b) (4) interventions, regardless of criticality, will be documented in the (b) (4) (b) (4) ((b) (4) and have associated task-related personnel monitoring that is held to Grade A limits. This will be complete by (b) (4) .
2. Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our aseptic processing operations and controls by (b) (4) .
3. For the traditional aseptic filling line in B105, all Grade A environmental monitoring performed through an (b) (4) manipulation, during active product manufacture, will have associated task-related monitoring that is held to Grade A limits. This will be documented in the environmental monitoring system, (b) (4) , effective by (b) (4) .
4. All non-EM (b) (4) aseptic manipulations will be evaluated, and associated task-related monitoring, held to Grade A limits, will be established by (b) (4) .
5. The formal aseptic intervention qualification courses will be revised to include a demonstration that the trainee understands the holistic sequence of events when executing an aseptic intervention, submitting the intervention, and being task monitored. This training will ensure that all trainees understand the necessary sequence of activities as described across procedures 001-005056, 001-002046, 001-007521, and 001-001698, prior to being qualified to execute aseptic interventions. This change will be implemented according to CAPA TR40226771 by (b) (4) .
6. Area-specific intervention reports (e.g., Cycle Summary Reports) will be updated to include documentation of the operator performing each intervention. In addition, all task-related monitoring will be reconciled not only to the intervention, but to the individual performing the intervention, as part of routine batch release per procedure 001-004754 *Environmental Monitoring Evaluation Report (EMER)*. These changes will be implemented by (b) (4) .
7. A series of quality stand-down meetings (department by department) will be executed across all GMP operations at the Lilly IPM site by (b) (4)
8. Procedure 001-001698 *Aseptic Personnel Monitoring for Parenteral Products Operations* will be revised to clarify the requirement for task-related monitoring after each unique aseptic unit installation which includes the aseptic connection. Unit installations will no longer be grouped. These task-related samples will be held to Grade A limits. The sample plan within (b) (4) and batch records will be updated to ensure separate (b) (4) monitoring is captured for each unique 'unit installation' including the aseptic connection. These changes will be implemented by (b) (4) (b) (4)
9. Routine personnel monitoring, which excludes task-related monitoring held to Grade A limits, will occur upon (b) (4) from the aseptic area. These samples will be held to Grade B limits as

they are not directly attributed to activity performed within the Grade A area. This will be complete by (b) (4) .

10. For B103, the (b) (4) differential pressure alarm delay for airlocks will be reduced to (b) (4) based on qualification data, equipment capability, operational utilization, and review of historical performance. The (b) (4) differential pressure alarm delay will be reduced to (b) (4) based on room pressure, DP measurement instrument variability, and active DP control response time. The rationale will be documented in the B103 Critical Operation Data (COD) documents. These changes will be implemented in B103 by (b) (4) (shutdown completion). A similar assessment will be conducted for the other aseptic manufacturing facilities, and modification to the differential pressure alarm delays will be made based on a documented rationale during the next planned facility shutdowns (b) (4) for B105A and (b) (4) for B105).
11. Procedure 001-002833, *Requirements for Performing and Documenting an EMPQ*, will be revised to require all Grade A critical adjacent locations to be sampled at (b) (4) while activity is occurring in this area. This monitoring will target the critical operational activities (e.g., sterile equipment set-up) with appropriately gowned personnel present and performing those activities. The minimum number of non-viable sampling locations as recommended by ISO 14644-1:2015 will be collected at (b) (4) within the 2021 non-viable particulate requalification (PEM-231), slated for execution following the B103 (b) (4) facility shutdown (b) (4) (b) (4)
12. Following execution of requalification sampling, task-related (b) (4) non-viable sampling locations will be selected within the Grade A critical adjacent zones and implemented into the routine Environmental Monitoring program. Sterile equipment set-up operations will be targeted for sample collection of (b) (4) particulate samples based on the nature of the operational activity. (b) (4) particulate sampling will occur as close to sterile equipment set-up operations as possible, without interference of the Grade A critical adjacent activities, to avoid potential impact to product sterility. This will be completed by (b) (4) .

Response to Observation 1.A

Detailed Response to Observation 1.A.1 Part 1: Aseptic Personnel are Monitored and Held to EM Limits on a Scientifically Justified Risk Basis

As previously described, Lilly IPM employs a (b) (4) approach outlined in procedure 001-007248 to conduct formalized risk assessments that provide the scientific rationale for a criticality rating of high, medium, or low risk for each Grade A intervention and manipulation based on established risk factors of (b) (4) . As documented in the "*B103 Vial Line Interventions Risk Assessment,"* an example of a high-risk intervention as determined through evaluation of the three risk factors is (b) (4) (b) (4) . An example of a medium-risk intervention is a (b) (4) while an example of a low-risk intervention is (b) (4) .

All high-risk aseptic interventions require personnel to monitor immediately after completion of the intervention, and these samples are held to Grade A limits. Likewise, personnel must monitor immediately after completion of select medium-risk interventions (those for which proximity factor is ranked as high), and these samples are also held to Grade A limits. Those aseptic interventions determined to have low risk do not currently require personnel task-related monitoring, as we have used our risk assessments and determined that these interventions have minimal risk to the product, product flow path, and the Grade A environment. Monitoring of the RABS (b) (4) occurs as part of the end of batch monitoring for each of the products listed in the observation.

No personnel monitoring samples associated with interventions or the end of batch RABS (b) (4) monitoring samples are held to Grade B limits. However, all personnel who enter an aseptic area must perform (b) (4) monitoring, prior to exit, (b) (4) per work shift for each area entered. These (b) (4) personnel samples are held to Grade B limits since personnel routinely traverse and perform activities (e.g., material transfer, sanitizations) in the Grade B areas. The "*Indianapolis Parenteral Manufacturing 3-Year Environmental Monitoring Evaluation*" report, which included evaluation of personnel data, indicates that the aseptic areas remained in a state of control, and there are no systemic environmental monitoring concerns. Our control strategy ensures sustained product quality and sterility assurance.

Even though we think the current approach outlined in our risk assessments is justified, Lilly IPM commits to implement the following actions to improve our environmental monitoring program.

Action

1. All Grade A open (b) (4) interventions, regardless of criticality, will be documented in the (b) (4) (b) (4)) and have associated task-related personnel monitoring that is held to Grade A limits. This change will be implemented according to change control TR40223712 by (b) (4) .
2. In addition, Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our aseptic processing operations and controls by (b) (4) (b) (4)

Detailed Response to Observation 1.A.1 Part 2: EM Personnel Are Held to Scientifically Justified Risk-Based Limits

The term *aseptic manipulation* is used to describe activities performed in the Grade A areas that are an inherent part of the manufacturing process while the term *aseptic intervention* is used to describe process-related activities performed in the Grade A areas that are corrective in nature. Environmental Monitoring (EM) is a type of aseptic manipulation.

For buildings with Restricted Access Barrier Systems (RABS), EM personnel perform routine monitoring (b) (4)) during batch production through the RABS (b) (4) This mitigates risk as the EM technician is separated from sterile components, equipment,

and product. The four routine monitoring examples cited in the observation were all executed through the RABS (b) (4) therefore, Grade A task-related monitoring is not required as detailed in the *"Multi-Product Plant Manipulations Risk Assessment."* EM personnel do perform Critical Surface Monitoring (CSM) of direct and indirect product contact equipment through (b) (4) (b) (4) but task-related EM technician personnel samples are collected (b) (4) with this monitoring and are held to Grade A limits. EM personnel also perform End of Batch (EoB) monitoring through (b) (4)(b) (4) as some locations within the RABS are not reachable with the RABS (b) (4) However, during EoB monitoring, product is not present and all CSM monitoring has already been completed. Therefore, the EM technician's daily personnel monitoring is performed prior to exiting the aseptic area and is held to Grade B limits.

In addition to the RABS lines, Lilly IPM reviewed its traditional filling line configuration (B105, Line (b)(4 to confirm that EM sampling was being performed in accordance with the approved risk assessment. For this area, EM personnel must perform routine monitoring through (b) (4) manipulations. According to the *"Insulin Plant Aseptic Manipulations Risk Assessment,"* EM sampling was specified to be a low-risk manipulation. It was determined to have minimal risk to the product, product flow path, and the Grade A Environment. These routine EM manipulations are simulated in every aseptic process simulation and data support that there is no impact to the Grade A environment. Like the RABS, there is task-related monitoring associated with all CSM samples which are held to Grade A limits. EoB monitoring is also performed after filling and CSM monitoring has been completed.

To improve the existing environmental monitoring program, Lilly IPM will implement the following actions.

Actions

1. For the traditional aseptic filling line in B105, all Grade A environmental monitoring performed through an (b) (4) manipulation during active product manufacture will have associated task-related monitoring that is held to Grade A limits. This will be documented in the environmental monitoring system, (b) (4) as detailed in change control TR40223712 effective by (b) (4) (b) (4).
2. All non-EM low and medium risk (b) (4) manipulations will be evaluated, and associated Grade A monitoring will be established by (b) (4)

Detailed Response to Observation 1.A.1 Part 3: Routine Trending of Grade A and Grade B Personnel Data

Lilly IPM has a holistic Environmental Monitoring Trending Program as detailed in procedure 001-001694, *Environmental Monitoring Data Review Process*. This trending program includes three pillars for continuous evaluation.

1. (b) (4)
2.
3.

(b) (4) for Grade B rooms, which includes personnel monitoring, for a rolling (b) (4)y period will generate a trend notification if more than (b) (4) samples are (b) (4) the approved alert limits. Alert limits are statistically established based on facility performance and distinguish results that are outside normal variability. Additionally, the trending program evaluates by room the Percent Positive ([Total Samples(b) (4) CFU / Total Samples performed] x (b) (4), which also includes personnel monitoring. This data is also reviewed continuously for a rolling (b) (4) period, and a trend notification is generated if the percent positive exceeds the statistically derived limit of(b) (4)%. Aseptic personnel are also trended individually to determine overall performance of general aseptic practices while in the aseptic area. This trending includes both Grade A and Grade B personnel data and is evaluated continuously over a rolling (b) (4) period. If an individual monitoring demonstrates recovery (i.e., (b) (4) CFU) more than (b) (4) times, during the rolling (b) (4) period, a trend notification is generated. All trends are investigated in accordance with the site's deviation management program.

Specific to this observation, we conducted a three-year evaluation of all daily personnel monitoring held to Grade B limits. This review included an evaluation of all batches where an individual was documented as having a non-zero daily personnel monitoring result. Results of this evaluation were documented in (b) (4) -approved, area-specific technical evaluation reports. A copy of the B103 vial line report is attached for your reference (Appendix B). There were no instances where the non-zero personnel monitoring result was noted as having a negative impact on the batch. In addition, review of the viable and total particulate data as documented in the "*Indianapolis Parenteral Manufacturing 3-Year Environmental Monitoring Evaluation"* report indicated that the aseptic areas remained in a qualified state demonstrating microbiological and particulate control, and there are no systemic environmental monitoring concerns. The control strategy ensures sustained product quality and sterility assurance.

As previously committed, task-related personnel monitoring is being implemented by (b) (4) all (b) (4) interventions. This monitoring will be held to Grade A limits and will be evaluated as part of batch release in addition to being actively trended in accordance with procedure 001-001694.

Detailed Response to Observation 1.A.2: Task-related Monitoring After Interventions

Lilly IPM distinguishes two classifications of aseptic personnel: 1) Qualified Aseptic Personnel and 2) Qualified Grade A Aseptic Personnel. Qualified Aseptic Personnel may enter the aseptic area but are not allowed to enter the Grade A space. Qualified Grade A Aseptic Personnel are those individuals who have completed and passed formal qualification training to perform aseptic interventions and/or manipulations (e.g., sterile equipment installation, environmental monitoring) within the Grade A area. All Grade A Aseptic Personnel are required per procedure 001-001698, *Aseptic Personnel Monitoring for Parenteral Products Operations,* to complete task-related monitoring for all high-risk and select medium-risk (proximity factor is ranked as high) interventions. For example, 1698-FORM-19, *"B103 Vial Filling Task-related Personnel Monitoring"* specifically delineates the interventions and manipulations requiring task-related monitoring for the B103 vial filling line. The results of this task-related personnel monitoring are held to Grade A limits and are recorded and maintained in the validated environmental monitoring database, (b) (4)

In response to this observation, Lilly IPM conducted an evaluation of all interventions performed during manufacturing over the past three years (January 1, 2018 through March 19, 2021) as documented in report, *IPM 3-Year Task-Related Personnel Monitoring Data vs Intervention Data Evaluation"* (Appendix C). Each intervention was evaluated to confirm that task-related monitoring was conducted where required by cross-checking lists of executed interventions from area-specific intervention reports (e.g., Cycle Summary Reports) against (b) (4) This cross-check was completed by correlating the date and time of the intervention with the documented task-related monitoring result. Consistent with the process already utilized for batch-related environmental monitoring data review as outlined in procedure 001-004574, *"Environmental Monitoring Evaluation Report (EMER),"* Lilly IPM evaluated whether the required task-related monitoring sample(s) for each intervention were taken at the correct time for each intervention requiring monitoring. Based on the three-year period in scope of the review, a total of (b) (4) interventions were identified that required task-related monitoring. Of the (b) (4) interventions requiring task-related monitoring, the cross-check confirmed that all but (b) (4) task-related monitoring samples were collected as expected. This confirms that monitoring is taking place after critical interventions as required by procedure. (b) (4) missed monitoring was associated with batch D299479 (Bamlanivimab), as listed in the 483 observation, and was investigated per TR40218667. The (b) (4) missed monitoring was identified during the cross-check and occurred on batch D341520 (Galcanezumab) on December 10, 2020 at 0640. This event was investigated per deviation TR40218863.

The three-year review also confirmed that all interventions requiring task-related monitoring were performed for batches D065359 (Glucagon), D321280 (Etesevimab), and D336907 (Bamlanivimab) noted in the observation. For each of these batches, Lilly IPM was able to identify the interventions performed from the relevant Cycle Summary Report (CSR) and confirm that task-related monitoring samples were recorded in (b) (4) at the corresponding days and time. However, during the review of this data, it was identified that the name of the operator who executed the intervention (and whose monitoring results are recorded in (b) (4) for the required task-related monitoring events) did not match the name of the operator who logged the corresponding intervention in the (b) (4)). Procedures 001-002046, *Managing Aseptic Interventions and Aseptic Manipulations During Filling Operations in B105 and B103*, and 001-007521, *Managing Aseptic Interventions and Aseptic Manipulations during Filling Operations in B105A*, provide instructions on how to perform and document the intervention activity on the (b) (4) in the (b) (4)). This includes the requirement that the operator who performs the intervention (and thus whose task-related monitoring samples should be entered for the corresponding intervention) must also log the intervention in the (b) (4) himself or herself.

Lilly IPM immediately investigated this documentation discrepancy per TR40215553. The investigation determined that some operators were utilizing a scribe system to log interventions to minimize unnecessary touching of frequently touched surfaces (as understood by procedure 001-005056, *General Aseptic Practices and Techniques for Parenteral Filling and Manufacturing Operations*). IPM Quality and Operations conducted an immediate flash communication (i.e., documented coaching on a specific topic) with all aseptic operators (B103 Pre-Filled Syringe Filling, B103 Vial Filling, B105 Vial Filling, and B105A Cartridge Filling) to clarify that the use of a scribe during aseptic activities as was currently being

executed was not an acceptable practice. As a result of the immediate action, the use of scribes to document interventions has been discontinued.

Notwithstanding the discrepancy between the identity of the operator in the ILS and (b) (4) IPM confirmed through the (b) (4) system that all interventions which required task-related monitoring can be associated with the person who performed the activity. In addition, operators are not permitted to self-monitor after performing critical interventions or manipulations, thus an EM technician or second qualified operator executed the task-related monitoring. Finally, ongoing assurance of product quality is supported by the existing batch review process in which the Environmental Monitoring Evaluation Report ensures task-related monitoring data are collected for all activities that require monitoring. Review of the viable and non-viable data as detailed in the "*Indianapolis Parenteral Manufacturing 3-Year Environmental Monitoring Evaluation"* report indicates that the aseptic area remained in a state of control, and there are no systemic environmental monitoring concerns. The control strategy ensures that no single sample represents the overall environmental state of the aseptic area, reducing risk of missed monitoring or action limit excursions. This multi-faceted control strategy supports that all the necessary aseptic environmental monitoring data are routinely collected, reviewed, and approved ensuring all areas remain in a state of control.

In addition to the documented flash communications that occurred, operators were formally retrained on good documentation practices associated with interventions per course PTR2217 which included a required rereading of procedures 001-002046 and 001-007521. The formal aseptic intervention qualification courses will be revised by (b) (4) according to TR40226771 to include a demonstration that the trainee understands the holistic sequence of events when executing an aseptic intervention, submitting the intervention, and being task monitored. This training will ensure that all trainees understand the necessary sequence of activities as described across procedures 001-005056, 001-002046 or 001-007521, and 001-001698, prior to being qualified to execute aseptic interventions. In addition, documentation of who performs each intervention is being added to the validated area-specific intervention reports (e.g., Cycle Summary Reports) by (b) (4). Not only will the task-related monitoring be reconciled with the intervention, but also with the individual performing the intervention, as part of the batch review process. Procedure 001-004754, *Environmental Monitoring Evaluation Report (EMER)*, will be revised by (b) (4) to clarify this requirement.

Furthermore, we are executing a series of quality stand-down meetings (department by department) across all GMP operations at the Lilly IPM site to communicate the changes associated with the action plans as well as reinforce clear expectations related to execution discipline, importance of documentation accuracy, completeness and traceability and data integrity principles, supplementing our existing quality update (GMP annual update) and data integrity training. We will deliver these coaching sessions with approved GMP training material and will record employee's attendance and acknowledgement of understanding of these principles. We commit to completing this action by (b) (4).

In summary, Lilly IPM investigated the events referenced in the observation and expanded the review of task-related monitoring. We verified that required task-related monitoring occurred as required except for

the two instances noted above, thus posing no risk to manufactured product. In connection with the investigation, IPM has also identified and implemented additional opportunities to improve documentation practices related to recording of interventions and task-related personnel monitoring.

Actions

1. The formal aseptic intervention qualification courses will be revised to include a demonstration that the trainee understands the holistic sequence of events when executing an aseptic intervention, submitting the intervention, and being task monitored. This training will ensure that all trainees understand the necessary sequence of activities as described across procedures 001-005056, 001-002046, 001-007521, and 001-001698, prior to being qualified to execute aseptic interventions. This change will be implemented according to CAPA TR40226771 by (b) (4).
2. Area-specific intervention reports (e.g., Cycle Summary Reports) will be updated to include documentation of the operator performing each intervention. In addition, all task-related monitoring will be reconciled not only to the intervention, but to the individual performing the intervention, as part of routine batch release per procedure 001-004754 *Environmental Monitoring Evaluation Report (EMER).* These changes will be implemented according to change control TR40223712 by (b) (4)
3. A series of quality stand-down meetings (department by department) will be executed across all GMP operations at the Lilly IPM site as described above by (b) (4).

Detailed Response to Observation 1.A.3: Task-Related Monitoring After Aseptic Connection

Procedure 001-001698, *Aseptic Personnel Monitoring for Parenteral Products Operations*, provides guidance for operations when performing 'unit installations,' which is installation of multiple sterile parts associated with a single process (e.g., (b) (4)). Aseptic manipulations identified as 'unit installations' within the approved *Multi-Product Plant Aseptic Manipulation Risk Assessment* (version 2, effective September 10, 2019) allow for task-related monitoring to occur upon completion of the entire activity. This 'unit installation' is inclusive of all sterile equipment installation for the unit (e.g., (b) (4) (b) (4)), as the qualified Grade A aseptic operator remains in an area protected by Grade A (b) (4)) throughout the activity. Procedure 001-001698 specifies that task-related personnel monitoring consists of either (b) (4) monitoring or (b) (4) and forearm monitoring based on the evaluated risk position and must be completed immediately after completion of pre-identified aseptic manipulations and prior to initiating any additional tasks or sanitization of (b) (4). This ensures that the samples, which are held to Grade A limits, are representative of all activities performed by the Qualified Grade A aseptic operator, including the aseptic connection. Any result(b) (4) is investigated per the deviation management system and impact to the batch is evaluated.

To improve the existing environmental monitoring program, Lilly IPM will implement the following action.

Action

1. Procedure 001-001698, A*septic Personnel Monitoring for Parenteral Products Operations,* will be revised to clarify the requirement for task-related monitoring after each unique aseptic unit installation which includes the aseptic connection. Unit installations will no longer be grouped. These task-related samples will be held to Grade A limits. The sample plan within (b) (4) and manufacturing tickets will be updated to ensure separate (b) (4) monitoring is captured for each unique 'unit installation' including the aseptic connection. These changes will be implemented according to change control TR40223712 by (b) (4) .

Detailed Response to Observation 1.A.4: Personnel Monitoring Upon Each Exit

As previously described, Lilly IPM employs a modified (b) (4) approach to conduct risk assessments for aseptic operations as set out in procedure 001-007248. This formalized risk assessment documents the rationale for a criticality rating of high, medium, or low for each Grade A intervention and manipulation based on established risk factors. This assessment justifies Grade A task-related monitoring based on 1) (b) (4) , 2)(b) (4) and 3) (b) (4) (b) (4) . Personnel task-related samples are collected for all personnel executing critical interventions and are held to Grade A limits.

Daily personnel monitoring is required for anyone qualified to enter the aseptic manufacturing area regardless of whether they enter the Grade A space. This monitoring is performed(b) (4) prior to exit is held to Grade B limits since personnel routinely traverse and perform activities (e.g., material transfer, sanitizations) in the Grade B area. The daily personnel monitoring is executed in addition to the Grade A task-related monitoring required of Grade A Qualified Aseptic Operators. These data are used to monitor gowning technique and are trended as outlined in procedure 001-001694. Personnel trending is inclusive of Grade A and Grade B data and is reviewed monthly by Operations and Quality personnel to identify and remediate short term trends or issues.

As discussed above in response 1.A.1. Part 3, we conducted a three-year environmental monitoring review of all daily personnel monitoring held to Grade B limits. This review included an evaluation of all batches where an individual was documented as having a non-zero daily personnel monitoring result. Results of this evaluation were documented in area-specific technical reports. Our review confirmed that there were no instances where the non-zero personnel monitoring result was noted as having an adverse impact on the batch. In addition, the "*Indianapolis Parenteral Manufacturing 3-Year Environmental Monitoring Evaluation"* of viable and total particulate data, which included evaluation of all personnel data (Grade A and Grade B), indicates that the aseptic areas remained in a qualified state demonstrating microbiological and particulate control, and there are no systemic environmental monitoring concerns.

In advance of this inspection, Lilly IPM had already identified actions including improvements to the existing environmental monitoring program by including the requirement for aseptic personnel to monitor upon each exit from the aseptic area. This action was outlined in Work Plan Item TR40131149. As part of this commitment to increase personnel monitoring frequency, Lilly IPM will expand our pre-existing improvements and implement the following action.

Action

1. Routine personnel monitoring, which excludes task-related monitoring held to Grade A limits, will occur upon each exit from the aseptic area. These samples will be held to Grade B limits as they are not directly attributed to activity performed within the Grade A area. This action will be completed according to change control TR40223712 by (b) (4)

Response to Observation 1.B

Introduction

Comprehensive control strategies exist to confirm maintenance of the qualified state of the classified areas. The IPM aseptic manufacturing facilities are designed and operated with an emphasis on contamination control with physical separation of different operational areas within the facility. The most critical areas are separated from support areas by segregated personnel and material airlocks dedicated to either entry or exit from the aseptic block. All airlocks have (b) (4) (b) (4) with (b) (4) system to ensure only (b) (4) is open at any given time. The duration that (b) (4) is open is strictly controlled (b) (4) (b) (4)

Air quality is established and maintained throughout the facilities by carefully balanced and controlled HVAC systems to establish a HEPA (High Efficiency Particulate Air) filtered, positive airflow from areas of higher cleanliness to adjacent, less clean areas. High levels of room cleanliness are also supported through high air change rates for each classified room in the facility (including all airlocks). All rooms classified as Grade C or better have a minimum of (b) (4) air changes per hour. Aseptic filling areas typically have much higher air change rates (e.g., vial filling room has approximately (b) (4) air changes per (b) (4)

A differential pressure (DP) cascade control strategy has been established such that the highest classified rooms in the facility are maintained at the highest air pressure, while adjacent lower classified rooms are maintained at lower air pressures. The facility is designed to maintain (b) (4) Pascals pressure differential or (b) (4) w.c. (water column) between adjacent rooms of different classification. This exceeds the minimum expected guidance DP of 0.04" w.c. or 10 Pa (per EU Annex 1 and cGMPs). Active DP control is in place to ensure specified over-pressurization.

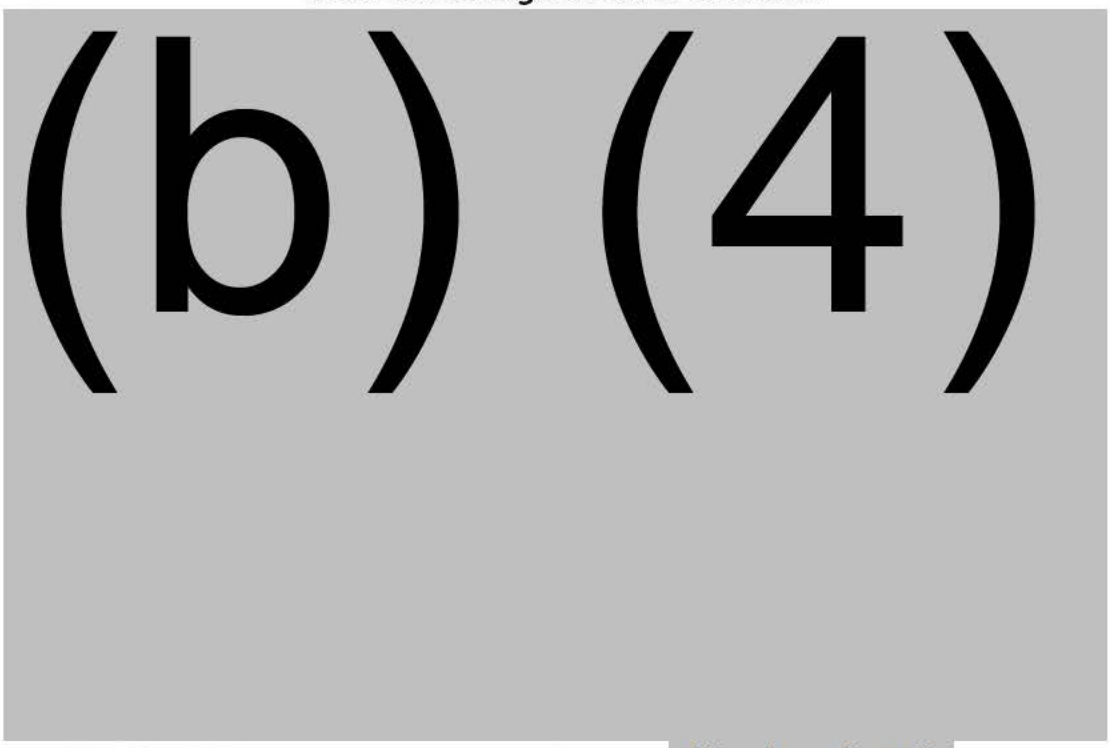
Where Restricted Air Barrier Systems (RABS) are utilized, the RABS provides separation between the filling line (most critical area, Grade A) and the operators and surrounding environment. This provides the highest level of protection to the zone of highest risk. The RABS systems maintain a continuous, unidirectional, downward flow of HEPA-filtered air to protect the filling line equipment and product. The RABS maintains a positive pressure differential from inside the RABS to the RABS exterior as well as to the (b) (4) These DPs are monitored (b) (4) . If any of the DPs associated with the RABS/Filling system or the (b) (4) drops below allowable limits, a filling line critical alarm will be generated, and the filling line will stop forward processing. Automated discard strategies are employed to ensure product protection. In addition to the DP related controls described above, both B103 filling lines (as well as the (b) (4) are equipped with continuous nonviable particulate monitoring

systems that will stop forward processing if they detect airborne particulate concentrations exceeding allowable limits.

DP control is actively monitored with established alarms that trigger response. All DP parameters and critical alarms are retained within a qualified data historian. In the event of a critical DP alarm, plant engineering personnel are immediately notified through a qualified system. Critical DP alarms also generate local audible and visual alerts on the production floor allowing operators to take actions to minimize adverse impact due to the alarm condition. All critical alarms are evaluated in accordance with the deviation management system. Refer to **Drawing 1: B103 Vial Filling and RABS Overview** as example of a visual depiction of the integrated differential pressure control strategy.

Drawing 1: B103 Vial Filling and RABS Overview

B103 Vial Filling and RABS Overview



DP = Differential Pressure
CNVPM = Continuous Nonviable Particulate Monitoring
RABS = Restricted Access Barrier System
AC/Hr – Air Changes Per Hour

Lilly IPM employs a holistic Environmental Monitoring (EM) program that provides assurance that the environment as controlled per the strategy detailed above is suitable for aseptic manufacturing. Routine

Environmental Monitoring (EM) samples are collected at specified frequencies from locations most representative of our manufacturing process and are utilized to assess the microbial and particulate control surrounding routine production operations.

Our holistic strategy provides assurance of environmental control and product protection. However, we will implement improvements in the program as discussed in the detailed responses below, including the following:

1. Although B103 data support the existing differential pressure alarm delays, the (b) (4) differential pressure alarm delay for airlocks will be reduced to (b) (4) based on qualification data, equipment capability, operational utilization, and review of historical performance. The (b) (4) (b) (4) differential pressure alarm delay will be reduced to (b) (4) based on room pressure, DP measurement instrument variability, and active DP control response time. The rationale will be documented in the B103 Critical Operation Data (COD) documents. These changes will be implemented in B103 by (b) (4) (shutdown completion). A similar assessment will be conducted for the other aseptic manufacturing facilities, and modification to the differential pressure alarm delays will be made based on a documented rationale during the next planned facility shutdowns ((b) (4) for B105A and (b) (4) for B105).
2. Procedure 001-002833, *Requirements for Performing and Documenting an EMPQ*, will be revised to require all Grade A critical adjacent locations to be sampled at (b) (4) while activity is occurring in this area. This monitoring will target the critical operational activities (e.g., sterile equipment set-up) with appropriately gowned personnel present and performing those activities. The minimum number of non-viable sampling locations as recommended by *ISO 14644-1:2015* will be collected at (b) (4) within the 2021 non-viable particulate requalification (PEM-231), slated for execution following the B103 (b) (4) facility shutdown period on (b) (4) .
3. Following execution of requalification sampling, task-related (b) (4) non-viable sampling locations will be selected within the Grade A critical adjacent zones and implemented into the routine Environmental Monitoring program. Sterile equipment set-up operations will be targeted for sample collection of (b) (4) particulate samples based on the nature of the operational activity. (b) (4) particulate sampling will occur as close to sterile equipment set-up operations as possible, without interference of the Grade A critical adjacent activities, to avoid potential impact to product sterility. This will be completed by (b) (4) .

Detailed Response to Observation 1.B.1: Existing Differential Pressure Alarm Delay is Supported by Qualification and Operational Data

The primary goal of establishing an appropriate delay for DP alarms is to provide a prompt detection of atypical pressure changes while allowing enough time to accommodate variability associated with DP measurement and control system dynamics as well as pressure fluctuations due to routine operations in the facility.

Lilly IPM has (b) (4) distinct critical DP alarm delays depending on the configuration and functionality of the (b) (4) rooms/areas being monitored – (b) (4) :

(b) (4) DP Alarm Delay

The (b) (4) critical DP alarm delay is associated with airlocks. The alarm delay is specified to allow for an appropriate amount of time for routine movement of personnel or materials through the airlocks as well as to accommodate varying durations of airlock door control timers. A formal qualification test case is executed for all airlocks to confirm the performance of the HVAC system serving the airlock. Specifically, this qualification test verifies an airlock's ability to maintain its particulate classification when the door between (b) (4) airlocks is held open for a period of (b) (4) .

This qualification test is conducted on each individual airlock to generate data supporting the (b) (4) DP alarm delay. This test involves (b) (4) . This test confirms the airborne particulate counts in the higher classification airlock/area does not exceed its airborne particulate limits while the airlock door is open.

In conjunction with this qualification test, each airlock is also tested for 'recovery' to verify its ability to quickly clear the airlock of airborne contaminants. The recovery tests verify that particulate conditions for each area, in the at-rest state, are achieved in the unmanned state after a short 'clean up period' of no greater than (b) (4) . This test is conducted by (b) (4) Acceptance criteria for this test is a (b) (4) in airborne particulate counts within (b) (4) . This test demonstrates the effectiveness of high air change rates from the HVAC system. For airlocks, the recovery rates are often significantly less than (b) (4) .

Following HVAC system qualification testing associated with airlock performance, environmental monitoring performance qualification studies are conducted to further assess the acceptable operation and use of airlocks under both at-rest and operational conditions per applicable room classifications and testing guidelines.

Review of qualification and operational data for B103, including recovery studies for the (b) (4) delay for airlocks, provides rationale for and supports acceptability of the existing differential pressure alarm delay.

(b) (4) DP Alarm Delay

This delay is associated with the following two facility configurations:

- DP is monitored between two rooms of different classification that are separated by equipment that facilitates the transfer of materials between them (e.g., (b) (4) (b) (4) (b) (4) (b) (4) , etc.)

- DP is monitored between a classified room and an adjacent (unclassified) technical space connected with a maintenance access or emergency egress door (not utilized during normal operations).

For the two configurations that have the (b) (4) alarm delay, a significant change in DP during normal operations is not expected. A DP alarm for these would indicate a failure of operational controls whether equipment-based or administrative. This delay has been specified based on the following factors:

- Room pressure is a dynamic parameter. Room pressure is influenced by many factors including (b) (4) .
- DP measurement instrumentation variability. DP measurements at low pressures are inherently more variable. Recommendation from ISPE baseline guide is to use a time-weighted rolling average when establishing alert/alarm delays to address this variability. For example, utilizing a (b) (4) or (b) (4) will help identify trends while limiting the appearance of "nuisance" alarms (*ISPE Baseline Guide – Sterile Product Manufacturing Facilities, Volume 3).*
- Active DP control response time. For rooms equipped with active pressure control, the time duration needed for room pressure control devices to react/adjust to room pressure changes must be accounted for. Several rooms incorporate (b) (4) " pressure control valves to affect a quicker response time to accommodate certain operations that have a frequent and more significant impact on room pressurization.

Review of B103 historical DP data as well as response times associated with various active pressure control devices provides rationale for and supports acceptability of the existing differential pressure alarm delay.

Although B103 data support the existing differential pressure alarm delays, Lilly IPM will execute the following actions to afford tighter differential pressure control which allows for well-timed detection of atypical pressure changes. The data review and approved rationale is documented in the *"B103 Critical Alarm Delay Rationale"* (Appendix D).

Action

1. For B103, the (b) (4) differential pressure alarm delay for airlocks will be reduced to (b) (4) based on qualification data, equipment capability, operational utilization, and review of historical performance. The (b) (4) differential pressure alarm delay will be reduced to (b) (4) based on room pressure, DP measurement instrument variability, and active DP control response time. The rationale will be documented in the B103 Critical Operation Data (COD) document.

These changes will be implemented in B103 according to change control TR40224509 by (b) (4) (b) (4) (shutdown completion). A similar assessment will be conducted for the other aseptic

manufacturing facilities, and modification to the differential pressure alarm delays will be made based on a documented rationale during the next planned facility shutdowns(b) (4) for B105A and (b) (4) (b) (4) for B105).

Detailed Response to Observation 1.B.2 and 1.B.3: (b) (4) Non-Viable Monitoring in Critical Adjacent Grade A Area

The B103 Vial Filling and (b) (4) Grade A classified RABS (Restricted Access Barrier Systems) provides protection for all high-risk operational activity. To demonstrate sustained particulate control within the RABS, continuous non-viable particulate monitoring (cNVPM) is performed for the duration of all operations (set-up through end-of-filling). Immediately adjacent to the RABS are Grade A critical adjacent (b) (4) hoods that supply Grade A HEPA filtered(b) (4) Like the RABS, the (b) (4) hoods are sampled continuously for non-viable particulates. The intent is to capture particulate data representative of the air quality being supplied over components and equipment parts surrounding the sterile equipment set-up process, as well as (b) (4) intervention activity. The continuous non-viable particulate sampling of the(b) (4) hoods is the primary method for monitoring the particulate air quality being supplied within the Grade A critical adjacent (b) (4) hoods. In addition, (b) (4) viable active air (b) (4) and viable surface (b) (4) sampling is performed within the Grade A critical adjacent (b) (4) hoods during initial sterile equipment set-up process and at a frequency of(b) (4) throughout the duration of the filling operation to demonstrate microbial control for the adjacent Grade A area. Viable passive air (b) (4) samples are collected at a frequency of(b) (4) within the Grade A critical adjacent (b) (4) hoods, with a target exposure of(b) (4) , with the intent to capture any transient airborne viable particulate event.

(b) (4)) was performed for the B103 Vial Filling Grade A RABS and Grade A critical adjacent (b) (4) hoods to provide documented visualization and evaluation of airflow patterns through static and dynamic testing of the (b) (4) protected spaces. In a static state with all RABS (b) (4) (b) (4) (b) (4) of the critical adjacent (b) (4) hoods indicates that the(b) (4) provided from the hood diffusers flows vertically downwards, below (b) (4) until it is pulled towards the low-level air returns adjacent to the RABS. During the dynamic state, with RABS (b) (4) and aseptic operators executing sterile equipment set-up and high-risk interventions, the visualization of the B103 Vial Filling RABS over-pressurization to the adjacent areas is apparent. While RABS (b) (4) are(b) (4) , airflow as it exits the RABS is approximately(b) (4) with the floor, with a (b) (4) (b) (4) and (b) (4) in the adjacent classified area. Airflow supplied by the critical adjacent (b) (4) hood is (b) (4) , until (b) (4) (b) (4) RABS (b) (4) Given the RABS and facility pressurization strategy and demonstrated airflow patterns surrounding critical operations, there is no potential particulate ingress from the Grade A critical adjacent area into the Grade A RABS.

Routine monitoring of the air being supplied to the critical adjacent environment and protective measures (e.g., (b) (4)) are in place to ensure an appropriate level of control. Review of the viable and non-viable data from the "*Indianapolis*

Parenteral Manufacturing 3-Year Environmental Monitoring Evaluation" demonstrated that the aseptic areas, including the B103 Grade A critical adjacent areas, remained in a robust state of control, and there are no systemic environmental monitoring concerns.

In addition, an Environmental Monitoring Performance Qualification (EMPQ) for non-viable particulates is conducted, at a minimum,(b) (4) The (b) (4) EMPQ is executed to provide documented evidence that the classified manufacturing environment is capable of meeting specified particulate acceptance levels based upon the proposed classification and approved control measures for the area. Guidance provided within *ISO 14644-1:2015* is utilized to determine the minimum number of non-viable sampling locations for qualification purposes. Sampling locations are determined based upon findings from the area (b) (4) to ensure the sampling locations are representative of the manufacturing environment and operational activities. Sampling locations are also selected to confirm that the site can adequately support evidence of microbial and particulate control. To ensure the appropriate number of non-viable sampling locations for qualification purposes is performed for the Grade A critical adjacent (b) (4) hoods, (b) (4) manual non-viable sampling locations are selected to supplement the routine cNVPM sampling locations. Both At-Rest (static) and Operational (dynamic) samples are collected. Monitoring during the Operational, or dynamic, state is performed to provide an evaluation of the level of total particulate environmental controls occurring in the classified manufacturing environment during routine processing operations. Sampling in the Operational state is performed when installation is functioning in the defined operating mode, and personnel are present within the manufacturing environment performing routine work activities. Review of the most recent annual non-viable requalification, PEM-218, indicates that (b) (4) non-viable samples were collected within the Grade A critical adjacent (b) (4) hoods in an operational state, while a batch was actively filling. Interventions were being performed within the shift that operational EMPQ samples were collected.

To better measure the particulate profile associated with (b) (4) activities within the Grade A critical adjacent zones, the following actions will be implemented.

Actions

1. Procedure 001-002833, *Requirements for Performing and Documenting an EMPQ*, will be revised to require all Grade A critical adjacent locations to be sampled at (b) (4) while activity is occurring in this area. This monitoring will target the critical operational activities (e.g., sterile equipment set-up) with appropriately gowned personnel present and performing those activities. The minimum number of non-viable sampling locations as recommended by *ISO 14644-1:2015* will be collected at (b) (4) within the 2021 non-viable particulate requalification (PEM-231), slated for execution following the B103 (b) (4) facility shutdown (b) (4) (b) (4).
2. Following execution of requalification sampling, task-related (b) (4) non-viable sampling locations will be selected within the Grade A critical adjacent zones and implemented into the routine Environmental Monitoring program. Sterile equipment set-up operations will be targeted for sample collection of (b) (4) particulate samples based on the nature of the operational

activity. (b) (4) particulate sampling will occur as close to sterile equipment set-up operations as possible, without interference of the Grade A critical adjacent activities, to avoid potential impact to product sterility.

These two actions are specific to B103 given the facility design. These actions will be implemented according to change control TR40223712 by (b) (4)

OBSERVATION 2

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed.

Specifically,

A. *Individual RAB* (b) (4) *on the aseptic vial line are not tracked. The firm stated the* (b) (4) *are replaced every* (b) (4) *while* (b) (4) *integrity testing is performed* (b) (4) *Failures in* (b) (4) *integrity are not considered deviations and are not investigated. Numerous* (b) (4) *failures were found in the Deviation Observation log:*

Observation #	***Date***	***Line***
TR 40209421	*08 FEB 21*	*B103 Vial Filling*
TR 40208503	*06 FEB 21*	*B103 Vial Filling*
TR 40192846	*17 DEC 20*	*B103 PFS*
TR 40188205	*06 DEC 20*	*B103 Vial Filling*
TR 40184073	*20 NOV 20*	*B103 PFS*
TR 40174573	*23 OCT 20*	*B103 PFS*
TR 40174245	*21 OCT 20*	*B103 Vial Filling*
TR 40167253	*22 SEP 20*	*B103 PFS*
TR 40164233	*21 SEP 20*	*B103 Vial Filling*
TR 40047970	*12 JUL 19*	*B103 Vial Filling*

(b) (4)

Due to the high rate of failed RABS (b) (4) *Tests occurring since September 2020 on the PFS and the Vial Filling lines in B103, a trend report was initiated on 16 Dec 20. This trend is still awaiting investigation.*

B. *The monitoring of the RAB* (b) (4) *is not based on the interventions performed with the* (b) (4) *On 2/23/21, the FDA investigators watched EM personnel sample the RABs* (b) (4) *at the end of production. We observed contact plates being used to monitor the fingertips on one side of the* (b) (4) *The RABs* (b) (4) *can be used in either direction, based on the intervention performed.*

C. *You filed a FAR regarding deviation TR40190443 dated 12/14/2020 for a cluster of glass breakage/cracked vial events. Your investigation is inadequate including the following reasons:*

1. *You did not adequately evaluate the scope or impact during this investigation. Specifically, you did not perform adequate retain reviews of the potentially impacted batches nor did you trend all batches filled on this line, B103.*

2. *You performed an engineering study to simulate glass vial breakage event(s). You did not document a protocol for this engineering study defining elements such as number of runs and your results (counts and severity/characterization of broken vials). Your engineer stated operators were present during this study to ensure forces applied simulated how the operators actually loaded the trays on the line. However, no documentation was captured to support the operator's attendance during the study. This event specifically impacts Bamlanivimab, EUA 90/94 which are filled in 20mL vials.*

D. *You receive glass vials as well as other components from "high risk" vendors. You established glass vial suppliers as high risk since they are primary packaging components. Your incoming glass vial inspections have failed and rejected numerous lots of these incoming vials for critical defects including* (b) (4) *defects. Investigations/vendor complaints are issued, however, no definitive root causes are established via vendor investigations. Follow up and/or review of vendor investigations are not always documented. Root causes routinely identify* (b) (4) *samples without scientific justification.*

E. *You do not consider the quality impact to previously inspected batches nor do you open a deviation if an operator fails requalification for manual or semi-automated visual inspection.*

Response to Observation 2

Introduction

As set forth in more detail below, Lilly IPM's deviation management system ensures that deviations are properly identified, assessed, investigated, and corrected. As also discussed below, the events in the

observation transpired prior to full implementation of a number of improvements to our deviation management system that were already in progress at the time of this inspection. We have investigated each of the events referenced in the observation and confirmed our original product quality impact decisions were correct and that we took appropriate action at the time of the events. We have also identified additional opportunities for improvement both with respect to the specific events discussed in the observation as well as our deviation management program.

Previous Deviation Management System

Under the deviation management system that was in place at the time of the events referenced in Observation 2, Lilly IPM classified each unexpected occurrence identified during a GMP activity as either an observation, a deviation, or a major deviation. All unexpected occurrences entered the system as an observation and were reviewed through daily cross-functional process team triage meetings, including QA, operations, and relevant technical support (engineering, QC, etc.). QA made final classification decisions and documented the decisions in the (b) (4) system. Events that did not meet the criteria to become deviations or major deviations were classified as observations. Observations were part of the overall deviation management system, and all observations and deviations, regardless of classification, required an assessment of the impact on product or material and/or data quality, as well as an event description and immediate actions performed. Individual observations did not require root cause analysis or CAPA plans, but when a trend of related observations was identified, then a trend record was initiated in (b) (4) to perform root cause analysis and identify CAPA to address root cause(s).

Recent Improvements

Based on learning from other Lilly sites, Lilly IPM began a series of internal assessments of the deviation management system to drive continuous improvement. Our CAPA review board, which has been in place for over ten years and consists of senior cross-functional representatives from QA, engineering, technical services, and operations, meets (b) (4) to review records prior to approval. Beginning in January 2020, we expanded the activities of the CAPA review board to include a (b) (4) focused review of closed observation and deviation records for rigor, completeness, and adherence to standards. In the first quarter of 2021, Lilly IPM began implementation of deviation management system program improvements to incorporate learnings from our review of our own observation and deviation records as well as learnings from other Lilly sites. The following improvements were already in progress at the time of the FDA inspection in February-March. Global standard revisions, local procedure revisions, formal training and informal learning sessions began in January 2021, and local procedure 001-001147 *Managing Deviations* will be effective by (b) (4).

a. All events are classified as deviations, and all levels of deviation, including deviation observations, require identification and documentation of the cause of the event.
b. All levels of deviation require a CAPA plan (e.g., correction, corrective and/or preventative action) based on scientific and quality risk management principles, such that actions are relevant and appropriate to the magnitude of the problem.
c. All data integrity lapses must be documented and investigated as deviations and identified as data integrity events for purposes of trending.

d. Additional guidance is provided for deviations with the potential for multi-site impact to ensure that all affected sites are informed and to ensure traceability of related investigation and CAPA records across the impacted sites.
e. Enhancements were made to strengthen the linkages between the quality deviation system and HR system.

As in the previous version of the program, all deviations must assess the impact on product or material and/or data quality, and justification for quality impact conclusions and decisions must be documented in the record.

Commitment for Further Improvement
Lilly IPM conducted a detailed review of each event referenced in Observation 2 and confirmed that we appropriately assessed the events at the time of occurrence for product quality impact and took appropriate actions in response to the events. We also identified the following additional opportunities for improvement with respect to our deviation management procedure and each of the events in subparts of Observation 2:

Actions to Further Enhance Our Deviation Management Program

1. Procedure 001-001147, *Managing Deviations* was revised to provide specific guidance to ensure investigators set an appropriate investigation scope and to require that the scope is clearly stated and justified in the record. Enhanced interview instructions are provided along with new interview templates which are designed to be more user friendly and accessible. A new trend investigation template was created to provide more specific guidance on required content and a due date of (b) (4) (b) (4) from creation will be applied to trend records. The revised procedure will be effective upon completion of training by (b) (4).
2. The percentage of approved records reviewed (b) (4) by the senior cross-functional team (including but not limited to quality assurance, engineering, technical services, and operations) will be increased to evaluate a greater percentage of records for completeness, robustness, adherence to new process requirements, etc. by (b) (4).
3. Deviation mentor positions will be created to teach, mentor, and guide investigators, and new instructor-led training will be delivered to lead investigators with modules focused on record creation and final impact assessment by (b) (4).
4. Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our deviation management program by (b) (4).

Additional Actions Specific to Subparts of Observation 2

5. All future (b) (4) failures will be investigated as deviations per the enhanced deviation management program, effective (b) (4). (b) (4) testing performance for the other Lilly IPM RABS filling line will be assessed based on learning from the completed B103 RABS (b) (4) management trend by (b) (4).

6. Statistically based action limits will be established for the (b) (4) management trending program and minimum timing requirements will be established for performance evaluation by (b) (4) (b) (4)
7. The RABS (b) (4) design will be modified to minimize false failures during the automated pressure decay test by (b) (4) .
8. (b) (4) of RABS (b) (4) will be monitored during environmental monitoring. Detailed monitoring technique instructions will be added to procedure 001-007772, *Environmental Monitoring of the Aseptic Classified in Parenteral Manufacturing Areas.* This change will be implemented according to change control TR40223712 by (b) (4) .
9. All reference and retention sample investigational activities must be conducted by qualified IPM QA visual inspection personnel, regardless of product type (EUA, clinical trial). Clarifications have been added to procedure 001-003526, *Reference and Retention Sample Program for Parenteral Products Operations in Indianapolis* which will be effective (b) (4)
10. Procedure 001-001764, *Technical Studies* will be modified to clarify documentation requirements and the use of study data to support GMP decisions by (b) (4)
11. For supplier and service provider complaints, a Lilly IPM technical approval step has been added before quality approval, to ensure that the supplier complaint responses are complete and scientifically justified. Timing expectations have been established for each step of the process and relevant metrics have been added to the supplier quality management program. Revised procedures 001-006046, *Complaints and Remarks to Suppliers*, and 001-006063, *Supplier Quality Management* will be effective (b) (4)
12. All visual inspection requalification failures now trigger a deviation to investigate quality impact to previously inspected batches as of **March 8, 2021**, per procedure 001-005386 (version 22), *Visual Inspection Qualification*. For other qualification programs, all requalification failures will be investigated for retrospective quality impact. An (b) (4) assessment process will be added to our training and qualification program to monitor requalification failure investigation and remediation process and to assess the overall health of each qualification program. A change control to implement the program improvements will be approved by (b) (4) .

Detailed Response to Observation 2.A: RABS (b) (4) Management

Lilly IPM's RABS (b) (4) management program is designed to assure product quality as described in Parenteral Quality Standard 001-018001, *RABS Operation and* (b) (4) *Monitoring Strategy for B103 and B105A*. (b) (4) are purchased sterile, via (b) (4) , and are installed under aseptic conditions. (b) (4) are replaced at a minimum of (b) (4) intervals, based on frequency of use and established life expectancy of the (b) (4)

The quality of (b) (4) is verified via two methods: 1) visual inspection using the (b) (4) ' method to inspect the (b) (4) and (b) (4) and 2) by (b) (4) . Visual inspection is performed (b) (4) and again (b) (4) to use of each (b) (4) (b) (4) testing is performed (b) (4) . (b) (4) failures are identified by detection of (b) (4) corresponding to a (b) (4) If a (b) (4) is identified in the (b) (4) then a failure investigation is documented

per 18000-SOP-01-FORM-01 *B103 RABS* (b) (4) *Replacement & Failure Evaluation*, the (b) (4) is replaced, and the new (b) (4) is integrity tested. The failure investigation form instructs operations to notify supervision to initiate an observation in the deviation management system.

Each B103 (b) (4) failure referenced in Observation 2.A was appropriately managed per Procedure 001-001147 *Managing Deviations* and evaluated to ensure no potential impact to product quality. Under the deviation management program in place at the time, root cause investigations (with CAPA plans) were not required for each individual observation but were conducted as needed in response to trends. As described in the Observation 2 response above, all future (b) (4) failures will be investigated as deviations per the enhanced deviation management program, effective (b) (4)

Our deviation management program correctly identified a signal (increased rate of (b) (4) integrity test failures), which led to the initiation of trend TR40191725 on December 16, 2020. As described above, each (b) (4) failure was assessed for impact to product quality in an observation through our deviation management program, and the trend was utilized to conduct a root cause investigation and identify CAPA. There were no time requirements for trend investigations because product quality impact is assessed and documented in the observation (which does have time requirements). To further enhance our deviation management program, timing expectations have been established for trend investigations as described in the response to Observation 2 above.

The increased failure rate investigated in trend TR40191725 corresponds to implementation of a new (b) (4) testing system in September 2020 as part of routine recapitalization efforts. The new (b) (4) testing system can identify leaks within the entire (b) (4) and port system, whereas the previous system tested the (b) (4) only. The trend investigation revealed that the (b) (4) port design and method of (b) (4) in the port can create (b) (4) in the (b) (4) which are detected by the new integrity testing system.

The B103 RABS (b) (4) (b) (4) (b) (4) (b) (4)
(b) (4) in the (b) (4) port allows a (b) (4)
(b) (4) .
Finally, a (b) (4)
.

(b) (4) (b) (4) results in (b) (4) only during integrity testing (not during routine use) due to the installation method of the testing device. The testing device is installed on the (b) (4) and the (b) (4) are (b) (4)
(b) (4) As such, (b) (4) to a region of lower pressure, through the (b) (4) During routine use of the (b) (4) the (b) (4) is

(b) (4) into the Grade A space. The (b) (4)(b) (4) and isolates the operator from the Grade A space. Potential leaks through the (b) (4) are covered by the (b) (4) as it is (b) (4) port, so there is no potential risk of ingress into the Grade A space.

The (b) (4) port design will be modified to reduce the potential for (b) (4) to occur. Based on the existing controls in place for RABS (b) (4) management in B103 and the proposed CAPA, the current (b) (4) (b) (4) replacement frequency is deemed appropriate.

To enhance the (b) (4) Management program, Lilly IPM will implement the following actions.

Actions

1. All future (b) (4) failures will be investigated as deviations per the enhanced deviation management program, effective (b) (4). (b) (4) testing performance for the other Lilly IPM RABS filling line will be assessed based on learning from the completed B103 RABS (b) (4) management trend by (b) (4).
2. Statistically based action limits will be established for the (b) (4) management trending program and minimum timing requirements will be established for performance evaluation by (b) (4) (b) (4).
3. The RABS (b) (4) port design will be modified to minimize false failures during the automated (b) (4) test by (b) (4).

Detailed Response to Observation 2.B: Environmental Monitoring of RABS (b) (4)

All RABS (b) (4) are monitored at the (b) (4) production batch, per procedure 001-007772, *Environmental Monitoring of the Aseptic Classified in Parenteral Manufacturing Areas*. RABS (b) (4) allow separation of qualified Grade A aseptic personnel from the Grade A RABS environment while performing Grade A activities. The monitoring is representative of the Grade A environment during the production of (b) (4) batch. The operator may use the RABS (b) (4) in either orientation, however RABS (b) (4) monitoring is intended to represent the Grade A environment and is not linked to any specific operator task. RABS (b) (4) monitoring is not intended to correspond to the side of the (b) (4) that the operator used. By randomly selecting which side of the (b) (4) to monitor, more variability is introduced into EM results, providing a more complete view of the Grade A RABS environment over time. This monitoring allows for data evaluation not only on a batch-by-batch basis, but over time to ensure the controls (e.g., airflow, disinfection, etc.) maintain the area in the proper state of control, based upon the initial (and on-going) qualification of the environment.

To further enhance our RABS Grade A monitoring strategy, we will implement the following changes:

Action

1. Both sides of RABS (b) (4) will be monitored during environmental monitoring. Detailed monitoring technique instructions will be added to procedure 001-007772, *Environmental*

Monitoring of the Aseptic Classified in Parenteral Manufacturing Areas. This change will be implemented according to change control TR40223712 by (b) (4)

Detailed Response to Observation 2.C: Glass Breakage Investigation

Lilly IPM performed an extensive, cross-functional investigation in response to signals within our quality system regarding glass breakage on 20 mL vial products manufactured in B103. Occurrences of cracked vials were documented and investigated in December 2020 per deviation TR40190443 and subsequently reported through a Field Alert Report (FAR), submitted on December 16, 2020. Specifically, during the packaging of Bamlanivimab batches (VL7910 batches D332489 and D332490), (b) (4) cracked vials were observed (b) (4) , respectively), and during the packaging of batch D336907 product residue was observed in a tray that had been used to transfer vials to the packaging line. IPM conducted a root cause investigation including all operational steps across the process flow to identify the source of glass damage. (b) (4) analysis determined that the fractures occurred on the outside of the vials in the heel region and were caused by a (b) (4) The investigation revealed variability in the operational practice of using a (b) (4) at the (b) (4) following the visual inspection process in B103. The (b) (4) is designed to arrange vials for transfer to trays (b) (4) The root cause was determined to be (b) (4) because the training did not describe the appropriate technique for use of the (b) (4) in sufficient detail. Operator interviews confirmed that newly trained operators, beginning June 25, 2020, applied active back pressure to the (b) (4) (instead of the intended passive approach). Corrective and Preventive actions were implemented to improve procedures and training related to the (b) (4) and appropriate use of the (b) (4)

To further support the scope at the time of the investigation, defect data from the inspection process for all batches manufactured on the Bl03 vial line, and user complaint data from January 1st to December 13th, 2020 were reviewed with no trends identified. Prior to the glass breakage associated with batches D332489, D332490 and D336907, there were no reports from packaging operations of broken vials from the Bl03 vial line. In addition, the other vial formats (3 mL,10 mL, and 50 mL) were evaluated for risk of breakage due to this root cause as part of an engineering study, concluding that the failure mode was isolated to the 20 mL vials used in B103.

The investigation concluded that the breakage occurred after the vial inspection process at the (b) (4) (b) (4) where vials are transferred to trays for transfer to packaging operations. All 20 mL vial batches manufactured in B103 with the potential for newly trained operator involvement (starting June 25, 2020) at the (b) (4) were considered in scope / potentially impacted by the failure mode.

To ensure removal of defects on impacted 20 mL vial batches in B103, a 100% reinspection and tightened (b) (4) was conducted for batches in-scope of the investigation and not yet released. The reinspection and (b) (4) data support that the defect rate is low and provide additional evidence that this is not a systemic issue. Therefore, it was concluded that there is no cause for concern with the quality of distributed batches.

Although improvements in documentation to support the conclusions of the investigation were identified during the course of the deviation review by FDA, a subsequent three-year review of data further confirms the conclusions made in the investigation. As discussed below, actions to supplement the investigation with this information have been taken and further CAPA to improve our documentation practices have been identified.

Detailed Response to Observation 2.C.1: Breadth and Depth of Investigation

As described above, deviation TR40190443 focused on 20 mL vial products filled in B103 because signals within our quality system were limited to 20 mL vial products, and because a root cause was identified early in the investigation which applied only to 20 mL vials filled in B103. In response to Observation 2.C Lilly IPM analyzed additional data encompassing all vial sizes produced in B103, as well as all other vial products manufactured at the site. A summary for each data set is provided below.

a. Defect Control Charts: Data from the 100% inspection and statistical sorting (b) (4) inspection) for all active vial production lines (B103, B107, B105 Diabetes Care) over three years does not show any related trends or signals of atypical performance through the completion of visual inspection and supports that the process was in control.

b. Intra Company Issues: A three-year review of intra company complaints was performed for all vial IPM products, searching for records related to cracked/broken vials. Review of these records confirms that none are related to the investigation in TR40190443.

c. External Complaints: A three-year review of external complaints was conducted for cracked vials and/or broken glass attributed to product from the IPM site. External complaint data support that there are no trends or atypical data related to heel glass breakage for all vial products at the IPM site.

d. Supplier Complaints (b) (4) and (b) (4) were queried for records generated on or after December 15, 2017 until March 29, 2021. The queries searched for records containing at least one of the item codes for all active vial specifications in (b) (4) Four relevant records were found during the query. Two of the four records were sent in response to TR40190443. One record in 2018 was identified as a previous instance of a similar issue in that it involved cracked/broken (b) (4) vials found during clinical trial packaging. The other record was unrelated as it involved a different vial size found at incoming inspection. Therefore, the data supports that there were no indicators of a systemic issue.

e. Glass Breakage Events: Glass to glass contact is inherent to the manufacturing process, therefore some glass breakage events are expected during processing. Glass breakage events are assessed per procedure 001-007063 *Documenting Discovery of Broken Glass* and documented on 7063-FORM-01 *Filling Broken Glass Report*. Therefore, a query was performed to identify all 7063-FORM-01 records issued to production and handling areas across the IPM site. Glass breakage

frequency by area correlated directly to glass consumption (filling) or throughput (handling). There were no indicators of atypical glass to glass contact issues, and no events similar to those observed in TR40190443.

The three-year review of defect data, intra company and external complaints, vendor complaints, and glass breakage events for all vial sizes at the IPM site did not reveal systemic issues and confirms the appropriateness of the scope, impact assessment, and conclusions in TR40190443. This assessment and all associated data, reports, and analysis is documented in Addendum TR40227731.

Reference samples (retains) were visually inspected during the investigation for deviation TR40190443. The products in scope of the investigation are manufactured by Lilly IPM, but due to the Emergency Use Authorization (EUA) status of Bamlanivimab and Etesevimab, the Lilly PR&D organization is responsible for the batches once they are released from Lilly IPM. Any visual inspection of Lilly IPM reference samples is performed by qualified Lilly IPM QA visual inspection personnel, but in this unusual circumstance related to the EUA status of the products, the lead investigator for deviation TR40190443 asked PR&D personnel to perform a visual analysis of the reference samples instead of requesting that the visual inspection be performed by IPM. We detected this error during the investigation for deviation TR40190443, and a subsequent task was assigned to a qualified Lilly IPM QA visual inspector to inspect the samples. During the FDA inspection we learned that the Lilly IPM QA inspector only visually inspected a sub-set of the original intended scope (he viewed the suspected "defects" identified by the PR&D QA representative). Deviation TR40216844 was opened to investigate the issue, and to perform and document a 100% visual inspection of all reference samples associated with investigation TR40190443 by qualified Lilly IPM QA visual inspection personnel. Zero critical defects (including glass breakage) were identified during the inspection, which is consistent with findings from the previous inspections. The results of the visual inspection support the conclusions in TR40190443.

Deviation TR40216844 concluded that procedure 001-003526, *Reference and Retention Sample Program for Parenteral Products Operations in Indianapolis* did not contain adequate instructions for conducting investigation tasks where reference samples are outside of Lilly IPM's custody. The procedure has been revised to clarify that the same requirements apply regardless of sample custody; all reference sample inspections for Lilly IPM products must be performed and documented by qualified Lilly IPM QA visual inspectors.

Detailed Response to Observation 2.C.2: Engineering Study

An engineering study was conducted to support deviation TR40190443. Operators involved in 20 mL batch processing reported a plausible root cause for glass breakage which involved applying (b) (4) (b) (4) to a (b) (4) designed to arrange vials for transfer to trays before (b) (4). Engineering conducted an experiment, in the presence of operators, to apply (b) (4) (b) (4) and observe for glass breakage. The experiment confirmed the reported root cause and produced glass breakage consistent with the complaint vial. However, the operators' signatures were not captured during the experiment, and although electronic force data was captured, a formal protocol was not utilized to

provide step-by-step instructions while conducting the experiment. We investigated the documentation gaps associated with the engineering study in deviation TR40214115. We confirmed that the study was executed with a calibrated (b) (4) which is appropriately set up in the Lilly component management system. The conclusions from the engineering study were summarized in a technical memo and within the TR40190443 investigation summary. Procedure 001-001764, *Technical Studies* will be revised by (b) (4) as stated in the actions section below to specifically require documentation of witnesses and participants during studies when relevant to the experiment, and to clarify documentation requirements and the use of study data to support GMP decisions.

In addition to the deviation management program enhancements described in the Observation 2 response above, we will take the following actions:

Actions

1. All reference and retention sample investigational activities must be conducted by qualified IPM QA visual inspection personnel, regardless of product type (EUA, clinical trial). Clarifications have been added to procedure 001-003526, *Reference and Retention Sample Program for Parenteral Products Operations in Indianapolis* which will be effective upon completion of training by (b) (4)
2. Procedure 001-001764, *Technical Studies* will be modified to clarify documentation requirements and the use of study data to support GMP decisions by (b) (4) .

Detailed Response to Observation 2.D: Supplier Quality Management

Introduction

Lilly IPM's supplier quality management program is designed to ensure that appropriate controls are in place to manage incoming purchased materials and components used in Lilly products and processes, and to ensure quality oversight for the ongoing evaluation of suppliers and service providers.

All incoming materials are purchased from approved suppliers that have been assigned a risk classification based on the criticality of the material to the product or process (i.e., the potential of the material to impact the control strategy). Specifically, we classify suppliers of primary container-closure components as "high risk" under procedure 001-006077 *Material Supplier and GMP Service Provider Management* because primary container-closure materials come into direct contact with the product.

Samples

(b) (4) samples may be used for incoming testing if permitted by the approved specification, which is governed by the quality agreement. Before authorizing the use of (b) (4) in the quality agreement, Lilly QA ensures that (b) (4) samples are representative of the supplier's entire manufactured batch, and the (b) (4) sampling process is reviewed by Lilly QA auditors (upon initiation of the (b) (4) agreement and as part of periodic supplier audits).

(b) (4) samples are placed in a representative or worst-case location (based on Lilly QA approved approach for that supplier and material) and are shipped to Lilly with the rest of the batch. Lilly warehouse personnel receive the batch, and Lilly QC conducts required testing on the incoming samples (b) (4) (b) (4)) per the approved specification. Failures trigger an analytical investigation through the deviation management program. If the analytical investigation concludes that the failure is a valid result, then Lilly QA is notified and the "Complaints and Remarks to Suppliers" (CARTS) process is initiated in accordance with procedure 001-006046, *Complaints and Remarks to Suppliers*. Any batch that does not meet established specifications for its intended use is rejected by QA. All incoming batches are reviewed and dispositioned (approved or rejected) by QA per procedure 001-001522 *Disposition of Purchased Materials and Release of Manufactured Items*.

Complaints and Remarks to Suppliers
When the CARTS process is initiated, Lilly Materials Management QA assembles a cross-functional team to review data, samples, and documentation associated with the failure to determine if a CARTS record is required and if so, then which type of supplier notification will be sent (complaint, remark, or remark Technical Information Request (TIR)). Under procedure 001-006046, if appropriate, QA populates the CARTS record in the (b) (4) system, the record is approved, and Materials Management QA sends the applicable supplier notification to the supplier.

The type of supplier notification drives the type of supplier response. Complaints require the supplier to complete a root cause investigation, report CAPAs planned or implemented because of the complaint, provide any additional testing results, and assess impact to other batches or materials supplied to Lilly. The Quality Agreement in place with each supplier defines the timeline for complaint responses, which is typically (b) (4) . Remarks are for awareness only and do not require a response. A remark Technical Information Request (TIR) requests the supplier to complete a technical review and informs the supplier that a response is expected (although not required).

QA evaluates the supplier's response to ensure that all required content is included per procedure 001-006046 (as described above). If unacceptable, the supplier is informed of the deficiency/ies and an updated response is requested. Once acceptable, the details of the response are recorded in the CARTS record. Any CAPAs and associated timing are documented in an assignment or task record. The record is then approved by QA. The complaint record is closed once all CAPAs have been implemented.

Investigation
Deviation TR40223780 was opened to revisit the specific supplier complaints referenced in Observation 2.D, along with a three-year assessment of the CARTS program, which included (b) (4) complaints and (b) (4) remarks related to primary packaging components in the prescribed timeframe. (b) (4) of the (b) (4) complaints are approved, (b) (4) are awaiting supplier response, and three are awaiting approval. Of the (b) (4) approved complaints, (b) (4) did not identify a confirmed root cause. Any batch that does not meet established specifications for its intended use is rejected, therefore there is no quality impact as a result of the failure to identify root cause at the supplier. CARTS records are reviewed periodically (where frequency is

defined by risk and supplier status) in supplier periodic performance evaluations (PPE) for all suppliers and at supplier relationship meetings (SRM) for select suppliers. Trends and action plans are reviewed in SRMs.

One CARTS record (TR20163594 (b) (4) – Critical Chip) specifically identified the (b) (4) sampling process as a root cause. Lilly returned the defective vial to the supplier ((b) (4) for analysis and root cause investigation (b) (4) ran the defective vial through their (b) (4) in-line inspection system (b) (4) times, and the vial was correctly identified as a defect each time. Based on the results of their trial, (b) (4) concluded that if the defect were present prior to their (b) (4) inspection step, it would have been identified and removed from the population. The defect must have been created after the (b) (4) (b) (4) inspection process and before the Lilly incoming inspection step. The steps between the (b) (4) (b) (4) inspection operation and Lilly incoming inspection include (b) (4) sampling, vial packaging, shipping, and the Lilly incoming receipt process. Although (b) (4) identified the (b) (4) sampling step as a potential root cause, vial packaging, shipping, or incoming steps could not be ruled out. Furthermore, the investigation did not identify any gaps related to the sample selection process or the representativeness of the (b) (4) samples. Lilly rejected the batch.

The (b) (4) sample is packaged into (b) (4)) and secured (b) (4) . The (b) (4) are placed in a worst-case location to increase detection of damage, should any occur during shipping and handling. If critical defects are identified in the (b) (4) sample then the rest of the population is considered impacted, and the entire batch is rejected. Shipping and handling damage is a special-cause event that applies only to a particular shipment. Recurrent shipping and handling issues would be identified and assessed through the periodic provider evaluation (PPE) program, with root cause analysis and CAPA where indicated.

IPM has received (b) (4) batches of glass from (b) (4) during the review period and rejected eight batches. The most recent audit report dated May 23, 2019 observed the supplier's (b) (4) process and approved continuance of (b) (4) samples. Additionally, the most recent periodic performance evaluation (PPE) for (b) (4) (ending September 30, 2020) did not identify any negative trends or shifts in quality. The (b) (4) process remains approved to provide representative samples. The next planned audit date is (b) (4) when the auditors will review CARTS issued since May 23, 2019 and again review the supplier's (b) (4) process.

There are also (b) (4) complaint records (including two awaiting approval) where the supplier determined that the defect occurred after their inspection system and identified shipping or handling post inspection as the most likely root cause. These investigations were completed by multiple (b) (4) sites ((b) (4) , (b) (4)) and (b) (4) (b) (4) was last audited on May 16, 2019, (b) (4) on December 10, 2020, and (b) (4) on September 23, 2019. As described in the previous paragraph, (b) (4) was last audited May 23, 2019. Lilly QA auditors observed the supplier's (b) (4) process and approved continuance of (b) (4) samples. Additionally, PPEs were completed with ending dates of December 31, 2018, September 30, 2020, and September 30, 2020 respectively and did not identify any

negative trends or shifts in quality. (b) (4) , and (b) (4) will be audited again in 2021. The auditors will review the findings of the CARTS prior to their audit and the (b) (4) process will again be reviewed. The (b) (4) process remains approved to provide representative samples. (b) (4) are positioned in worst case locations on the pallet and in shipping. All batches with (b) (4) process or shipping/handling potential root causes have been or will be rejected (disposition of (b) batch is still in progress). The control strategy elements ((b) (4) (b) (4)) function symbiotically to ensure that (b) (4) samples remain representative.

Lilly IPM's supplier quality management program appropriately detected and reacted to incoming component failures. However, to further enhance our program we will take the following action.

Action

1. For supplier and service provider complaints, a Lilly IPM technical approval step has been added before quality approval, to ensure that the supplier complaint responses are complete and scientifically justified. Timing expectations have been established for each step of the process and relevant metrics have been added to the supplier quality management program. Revised procedures 001-006046, *Complaints and Remarks to Suppliers*, and 001-006063, *Supplier Quality Management* will be effective (b) (4)

Detailed Response to Observation 2.E: Requalification Failure Investigations

The Lilly IPM qualification program is designed to ensure our personnel are trained and have demonstrated capability to perform critical job tasks. Personnel must be qualified prior to performing assigned functions, duties, or tasks independently. Qualification is achieved through education, experience, and training or a combination thereof, needed by the individual to perform an assigned function, duty, or task. Continued training ensures that personnel remain proficient in their function and in their understanding of the quality system. When an employee is disqualified from performing a specific task, the employee may retrain and requalify through the remediation program to regain the ability to perform that task.

Visual Inspection Requalification

Lilly IPM investigated all (b) (4) visual inspection re-qualification failures to assess quality impact for the last four years (2017-2021) in deviation TR40216979. (b) (4) operator re-qualification failures and (b) (4) requalification failures were identified.

To determine whether any of the failing operators contributed to a higher proportion of defects being passed through to the (b) (4) inspection step, a query was performed to identify all batches from the prescribed timeframe with (b) (4) failures. The (b) (4) inspection is a statistical audit on the accepted units of the inspected population, performed by qualified QA visual inspection personnel, as a check of the quality level prior to batch distribution. The (b) (4) population size is based on (b) (4) General Inspection Level II sampling plans. Lilly IPM requires a minimum sample size of (b) (4) units in order to have sufficient

population size to support a (b) (4)(b) (4) with a Pass / Fail criterion of (b) (4) (b) (4) batches were identified with (b) (4) inspection failures within the prescribed timeframe.

The batch records were reviewed to determine which operators performed visual inspection. None of the (b) (4) operators with failed requalification were involved in the (b) (4) batches with (b) (4) failures. The investigation concluded that there was no retrospective product impact from any visual inspection personnel requalification failure. To ensure that retrospective impact of future visual inspection re-qualification failures is assessed, procedure 001-005386 *Visual Inspection Qualification* has been updated (and is effective; version 22) to require a deviation to investigate quality impact of previously inspected batches if an operator fails requalification.

All Requalification

To ensure a comprehensive action, Lilly IPM then expanded this evaluation to assess all GMP personnel requalification training failures and for-cause qualification revocations at the site. All requalification failures and revocations occurring over the previous three-year period were investigated in deviation TR40225430. Requalification failures and revocations are investigated at the time of the event and impact is assessed for the batch(es) in scope at the time, but TR40225430 was opened to investigate retrospective impact. For each program with personnel requalification failures or revocations, the investigation evaluated the criticality of the associated task and the other control system elements assuring product quality.

A detailed analysis was performed for qualification programs including (b) (4) . The investigation concluded that there was no product impact from any personnel requalification failure or for-cause revocation.

To enhance the site qualification program, Lilly IPM will implement the following action.

Action

1. All visual inspection requalification failures now trigger a deviation to investigate quality impact to previously inspected batches as of **March 8, 2021**, per procedure 001-005386 (version 22), *Visual Inspection Qualification*. For other qualification programs, all requalification failures will be investigated for retrospective quality impact. An (b) (4) assessment process will be added to our training and qualification program to monitor requalification failure investigation and remediation process and to assess the overall health of each qualification program. A change control to implement the program improvements will be approved by (b) (4) .

OBSERVATION 3

Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes.

The following discrepancies were noted during the review of media fills and batch records which were executed on the B103 vial filling line. Products aseptically filled on this line include but are not limited to Ramucirumab, Glucagon, (b) (4) *, Olaratumab,* (b) (4) *,* (b) (4) *, Bamlanivimab, and Etesevimab. Specifically,*

A. *Media Fills*
   1. *Interventions performed during media fills do not reflect routine production. The firm normalizes the number of inherent interventions obtained for the entire year to determine the number of interventions performed per* (b) (4) *vials. They do not trend the frequency/type of interventions occurring per batch. For* (b) (4) *media fills performed annually on the vial filling line, the firm only performs the* (b) (4) *inherent interventions.*

   2. *Adequate justification was not provided to support of how the conditions simulated during your Fill Duration Challenge – NLT* (b) (4) *in Media fill MF0116 – MF0271, D291263 is reflective of routing manufacturing.*

   3. *Fatigue is not adequately challenged. Filling Operator Extended Personnel Shift was listed as being challenged for 14 hours, 9 minutes (Protocol Required Challenge NLT* (b) (4) *) during MF0273, Batch D256292 per APS Summary report, effective July 6, 2020. An aseptic operator's shift is* (b) (4) *. The media fill D256292 did not support the operator working on the aseptic line for 14 hours, 9 minutes. Management confirmed the operator did not have to work on the aseptic fill line for the entire time they are challenging fatigue. They stated they do not consider the time the operator is working in the aseptic B103 vial filling line during the fatigue challenge, instead the monitor the length of the operators shift, regardless of where they are working. As performed by the firm, the fatigue challenge does not ensure the operator maintains aseptic technique even when they are fatigued.*

B. *Aseptic Processing*
   1. *SOP 001-005056 General Aseptic Practices and Techniques for Parenteral Filling and Manufacturing Operations, v22, dated 12/16/19, section 5.7.2 states "All aseptic personnel must use the appropriate* (b) (4) *terminal within the aseptic area to log in and log out from the areas identified within the applicable* (b) (4) *". Management stated they use an electronic entry/exit log for tracking the number of people who work in the B103 aseptic vial line, however they do not use this electronic system to reconcile*

who is in the room during production. This log is not controlled. Operators can make adjustments to this log to alter the number of persons in the room when people forget to log in/out. What is documented in the batch record does not correlate to what is listed in the electronic log. For example:

a. *During the execution of D349899, VL795002, LY3832479 starting on* (b) (4) *:*
   - (b) (6) *did not sign into the log but is recorded as performing set-up of the line at 11:24 am and is documented as leaving at 11:27 am.*
   - (b) (6) *is documented as performing setup activities at 11:11 am and 11:23 am but according to the electronic entry/exit log, he did not sign into the aseptic fill line area until 3:22 pm.*
   - (b) (6) *is documented as performing 3 interventions on* (b) (4) (b) (4) *yet according to the electronic log,* (b) (6) *was not documented being in the aseptic fill vial line for the entirety of the run.*

b. *During the execution of D308778, VL701991, LY3819253 dated :*
   i. (b) (6) *) is documented as performing interventions at* (b) (4) (b) (4) *but according to the electronic entry/exit log,* (b) (6) *did not sign into the aseptic fill line area until 5:52 pm.*

c. *Environmental Monitors are not logged into the electronic entry/exit log, even though they are in the aseptic area and performing EM on the line.*

2. *Not all activities performed in the aseptic area are documented. The firm does not document who and when aseptic manipulations are performed (i.e. addition of stoppers, environmental monitoring).*

3. *The firm did not have scientific justification for removing some coded interventions from their* (b) (4) *system used to document interventions during production. These interventions were still occurring (although at low frequency). No rational could be provided as to why interventions occurring less frequent were kept while some interventions occurring at higher frequencies were removed.*

4. *Quality oversite of the aseptic B103 vial filling line is not documented. 001-004190 Responsibilities of Personnel Working in Indianapolis Parenteral Manufacturing states under QA Responsibilities in section 2.3.6, "Must ensure its regular presence in all operational areas". No documentation was provided to support you perform quality oversight of aseptic filling.*

Response to Observation 3

Introduction

Lilly IPM Sterility Assurance Control Strategy Overview

A holistic sterility assurance control strategy has been established at Lilly IPM to ensure, with a high degree of confidence, that products are free of microbial contamination. The site strategy is systematically structured into functional elements that contribute to the assurance of product sterility and is inclusive of all facilities operating within the site.

Each sterility assurance element, and the inter-connectivity between them, is briefly described as follows:

Infrastructure & Infrastructure Maintenance
The infrastructure within IPM is comprised of the design, construction, qualification, control, and utilization of the physical facilities, equipment, and utility systems utilized in the aseptic manufacturing process. Infrastructure maintenance is comprised of the (b) (4) .

Process & Product
Processes used in the manufacture of sterile products consider the contributions of (b) (4) in support of overall sterility assurance. Products have been designed with consideration of sterility assurance needs including (b) (4)

Measures
There are multiple indicators used at Lilly IPM to determine acceptability of aseptic processes and individual batches including (b) (4) .

Overall, the elements of the Lilly IPM sterility assurance strategy are holistically designed, implemented, and executed to collaboratively ensure that products are consistently free of microbial contamination. The Lilly IPM sterility assurance control strategy is executed in a manner which is representative of routine production activities.

For continuous improvement, Lilly IPM was already evaluating its sterility assurance control strategy for continued improvements and on-going alignment with evolving global requirements.

Actions

1. A line-specific maximum intervention threshold for production batches will be established, supported by the maximum number of interventions demonstrated in the APS program. This will be completed by (b) (4) .
2. Procedure 001-007197, *Aseptic Process Simulation Program Strategy* will be revised to require that routine interventions executed within APS will represent each functional zone of the filling line outlined in line-specific intervention risk assessments. This requirement will be implemented by(b) (4) .
3. Procedure 001-007197, *Aseptic Process Simulation Program Strategy* will be revised to require that maximum fill duration is challenged by processing (b) (4) filled units and non-(b) (4) filled units to reflect continuous operations in alignment with *PDA Technical Report 22- Process Simulation for Aseptically Filled Product (revised 2011)*. Continuous operations will inherently address operator fatigue as outlined in Observation 3.A.3. This requirement will be implemented by(b) (4) (b) (4)
4. Procedure 001-007197, *Aseptic Process Simulation Program Strategy* will be revised to require that (b) (4) units be filled for a pre-determined time-period after execution of critical interventions that occur during processing of empty units between filling orders. This requirement will be implemented by (b) (4) .
5. Procedure 001-007197, *Aseptic Process Simulation Program Strategy* will be revised to(b) (4) the total duration of filling (b) (4) units on each individual shift. This requirement will be implemented by (b) (4) .
6. The (b) (4) application will be revised to require decrement and increment of the number persons in the defined area to be verified. Implementation of this will be completed by(b) (4) .
7. (b) (4) terminals will be installed at the aseptic area gown room entrances and at the aseptic area exit airlocks. Physical location of the terminals by points of(b) (4) will help to reduce human error (i.e., forgetting to log in/out) by being placed physically in the (b) (4) pathways. This change will be implemented by (b) (4)
8. To further reinforce aseptic processing operational support, Aseptic Process Mentor positions will be created to mentor, coach, guide and lead aseptic manufacturing training and qualification programs. These positions will be effective by(b) (4)
9. Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our aseptic processing operations and controls and our aseptic processing simulation program by(b) (4) .

10. The area-specific intervention/manipulation reports (e.g., cycle summary reports) will be updated for the other production areas to document the manipulations no later than (b) (4) according to change control TR 40205132 and TR 40180833.
11. Procedure 001-007044 *Sterility Assurance Risk Management at the IPM Site* and 7044-TEMP-03 *Aseptic Interventions and Aseptic Manipulations Risk Management Template* will be revised to include requirements and content specific to the comprehensive documentation of rationale for the removal or addition of coded interventions. Implementation will be completed by (b) (4) .
12. Procedure 001-007997, *Parenteral Quality Manufacturing Oversight*, has been created to formalize floor walk-throughs in aseptic production areas and to define expectations, instructions, and frequency for the Quality Check process in Lilly IPM. The Quality Check process applies to all operational and QC Lab areas and requires physical observation/evaluation of the area using tools and guides listed in the procedure. For example, comparing the observed area practice to the procedure for an identified task. QA is responsible and accountable for the performance, documentation, evaluation and reconciliation of the Quality Check process and outcomes as outlined in procedure 001-007997. The procedure will be effective (b) (4) .
13. Additionally, effective by (b) (4) , a QA for Sterility Assurance consultant role will be created to lead the quality oversight program for aseptic operations and to mentor QA floor support and Sr. QA floor specialists in aseptic processing quality and compliance attributes.

Response to 3.A

Detailed Response to Observation 3.A.1: Routine Production Interventions Represented in the Aseptic Process Simulation (APS) Program

Lilly IPM's APS program currently ensures representation of all interventions (b) (4) , and all interventions in routine production batches are evaluated for impact to product quality. Although there is not a maximum threshold established per routine production batch, implementation of an overall maximum intervention threshold per production batch would provide additional assurance that the cumulative potential sterility risk of aseptic interventions is evaluated as part of the batch disposition process.

Procedure 001-007248*, Strategy for Managing Aseptic Interventions and Aseptic Manipulations at the IPM Site,* outlines the overarching process in which interventions are established, executed, and assessed at Lilly IPM. The term *aseptic manipulation* is used to describe activities performed in the Grade A areas that are an *inherent* part of the manufacturing process while the term *aseptic intervention* is used to describe process-related activities performed in the Grade A areas that are *corrective* in nature. For context, aseptic manipulations include but are not limited to (b) (4) (b) (4) . In contrast, activities that require operators to enter the Grade A space to perform corrective activities include but are not limited to (b) (4) . Any

time interventions are performed, operators are required to execute corrective activities using aseptic technique stipulated in procedure 001-005056, *General Aseptic Practices and Techniques for Parenteral Filling and Manufacturing Operations*. Additionally, intervention-specific protective measures (such as (b) (4)) and approved discard strategies ensure maintenance of the aseptic environment and protection of product quality.

As mentioned in the Introduction to the Observation 1 Response, Lilly IPM employs a HACCP approach outlined in procedure 001-007248 to guide the creation of formalized risk assessment documents that provide the rationale for a criticality rating of high, medium, or low risk for each Grade A intervention and manipulation based on established risk factors of (b) (4) .

Regardless of the risk of the intervention (described above), per procedure 001-007197, *Aseptic Process Simulation Program Strategy*, aseptic interventions are further categorized by the Lilly IPM APS Program as either "routine" or "non-routine" based on frequency of occurrence from the previous year's routine production batches. All routine interventions are challenged (b) (4) APS batch supporting the (b) (4) program at a frequency that (b) (4) frequency observed during production batches. Non-routine interventions are simulated in the (b) (4) APS program at a minimum of (b) (4) for each respective filling line.

To evaluate and respond to variability during processing, Lilly IPM has established a statistically based process in accordance with approved document *"Modified Approach for Establishing High-Risk Intervention Limits at the IPM Site"* to differentiate between common-cause and special-cause variability with respect to aseptic interventions. Each aseptic processing line fills a variety of products characterized by different batch sizes and speeds. Both line speed and batch size impact the overall length of batch-specific fill durations.

While accounting for the variability described above, criterion based upon control chart limits were implemented as detailed in procedure 001-002046, *Managing Aseptic Interventions and Aseptic Manipulations During Filling Operations in B105 and B103*, to facilitate identification of atypical intervention rates (independent of batch size) for routine production batches. By normalizing this data, the influence of batch size and fill duration is minimized, allowing for better trending and differentiation of special-cause from common-cause variability relative to interventions.

Control chart limits are established for low- and medium-risk aseptic interventions based upon statistical evaluation of historical data. High risk intervention limits are set conservatively at a maximum of (b) (4) (b) (4) intervention per batch. The types and number of interventions performed are evaluated against these control chart limits and captured in an area specific intervention report. Additionally, a batch-specific environmental monitoring evaluation is performed including (b) (4) Both the intervention report and the environmental monitoring evaluation are reviewed by Quality as part of the batch disposition process. If

any control chart limits or environmental monitoring limits are exceeded, the deviation management system is used to evaluate potential impact to the batch.

In addition to using production data to inform the APS program and assure product quality, trending and review of all aseptic interventions is performed. Per procedure 001-007248, control chart limits are cross-functionally assessed, on (b) (4) basis, to determine if updates to limits are required based on changes in frequency of interventions. As part of this (b) (4) assessment, the previous year's aseptic intervention frequency data across all commercial batches is utilized to evaluate any changes in performance with respect to intervention frequency.

An analysis was performed, *APS Intervention Retrospective Analysis Jan2018 - Feb2021* (Appendix E), which summarized the highest number of aseptic interventions validated within an APS batch (during the referenced time frame) and evaluated if any B103 Vial product batches exceeded that number in the same time frame.

This analysis concluded that (b) (4) APS batches, representing a total of (b) (4) media filled units, were successfully filled on the B103 Vial Filling Line with no turbidity observed. The highest number of interventions performed in any specific APS batch was (b) (4) (MF0118-MF0305, D316885; October 2020). Of these batches, only one product batch (Glucagon batch D065359, April 2019) was identified as having exceeded the APS maximum interventions challenged (b) (4) with a total of (b) (4) interventions performed. During the batch review process, this batch was recognized as having exceeded the CCL associated with 'low risk' interventions and was investigated at the time for sterility assurance impact via the site deviation management process. The investigation reviewed all relevant sterility assurance data including, (b) (4) (b) (4) All results met acceptance criteria demonstrating that the B103 Vial Line RABS environment remained in a qualified and acceptable state-of-control throughout batch processing. Additionally, all interventions performed during batch D065359 were approved interventions per (b) (4), *Intervention Codes, Corrective/Protective Measures, and Discard Strategies (B103 Vial Filler/* (b) (4) *)* and were previously successfully challenged by the B103 Vial Line APS program. There was no impact to product safety or quality resulting from the interventions executed during batch D065359.

Actions

1. A line-specific maximum intervention threshold will be established, supported by the maximum number of interventions demonstrated in the APS program. This threshold will be based on an (b) (4) review of routine production batches. Lilly IPM commits to implement this change via change control TR40223712 by (b) (4)

2. Additionally, Lilly IPM commits to challenging additional routine interventions during all annual APS batches to better simulate worst-case operating conditions. Lilly IPM Procedure 001-007197, *Aseptic Process Simulation Program Strategy* will be updated to ensure that routine interventions are represented in each functional zone of the filling line (e.g., incoming

(b) (4)) as outlined in line-specific intervention risk assessments. This approach will ensure frequent intervention activities, and associated microbiological risks, are represented within these zones during each (b) (4) APS, and will address processing variability of production conditions. To align with the next scheduled B103 Vial Filling APS batch, Lilly IPM commits to implementing these site APS program changes as described by (b) (4)

Detailed Response to Observation 3.A.2: Routine Production Fill Duration Represented in Aseptic Process Simulations

Lilly IPM has established a representative aseptic process simulation (APS) program, as described in procedure 001-007197, *Aseptic Process Simulation Program Strategy*. The program is designed to demonstrate that the combination of equipment, personnel, environment, and processes are capable of consistently producing sterile product batches. Maximum fill duration is one aseptic processing attribute that is challenged by the program on (b) (4) basis. This challenge is defined as the maximum filling time (from start- of- fill to end- of- fill) allowable for product batches, on a single set of sterile product contact parts, prior to a filling equipment changeout. For the B103 Vial Filling Line, the maximum filling duration has been validated at (b) (4) hours (from the start of filling to the end of filling).

The Lilly IPM APS program currently employs an approach to challenging filling duration that utilizes defined intervals of active filling that occur throughout the duration of each simulation. The APS program specifies that (b) (4) active filling intervals occu (b) (4) shift, at periods that represent the approximate (b) (4) of each shift. The significance to the (b) (4) of each fill shift is linked to the inherent manipulations associated with start-up of the line (e.g., sterile equipment set-up) and similar risks at the end of the shift (e.g., operator fatigue). Additionally, the APS program specifically challenges the start- and end- of- fill activities, thereby capturing microbiological data representative with the beginning and end of batch processing that each commercial product experiences.

The current APS maximum fill duration challenge is representative of the production process in that the validated maximum filling duration of product batches was always challenged by exposing sterile equipment, along with intermittent filling, to the Grade A environment for that maximum time-period. In addition, the APS design results in a worst-case intensity of interventions (b) (4) (b) (4)), relative to commercial product.

Any commercial production batch which exceeds the validated APS maximum fill duration would be investigated by the Lilly deviation management system.

There were (b) (4) batch rejections relating to any sterility assurance measure (e.g., environmental monitoring, sterility testing) as described by the site sterility assurance control strategy. Complaint and

pharmacovigilance data did not identify any instances of manufacturing-introduced microbiological contamination and there is no impact to product quality. Additionally, a review of the APS summaries for each year shows that all program requirements were met.

Based on this data review, and the design of the IPM APS program, the maximum aseptic fill duration has been validated on the B103 Vial Filling Line. However, we will incorporate changes to the APS program as described below to ensure expanded representation of the worst-case challenge to the maximum filling duration.

Actions

1. Lilly IPM commits to improving the manner that the APS program challenges maximum fill duration such that the impact of continuous operations is more fully represented. In alignment with *PDA Technical Report 22- Process Simulation for Aseptically Filled Product (revised 2011)*, Lilly IPM will update Procedure 001-007197, *Aseptic Process Simulation Program Strategy* to require the processing of (b) (4) filled units and non(b) (4) filled units. The APS design will evaluate the worst-case cumulative risk of microbiological contamination associated with (but not limited to) (b) (4) . Lilly IPM commits to implementing these site APS program changes as described by(b) (4) .

2. For any critical interventions that occur during processing of empty units between filling orders, units will be filled with growth media for a pre-determined time-period (post-intervention) to capture any potential microbiological risk/impact associated with the activities. This requirement will be incorporated into Procedure 001-007197, *Aseptic Process Simulation Program Strategy*. Lilly IPM commits to implementing these site APS program changes as described by(b) (4) , (b) (4)

3. Additionally, Lilly IPM will update Procedure 001-007197, *Aseptic Process Simulation Program Strategy,* to increase the total duration of filling (b) (4) units on each individual shift to ensure a robust challenge of operational activities including interventions into the critical filling area, personnel, and equipment operations. On (b) (4) basis there will be linkages established between routine production batches, and APS demonstrated data. Lilly IPM commits to implementing these site APS program changes as described by(b) (4) .

Detailed Response to Observation 3.A.3: Demonstration of operator fatigue in aseptic process simulations

Lilly IPM's APS program currently challenges extended personnel fatigue in a way that represents the elapsed duration of work, consistent with commercial production, performed by an aseptic operator. As described more fully below, our current approach is supported by existing controls and data demonstrating that the control strategy is effective. Nonetheless, we are implementing enhancements to the APS program to ensure that it more fully accounts for continuous aseptic filling.

As outlined in procedure 001-007197, *Aseptic Process Simulation Program Strategy*, the Lilly IPM APS Program challenges an extended (shift duration is extended beyond routine) aseptic operating shift to demonstrate that operator fatigue at the end of a shift does not have an adverse impact on aseptic technique during processing. Across the extended shift, (b) (4) active filling intervals occur at approximately the (b) (4) of the shift. Filling during the (b) (4) interval does not cease until the minimum extended shift duration is achieved.

For the B103 Vial Filling Line, the established standard operating shift is (b) (4), with an extended personnel fatigue shift challenge of not less than (NLT) (b) (4).

The way in which fatigue has been challenged by Lilly IPM is representative of commercial batch activities. Across the APS fatigue shift, aseptic operators participate in filling media units, which requires them to perform aseptic manipulations (i.e., inherent interventions) and aseptic interventions (i.e., both routine and non-routine interventions). Operators execute multiple aseptic area entries and associated gown changes within this operating shift. Additionally, other routine manufacturing support activities such as area sanitization, unloading of (b) (4) and training occur between periods of active filling while being on site for the duration of the shift.

In addition to the use of the APS program to demonstrate that fatigue does not impact an operator's ability to execute appropriately, there are other control strategies utilized during aseptic filling activities to mitigate potential impacts of operator fatigue. During filling operations, other types of aseptic manipulations (i.e., (b) (4)) and aseptic interventions (i.e., (b) (4)), require ingress into the Grade A space via RABS (b) (4) or (b) (4) Prior to entry, product units are (b) (4) from the vicinity of where the activity will take place. This minimizes the potential for adversely impacting units when performing the required activity. Personnel are required to execute activities using aseptic technique stipulated in procedure 001-005056, *General Aseptic Practices and Techniques for Parenteral Filling and Manufacturing Operations*. When aseptic interventions are performed, intervention-specific protective measures and approved product discard strategies ensure minimal impact and risk of contamination. Critical aseptic interventions associated with product contact equipment have associated operator task-related monitoring, providing a microbiological measure of aseptic technique. Throughout (b) (4)

(b) (4) is collected, capturing the environmental conditions associated with operator ingress into the Grade A space. At the end of each batch, (b) (4) (b) (4), is performed.

As referenced in Observation 3.A.2, all relevant sterility assurance data (including (b) (4) (b) (4)) demonstrate that the B103 Vial Line RABS environment remained in a qualified and acceptable state-of-control throughout batch processing including the potential effects of operator fatigue.

Actions

1. As the APS program will be updated to include continuous aseptic processing of units through the duration of an APS (refer to response to Observation 3.A.2), this will also increase the rigor around the fatigue portion of the simulation. Lilly commits to implementing this site APS program change by (b) (4) .

Response to 3.B

Detailed Response to Observation 3.B.1: Allowable Number of Personnel in Aseptic Processing Area

Lilly IPM has implemented an extensive control strategy to prevent microbiological contamination of products. The aseptic filling areas at Lilly IPM have established boundaries, which have associated limits for maximum number of personnel based upon the area aseptic process simulation (APS) program. These are derived from the maximum number needed for operations including environmental monitoring. These boundaries are documented in procedure 001-005056, *General Aseptic Practices and Techniques for Parenteral Filling and Manufacturing Operations*. Additionally, signage exists indicating the maximum number of personnel allowed in the boundary of the aseptic area.

The (b) (4)) is utilized by aseptic personnel to document the total number of personnel into and out of those defined boundaries within the aseptic processing areas, via (b) (4) (b) (4) (b) (4)) terminals within those spaces. The system is not intended to attribute specific activities to any individual operator; it is merely intended to capture data that supports our analysis of the maximum allowed personnel in each space where it is in use.

Personnel that enter the aseptic areas must pass extensive education and training to gain electronic access to the appropriate aseptic area(s). All personnel entering the aseptic grown rooms are required, per procedure 001-001698, *Aseptic Personnel Monitoring for Parenteral Products Operations*, to sign in and document the date and time of entry in 1698-FORM-01, *Aseptic Area Entry Logbook*.

Deviation 40224147 was initiated to investigate the root cause, determine impact, and identify corrective actions for discrepancies identified with the *Log In* and *Log Out* process. Our investigation determined that there were inconsistencies between procedure 001-005056, *General Aseptic Practices and Techniques for Parenteral Filling and Manufacturing Operations,* and its associated training, POV0163. This, as well as location of the (b) (4) terminals, led to confusion and/or inconsistent use of the log. Procedure 001-005056 and training course POV0163 were updated immediately, and aseptic personnel were retrained by (b) (4) (b) (4) to emphasize that each person (including EM) must log in/log out of the area individually using the (b) (4) entry/exit log. Our investigation determined that the documentation discrepancies identified did not impact product quality. The entry/exit log data generated during processing of the batch is evaluated (via the (b) (4) Area Entry-Exit Log Report) as part of the batch review process to ensure that the maximum number of personnel was not exceeded. If an issue is detected, it is managed in accordance with the deviation management process.

In addition, the sterility assurance control strategy, as described in the Introduction for Response 3, delineates the controls in place to protect both the aseptic environment and the product. Evaluation of the impact of these discrepancies to the sterility Critical Quality Attribute (CQA) was conducted. The impact to the sterility CQA would have been prevented and/or detected via the sterility assurance controls listed below:

- Facility/equipment design ((b) (4) , (b) (4) detailed in Sterility Assurance Strategy (procedure 001-007081)
- Aseptic Personnel Daily and Task-related Monitoring (procedure 001001698)
- Aseptic Area Environmental Monitoring (procedure 001-007772) and Environmental Monitoring Data Review Process (procedure 001-001694)
- Batch Release Sterility Testing (Product Specifications)

A comprehensive review of our environmental monitoring data confirmed state of control of the aseptic areas (See Appendix A, *Indianapolis Parenteral Manufacturing 3-Year Environmental Monitoring Evaluation.*).

As stated previously, there is personnel awareness of the limit through training and physical signage in the area stating the maximum number of individuals allowed in the boundary of the aseptic area. In addition to the correction that has already been completed, we will implement the following improvement actions.

Action

1. The (b) (4) application will be revised to require decrement and increment of the number persons in the defined area to be verified. Implementation of this will be completed by (b) (4) .
2. (b) (4) terminals will be installed at the aseptic area gown room entrances and at the aseptic area exit airlocks. Physical location of the terminals by points of (b) (4) will help to reduce human error (i.e., forgetting to log in/out) by being placed physically in the (b) (4) pathways.

Log In will occur immediately prior to the start of the gowning process for the aseptic areas. All aseptic personnel will be required to *Log Out* immediately prior to exiting the aseptic area. This will allow control of personnel entering the aseptic areas, during production activities, and ensure the qualified number of individuals are not exceeded. Additionally, this revision to the system will allow confirmation of training completion, identification of maximum time gowned, and enable simpler reconciliation of exit monitoring. Implementation for Phase II will be completed by (b) (4)

3. To further reinforce aseptic processing operational support, Aseptic Process Mentor positions will be created to mentor, coach, guide and lead aseptic manufacturing training and qualification programs. These positions will be effective by (b) (4)
4. Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our aseptic processing operations and controls and our aseptic processing simulation program by (b) (4) .

Detailed Response to Observation 3.B.2: Documentation of Aseptic Manipulations

The term *aseptic manipulation* is used to describe activities performed in the Grade A areas that are an inherent part of the manufacturing process. Examples of aseptic manipulations include activities such as initial sterile equipment installation, addition of components and environmental monitoring. Procedure 001-007248, *Strategy for Managing Aseptic Interventions and Aseptic Manipulations at the IPM Site,"* provides guidance for execution and documentation of aseptic manipulations. When performing aseptic manipulations required by a product's manufacturing instructions, their execution is to be documented as specified in the applicable local procedure.

Documentation associated with the collection of all environmental monitoring samples, including date/time and personnel, is documented by EM personnel within the (b) (4) laboratory information management system (LIMS) in accordance with procedure 001-007772, *Environmental Monitoring of the Aseptic Classified in Parenteral Manufacturing Areas*. (b) (4) is the system that is used to document all environmental monitoring activities within the facilities. This system does have attributable data confirming who performed the sampling along with the date and time performed.

Other aseptic manipulations such as component addition that are inherent to the manufacturing process are validated as part of each APS. Therefore, there was not a requirement for their documentation. However, this practice was modified effective March 01, 2021 for the B103 vial line, with the revision on procedure 001-007248. All manipulations, except for environmental monitoring that will continue to be documented in (b) (4) are required to be documented in the (b) (4) including who performed the manipulation. Documentation of the manipulations are now listed on the area-specific intervention/manipulation report (e.g., cycle summary report). These data are evaluated as part of the batch review process.

Action

1. The area-specific intervention/manipulation reports (e.g., cycle summary reports) will be updated for the other production areas to document the manipulations no later than (b) (4) , (b) (4) according to change control TR 40205132 and TR 40180833.

Detailed Response to Observation 3.B.3: Scientific justification for addition / removal of aseptic interventions

Lilly IPM has a risk-based program for assessing aseptic interventions. This program ensures that an annual review of all currently approved aseptic interventions is performed by a cross-functional team (Quality, TS/MS, Engineering, Operations) per procedure 001-007044, *Sterility Assurance Risk Management at the IPM Site*. The cross-functional team evaluates and reaches a determination regarding whether each aseptic intervention code can and should be approved into or removed from the population of currently approved interventions. The decision to change the status of an aseptic intervention code is documented per 7044-TEMP-03, *Aseptic Interventions and Aseptic Manipulations Risk Management Template*, and implemented through the change management process.

Interventions authorized to be performed on each aseptic filling line are assigned alpha-numeric codes for identification and quantification purposes. Codes are designated based on (b) (4) (b) (4) . A total of (b) (4) interventions were recommended for addition, modification, or removal in the *B103 Vial Line Aseptic Intervention Risk Assessment* (version 11, approved on April 3, 2019). This review is documented in the *B103 Vial Line* (b) (4) *– Intervention Add-Remove Evaluation*, with the outcomes summarized below:

- (b) (4) were open (b) (4) interventions and the cross functional review team recommended removal to further reduce/remove risk to the Grade A environment.
- (b) (4) intervention codes were removed and reassigned as other codes (below)
- (b) (4) new codes were created – the previous (b) (4) interventions that were reassigned new codes (as the team determined the activities should be moved to a different zone within the filler and new numbering system), along with (b) (4) new codes that were created due to two interventions being separated into (b) (4) distinct interventions
- (b) (4) intervention codes had the description modified to provide better clarity for the activity.
- (b) (4) codes were new codes requested by operations during the cross functional review.
- (b) (4) intervention codes were recommended for removal without specific justification.

For the (b) (4) codes recommended for removal without a specific justification, our investigation determined that these codes represented infrequently performed interventions. We also confirmed that this rationale is supported because there have been (b) (4) non-coded interventions performed and documented for the B103 Vial line that match these interventions/codes since they were removed. If non-coded interventions occur, they are documented at the time the intervention is performed and reviewed by QA as part of the batch disposition.

Deviation TR40224690 was generated to investigate the reason why the rationale for recommending addition, modification, or removal of interventions was not documented in the *B103 Vial Line Aseptic Intervention Risk Assessment* (version 11, approved on April 3, 2019). The deviation investigation determined that documentation of the recommendations identified by the cross-functional team during the annual assessment is not required per procedure 001-007044, Section 5.6 (Aseptic Interventions and Aseptic Manipulations Risk Management).

Although the rationale wasn't documented, the risk-based evaluation of the interventions that was conducted utilized a HACCP-based approach to analyze the risk associated with aseptic interventions. This process was selected since it provides a structured method for applying scientific principles to analyze, evaluate, prevent, and control potential risks and is well suited to identify risks associated with microbial hazards. The documented results from the assessment support are in alignment with the Aseptic Intervention and Sterility Assurance Control Strategies and support product quality. The changes that were made reduced risk (removal of (b) (4) interventions), re-coded, or removed infrequently used interventions.

Based upon the above, there is no product quality impact because of any of the changes recommended in *B103 Vial Line Aseptic Intervention Risk Assessment* (version 11, approved on April 3, 2019).

Actions

1. Procedure 001-007044 *Sterility Assurance Risk Management at the IPM Site* and 7044-TEMP-03 *Aseptic Interventions and Aseptic Manipulations Risk Management Template* will be revised to include requirements and content specific to the comprehensive documentation of rationale for the removal or addition of coded interventions. Implementation will be completed by (b) (4) (b) (4)

Detailed Response to Observation 3.B.4: Quality Oversight of the 103 Vial Filling Line

Lilly IPM's Quality Assurance (QA) organization is independent from production. QA is responsible for ensuring that all products and materials meet the quality requirements for their intended use and that quality systems are created, monitored, and maintained. Lilly IPM QA unit has team members focused in the following areas: quality systems and GMP compliance processes, QA for QC support, complaints investigation, material and supplier management, stability management, visual inspection, batch disposition and floor support for manufacturing operations. The Quality Lead Team (QLT) consists of quality and functional management and is responsible for the implementation, control, sustainment, monitoring and documentation of the Quality System. QLT provides cross-functional leadership and oversight of product quality, GMP compliance and the CAPA program for the site. At the operations support level, QA representatives, while independently reporting through the Quality organization, are embedded into cross-functional process teams whose focus is a specific production area (for example,

B103 Vial Filling and inspection area and process). The process team has direct accountability for all unit operations under its responsibility to ensure the process is in control, capable and compliant and the team is co-located near the production area they support. The process team addresses issues, ensures continuity between shifts, reviews process monitoring outputs, changes and continuous improvement initiatives and ensure shop floor oversight. Additionally, 24/7 on-site, routine dedicated support is provided by the QA specialist team to provide oversight, review, and approval of GMP documents and respond to immediate area needs. By design and as executed in our site's operations, QA is present during production activities, and available always should any issues arise.

In particular, QA personnel are directly involved in all quality related matters including production support activities in day-to-day operations, evaluation of non-conformances, process changes and continuous improvement initiatives as incorporated in procedures. On a daily basis, QA personnel lead, mentor and coach site personnel on quality matters associated with GMP production including batch review and disposition; provide guidance and feedback to operational areas to ensure GMP compliance; lead process team discussions and perform triage for unexpected events; review and/or approve GMP documentation such as batch records, procedures, protocols (validation, C&Q, investigational), technical studies, change controls, specifications, deviations, annual product reviews, maintenance action plans, equipment cycle summary reports, manufacturing ticket check-in, release of sanitization agents and pH adjusters.

Examples of task or process specific driven activities include but are not limited to:

- Aseptic Areas: documented Quality observation of aseptic process simulations (e.g., media fills) from sterilization thru final inspection as described in procedure 001-001693, *Aseptic Process Simulations for Parenteral Product Aseptic Processing*
- Aseptic Areas: participate in existing business process for completing cross-functional (including QA) floor walk-throughs in aseptic production areas with observational focus on aseptic area behavior and practices. Outcomes of this process were shared during inspection.
- Classified Areas: engagement in area recovery and inspection in response to events with potential to compromise general or classified areas as described in procedure 001-001688, *Actions to Be Taken After General and/or Classified Areas Have Been Compromised*, and 1688-TEMP-01 *Recovery Plan Document* including physical confirmation of area readiness based on observed state
- Engagement in area visual inspection, evaluation of risk level and definition of corrective actions as outlined in procedure 001-007619, *Visual Inspection of Equipment and Zones*
- Engagement in HOLD strategy design, return to service, final release and final accountability of HOLD labels as described in procedure 001-001636, *Use of HOLD Status in Parenteral Product Operations*
- Inspection of the site via engagement in Site Self Inspection process as outlined in procedure 001-001751, *Parenteral Site Self Inspections*

Quality presence is outlined in role descriptions, expectations, and site procedures. Day to day and site activity support occurs as described above and is described in procedures so that the required quality actions and oversight are linked by tasks and processes.

Lilly IPM recognizes the opportunity to formalize a program to document the Quality dedicated floor check process already in place and strengthen the existing documentation of quality oversight activities through the following actions:

Actions

1. Procedure 001-007997, *Parenteral Quality Manufacturing Oversight,* has been created to formalize floor walk-throughs in aseptic production areas and to define expectations, instructions, and frequency for the Quality Check process in Lilly IPM. The Quality Check process applies to all operational and QC Laboratory areas and requires physical observation/evaluation of the area using tools and guides listed in the procedure. For example, comparing the observed area practice to the procedure for an identified task. QA is responsible and accountable for the performance, documentation, evaluation and reconciliation of the Quality Check process and outcomes as outlined in procedure 001-007997. The procedure will be effective (b) (4)
2. Additionally, effective by(b) (4) , a QA for Sterility Assurance consultant role will be created to lead the quality oversight program for aseptic operations and to mentor QA floor support and Sr. QA floor specialists in aseptic processing quality and compliance attributes.

OBSERVATION 4

Employees engaged in the manufacture, processing, packing and holding of a drug product lack the training required to perform their assigned functions.

Specifically, your vision inspection process is inadequate. You depend on this inspection process to reject critical and major defects including but not limited to units presenting with (b) (4) , (b) (4) *, etc. Your visual inspection processes are used to inspect numerous finished products filled in buildings 103, 105 and 107 including but not limited to: Cyramza, BLA 125477, approved 2014; Bamlanivimab, EUA 90/94; Portrazza, BLA125547, approved 2015.*

A. Your visual inspection training qualification requires operators to appropriately reject (b) (4) *of* (b) (4) *to pass and has not established a lower limit regarding major defects.*

B. Your manual and semi-automated visual inspection (b) (4) *are inadequate. Your* (b) (4) *have not been characterized to ensure operators can reliably, repeatedly and accurately reject defective units. For example, you have not measured the size of each type of defect embedded in the* (b) (4) *to ensure you understand the relationship between defect size and operator capability.*

C. *You have established one visual inspection* (b) (4) *which is used to qualify operators during their initial visual inspection qualification effort. You reuse this one visual inspection defect* (b) (4) (b) (4) *times within approximately a* (b) (4) *period. Using one* (b) (4) *may allow operators to acclimate to the* (b) (4) *and does not present operators with worst case conditions.*

D. *You do not challenge fatigue on* (b) (4) *basis regarding your visual inspection training program.*

E. *You do not require periodic requalification of incoming vial visual inspection operators using simulated inspection conditions. Operators are trained initially using your incoming vial test* (b) (4) *and are not required to requalify using our incoming vial inspection test* (b) (4) *after this initial qualification effort. Your incoming visual inspection process is used to inspect incoming vials to include 3mL – 50mL vial sizes.*

F. *You have established one visual inspection training* (b) (4) *regarding incoming vial inspection. This incoming vial inspection* (b) (4) *harbors* (b) (4) *critical defects including but not limited to* (b) (4) (b) (4) *and approximately* (b) (4) *. These critical defects do not present worst case conditions to incoming visual inspectors. Your incoming inspection process is used to inspect incoming vials to include 3mL through 50mL vial sizes.*

Response to Observation 4

Introduction

The Lilly IPM qualification program is designed to ensure our personnel are trained and have demonstrated capability to perform critical job tasks. All personnel must understand the impact of their activities on the product and the patient. Personnel must be qualified prior to performing assigned functions, duties, or tasks independently. Qualification is achieved through education, experience, and training needed by the individual to perform an assigned function duty or task, and then through a series of initial and ongoing assessments. Continued training ensures that personnel remain proficient in their activities. The training program includes documented training on the purpose of the visual inspection, the inspection process and procedures, the review of known types of defects, the defect classification, the ability to properly handle and detect the defects.

Through this training activity, new operators are mentored by a qualified visual inspection operator until they reach proficiency. Performance qualification assessment is performed and documented before the operator can perform any independent inspection activities.

Visual inspection qualification applies to manual inspection processes and semi-automated inspection processes. Operators are independently qualified on these two processes for each different product platform (b) (4)) and for each product presentation (b) (4) , (b) (4)

The qualification of all inspection personnel utilizes approved test (b) (4) to be inspected under normal operating conditions, including (b) (4) (b) (4) The qualification program includes (b) (4) consecutive successful qualification tests to demonstrate consistent performance for initial qualification of new operators. After initial qualification, the operator qualification is maintained through successful completion of the (b) (4) requalification test and vision test.

As part of an established continuous improvement program, Lilly IPM has holistically evaluated the Visual Inspection Qualification program for Parenteral Products, including (but not limited) to requirements for qualification of personnel responsible for performing manual and semi-automated inspection operations.

A review of the last three Annual Product Reviews (APR) for each commercial product indicates no trends in complaints that indicate failure of the visual inspection processes, or its associated training and qualification programs.

The Lilly IPM visual inspection qualification strategy has been under regular evolution to integrate improvements identified to enhance our practices and maintain alignment with industry guidance.
At the time of this inspection, several improvements were already in process, such as harmonizing the requirements for the acceptance criteria for operator qualification, the requirements for the inspection conditions and the requirements for test (b) (4) composition (per Common Quality Practice CQP-408-4, *Qualification of Inspectors for Manual and Semi-Automated Inspection of Parenteral Products* and PPN-LD-261, *Visual Inspection Qualification Strategy for Parenteral Products*).

Actions

The in-process inspection qualification program enhancements, as well as new program improvements in response to the individual findings reported in Observation 4, including for the Incoming Inspection processes, are detailed in the responses below. In summary, Lilly IPM commits to the following:

1. The new acceptance criteria for critical (b) (4)% acceptance criteria) and major defects (b) (4)% acceptance criteria) have been implemented, by updating procedure 001-005386 *"Visual Inspection Qualification"* (version 23 will be effective April 19, 2021). All inspection operators will be requalified according to these updated criteria by (b) (4) for B103 solution vial inspection operators, and by (b) (4) for the other areas of the site.
2. A characterization assessment for B103 Solution Vial qualification (b) (4) using probability of detection as a consideration has been conducted ((b) (4) 1, *B103 Vial Solution Test* (b) (4) *Distribution update for alignment with* (b) (4) *and Probability of Detection (PoD),*

Appendix F*).* Based on this assessment, the defect distribution table for vials (b) (4)) has been updated to align its defect composition, and the corresponding test (b) (4) will be improved as needed to ensure operators are capable to identify defects in worst-case conditions. Using these (b) (4) B103 vial operators will be requalified by(b) (4) .

3. For other product presentations and platforms, a detailed characterization of the defects included in all the current test (b) (4) used for visual inspection qualification at Lilly IPM has been performed and documented in the technical report, MST08802*, Characterization of operator qualification* (b) (4) *Summary Report* (Appendix G) to complement the (b) (4) composition description provided in the defect distribution tables.
4. To further reinforce visual inspection operational support, a Visual Inspection Process Mentor position will be created to mentor, coach, guide and lead the visual inspection training and qualification program. This position will be effective by (b) (4) .
5. Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our visual inspection process and the visual inspection qualification program by(b) (4) .
6. A minimum of (b) (4) will lapse between two qualifications for the same (b) (4) by the same operator. The procedure 001-005386, *Visual Inspection Qualification* (version 23)*,* has been revised accordingly and will be effective (b) (4)
7. During the initial operator qualification process, different qualification test (b) (4) will be used with a single operator between (b) (4) qualification tests, while adhering to the corresponding defect distribution table. Additional defect qualification (b) (4) will be implemented with the new defect qualification (b) (4) as they become fabricated. The procedure 001-005386, *Visual Inspection Qualification* (version 23) has been revised accordingly and will be effective (b) (4)
8. An annual fatigue assessment has been established for all visual inspection operators, by revising procedure 001-005386, *Visual Inspection Qualification.* The procedure version 23 will be effective (b) (4) .
    a. Operators will be challenged for fatigue (b) (4) they take an (b) (4) requalification test for manual inspection, for all platforms and products.
    b. For the subset of operators who are also requalifying on semi-automated inspection, they will be also challenged for fatigue(b) (4) a year on semi-automatic equipment.
9. All the visual inspection operators will be requalified under those new conditions that include operator fatigue challenge by (b) (4) .
10. The training curricula on glass defects for incoming laboratory technicians (PAS0332, *Incoming Vial Inspection Qualification,* and PAS0410, *Incoming Long Syringe Barrel Inspection Qualification)* have been updated for glass defect inspection requalification to occur (b) (4) . All incoming laboratory technicians trained on those two curricula have been requalified.
11. A characterization assessment for vial defects has been conducted on available historical data for vial glass components and documented in(b) (4) *, Assessment of Glass Vial Defects Visual Inspection* (b) (4) (Appendix H). Based on this characterization assessment, the existing vial qualification (b) (4) will be updated with the revised defect composition in type and quantity by (b) (4) (b) (4) All laboratory technicians will be requalified by(b) (4) .

12. To further ensure the individual defects in the (b) (4) are representative of the defects observed through the incoming inspection process, a data collection process will be established to collect qualitative information on each found defect. This will allow the characterization assessment to remain current over time. Instructions to capture the details of each found defect (size/location) will be added to the (b) (4) vial method and implemented by (b) (4) .
13. A routine review of the historical defect data will be performed to ensure the training qualification (b) (4) remain characterized accordingly. As such, an assessment will be conducted by (b) (4) to review the collected characterization data for the next year and to drive changes to the vial test (b) (4) Laboratory technicians will be requalified with the new test (b) (4) upon their next planned (b) (4) requalification. This process will be governed by a new procedure which will be implemented by (b) (4)

Detailed Response to Observation 4.A: Visual Inspection Qualification Acceptance Criteria

The acceptance criteria for critical defects had historically been (b) (4)% for all platforms in Lilly IPM. Per PPN-LD-261, *Visual Inspection Qualification Strategy for Parenteral Products,* recommendation, this threshold was raised to (b) (4)% in December 2020 for Insulin products (vials and cartridges) and (b) (4) products, as defined in the Lilly IPM procedure 001-005386, *Visual Inspection Qualification.*

To continue to improve the inspection qualification program, the acceptance criteria for the inspection operator qualification will be enhanced. The operator qualification criteria for the critical defects will be aligned to (b) (4)% across all the products and platforms (vials, syringes, and cartridges). A qualification criterion will be implemented at (b) (4)% for the major defects across all the platforms per CQP-408-4, *Qualification of Inspectors for Manual and Semi-Automated Inspection of Parenteral Products.*

Lilly IPM's (b) (4) visual inspection processes are already demonstrating the ability to operate at those enhanced detection levels. Lilly IPM commits to the following improvements per change control TR40227754:

Action

1. The new acceptance criteria for critical (b) (4)% acceptance criteria) and major defects (b) (4)% acceptance criteria) have been implemented, by updating procedure 001-005386 *"Visual Inspection Qualification"*.
   All inspection operators will be requalified according to these updated criteria by (b) (4) for B103 solution vial inspection operators, and by (b) (4) for the other areas of the site.

Detailed Response to Observation 4.B: Visual Inspection Qualification (b) (4)

The requirements for the Qualification test (b) (4) are defined in Lilly IPM procedures. Our current process to establish the test (b) (4) ensures their distributions represent the product defect profile observed in the production process. Requirements for composition of the test (b) (4) used for visual inspection qualification are described in the procedure 001-005386, *Visual Inspection Qualification*, and the defect distribution

tables for each platform (vials, cartridges, syringes) are detailed in the related documents (b) (4) (b) (4)

Specifically, per procedure 001-005386, *Visual Inspection Qualification*, the number of units in a test (b) (4) is based on the inspection pace and must be sufficient to provide a test duration equivalent to a production inspection interval and the qualification exercise assesses the operator inspection technique.

The defect distribution (number of critical, major, minor defects) within a test (b) (4) is weighted toward the critical defects to demonstrate a higher focus on performance level for higher impact classifications. In the test (b) (4) population, the quantities, and types of defects within each defect class (critical, major, minor) are derived from historical process data. An annual historical review of production defects for all product/process is performed by QA and TS/MS, and the (b) (4) are updated as necessary to ensure the defect types and quantities in the test (b) (4) remain representative of those found in the production process.
Lilly IPM has been evaluating the defect selection process for the qualification test (b) (4) At the time of the inspection, several improvements were already in progress to better characterize defects that are presented to inspection operators during the qualification process.

Per CQP-408-4, *Qualification of Inspectors for Manual and Semi-Automated Inspection of Parenteral Products*, the optimized approach for defect selection is based on probability of detection of defects (PoD). This methodology referenced in USP <1790> *"Visual Inspection of Injections"* allow to assign a detection frequency to a well-defined defect standard by conducting repeated manual inspection, with the recommendation to consider the defects with a probability of detection (PoD) above (b) (4)% ("the reject zone") to constitute the qualification test (b) (4) Considering the multiple product presentation manufactured in IPM (b) (4)) and inspection process (manual, semi-automated and automated), we have adopted a phased approach for the detection threshold studies. This approach will allow for a sequential delivery of the different platforms. For example, the Insulin products (vials and cartridges) were implemented in December 2020 per Quality Plan item TR40104556.

To improve the qualification test (b) (4) utilized to qualify visual inspection operators, Lilly IPM will implement the following actions per change control TR40227754.

Actions

1. A characterization assessment for B103 Solution Vial qualification (b) (4) using probability of detection as a consideration has been conducted (b) (4) *B103 Vial Solution Test* (b) (4) *Distribution update for alignment with* (b) (4) *and Probability of Detection (PoD),* Appendix F*)*. Based on this assessment, the defect distribution table for vials (b) (4)) has been updated to align its defect composition, and the corresponding test (b) (4) will be improved as needed to ensure operators are capable to identify defects in worst-case conditions. Using these (b) (4) B103 vial operators will be requalified by (b) (4) (per response 4.A).
2. For other product presentations and platforms, a detailed characterization of the defects included in all the current test (b) (4) used for visual inspection qualification at Lilly IPM has been performed

and documented in the technical report MST08802, *Characterization of operator qualification test sets Summary Report* (Appendix G) to complement the (b) (4) composition description provided in the defect distribution tables.

Additionally, to further enhance the current qualification test (b) (4) utilized for visual inspection qualification, as mentioned above, Lilly IPM is continuing the efforts engaged to holistically reassess the defect standards to include in the inspection qualification (b) (4) for all platforms and product presentations by leading supplemental detection threshold studies to support standards selection based on their demonstrated rejection probability. All the qualification test (b) (4) will be redefined, and new qualification (b) (4) created or updated accordingly. This (b) (4) improvement commitment is being tracked by the Lilly IPM Quality Plan (TR40228986).

3. To further reinforce visual inspection operational support, a Visual Inspection Process Mentor position will be created to mentor, coach, guide and lead the visual inspection training and qualification program. This position will be effective by (b) (4)
4. In addition, Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our visual inspection process and the visual inspection qualification program by (b) (4) .

Detailed Response to Observation 4.C: Test Administration Conditions

The requirements for the visual inspection qualification test (b) (4) and for the inspection conditions to perform the qualification test are defined in the procedure 001-005386, *Visual Inspection Qualification*. Given the composition of the defect (b) (4) (large test (b) (4) size, high number of defects for each defect class) and the inspection conditions (maximum allotted timeframe to complete the qualification), the risk for operator acclimation is considered minimal. Furthermore, the qualification test units are identified in order not to reveal to the operator the good vs. defective units (blind test), and the defective units are randomly distributed in the test (b) (4) among the good units every time the test is administered.

To further reduce the risk of acclimation, Lilly IPM will implement the following improvements per change control TR40227754.

Actions

1. A minimum of (b) (4) will lapse between (b) (4) qualifications for the same (b) (4) by the same operator. The procedure 001-005386, *Visual Inspection Qualification* (version 23), has been revised accordingly and will be effective (b) (4)
2. During the initial operator qualification process, different qualification test (b) (4) will be used with a single operator between (b) (4) consecutive qualification tests, while adhering to the corresponding defect distribution table. Additional defect qualification (b) (4) will be implemented with the new defect qualification (b) (4) as they become fabricated. The procedure 001-005386, *Visual Inspection Qualification* (version 23), has been revised accordingly and will be effective (b) (4) .

Detailed Response to Observation 4.D: Annual Fatigue Assessment

The visual inspection qualification program takes into consideration worst case scenarios including requirements such as (b) (4) . Per procedure 001-005386, *Visual Inspection Qualification*, during the initial qualification of the inspection personnel, one of the (b) (4) qualification runs must be completed at the end of the shift to challenge operator capability to inspect under fatigued conditions. The (b) (4) requalification tests are scheduled randomly within the shift time to be representative of the production conditions, which means some requalification activities are performed at the end of the shift.

To further ensure consistent challenge of operator fatigue on an ongoing basis, Lilly IPM commits to include additional operator fatigue assessment as part of the (b) (4) requalification program per change control TR40227754, and will requalify operators earlier than their next planned (b) (4) qualification test.

Actions

1. An (b) (4) fatigue assessment has been established for all visual inspection operators, by revising procedure 001-005386, *Visual Inspection Qualification.* The procedure version 23 will be effective (b) (4) .
    a. Operators will be challenged for fatigue every time they take (b) (4) requalification test for manual inspection, for all platforms and products.
    b. For the subset of operators who are also requalifying on semi-automated inspection, they will be also challenged for fatigue (b) (4) on semi-automatic equipment.
2. All the inspection operators will be requalified under those new conditions that include operator fatigue challenge by (b) (4)

Detailed Response to Observation 4.E: Annual Requalification for the Incoming Process

Per training qualification PAS0332, *Incoming Vial Inspection Qualification,* incoming laboratory technicians are initially qualified to perform incoming vial visual inspection, and then (b) (4) undertake

a visual examination per PTR0996, *Routine Vision Testing,* to ensure adequate vision acuity to demonstrate continued suitability to execute this assay.

Visual controls involving glass components take place throughout the whole manufacturing process (i.e., (b) (4) etc.), and product units are visually inspected at (b) (4) after being filled, which provides assurance that potential defects that would be overlooked during the incoming inspection process will be discarded before reaching our patients.

To enhance the Incoming Inspection Qualification process, Lilly IPM commits to increase the requalification frequency to occur on (b) (4) basis.

Actions

1. The training curricula on glass defects for incoming laboratory technicians (PAS0332, *Incoming Vial Inspection Qualification,* and PAS0410, *Incoming Long Syringe Barrel Inspection Qualification)* have been updated for glass defect inspection requalification to occur (b) (4) All incoming laboratory technicians trained on those two curricula have been requalified.

Detailed Response to Observation 4.F: Defect Characterization for the Incoming Process

Qualification of incoming laboratory technicians is conducted using (b) (4) visual inspection training (b) (4) This (b) (4) totals (b) (4) vials that span the range of the vial product family (3 to 50 mL) and includes (b) (4) critical defects, (b) (4) major defects and (b) (4) minor defects. This (b) (4) was established based on the known historical prevalence of defect types observed by the incoming laboratory.

To continue to improve the existing incoming inspection qualification program, Lilly IPM will implement the following actions:

Actions

1. A characterization assessment for vial defects has been conducted on available historical data for vial glass components, and documented in (b) (4) *, Assessment of Glass Vial Defects Visual Inspection* (b) (4) (Appendix H). Based on this characterization assessment, the existing vial qualification (b) (4) will be updated with the updated defect composition in type and quantity by (b) (4) (b) (4) All laboratory technicians will be requalified by (b) (4) .
2. To further ensure the individual defects in the (b) (4) are representative of the defects observed through the incoming inspection process, a data collection process will be established to collect qualitative information on each found defect. This will allow the characterization assessment to remain current over time. Instructions to capture the details of each found defect (size/location) will be added to the (b) (4) vial method and implemented by (b) (4) .

3. A routine review of the historical defect data will be performed to ensure the training qualification (b) (4) remain characterized accordingly. As such, an assessment will be conducted by (b) (4) to review the collected characterization data and to drive changes to the vial test (b) (4) Laboratory technicians will be requalified with the new test (b) (4) upon their following annual requalification. This process will be governed by a new procedure which will be implemented by (b) (4).

OBSERVATION 5

The written stability program for drug products does not include reliable, meaningful and specific test methods.

The firm has not ensured that the methods used during the stability testing of Bamlanivimab or Etesevimab are stability indication even though these methods are being used to support expiry dates. Management confirmed they do not review peak purity or (b) (4) *during any* (b) (4) *studies performed at this facility. For example, the firm currently using Method* (b) (4) *for the determination of* (b) (4) *and* (b) (4) *to determine the current expiry date of Bamlanivimab. Reviewing the ongoing* (b) (4) *studies being performed by the firm, large discrepancies in* (b) (4) *were noted during the following* (b) (4) *conditions:* (b) (4) (b) (4) *These discrepancies have not been investigated. In addition, the firm does not ensure that degradation peaks are not forming under the main peak of interest or the matrix peak.*

Response to Observation 5

Lilly PR&D ensures that the methods used to establish and support expiry dating for our products are stability indicating. As discussed more fully below, we have developed and implemented reliable, meaningful, and specific methods that are phase-appropriate for bamlanivimab and etesevimab based on scientific justification. In addition, Lilly recognizes the importance of ensuring accurate and reliable stability data. We have fully investigated the noted data discrepancies, generated supplemental data that further support the stability-indicating property of the size exclusion chromatography method, and we commit to improving our process to investigate such discrepancies when they occur. Our responses addressing each of these elements of the observation are as follows.

Scientifically Sound, Phase-Appropriate Stability-Indicating Methods Used for Bamlanivimab and Etesevimab

The methods used during the stability testing of bamlanivimab and etesevimab are stability indicating and consistent with global regulatory guidance[1-4] and industry expectations[5] for monoclonal antibodies at this

stage of development. These methods and associated data are described in detail in IND (b) (4) (bamlanivimab) and IND (b) (4) (etesevimab), and cross-referenced from EUA 000090 (bamlanivimab) and EUA 000094 (bamlanivimab and etesevimab). The approach that Lilly uses to establish stability-indicating methods is summarized here.

Lilly's approach to developing and validating stability-indicating analytical methods differs between small molecules and biologics such as monoclonal antibodies. For small molecules, the process described in ICH Q1A(R2)[6] as well as in an internal development guidance document (The Assessment of (b) (4) for Drug Product Analytical Development: White Paper & Decision Tree) is followed during (b) (4) degradation studies, including assessing peak purity and((b) (4) For large molecules, the approach is different due to the inherent heterogeneity of large molecules and the limitations of the analytical technologies.

Recombinant DNA-derived antibodies are subject to a wide variety of chemical or physical modifications during expression/synthesis, processing, and storage. For example, modifications to a molecule produced from cell culture can result from pre-translational, translational, and post-translational intracellular events as well as various chemical, enzymatic, and physical processes.[7] As a result of these various potential modifications, recombinant DNA-derived antibodies contain a variety of molecular variants causing a heterogenous final product. Due to this inherent heterogeneity and the technical limitations of any single test, Lilly employs an integrated, multi-method and holistic analytical approach.

The suitability of individual test methods is also determined using phase-appropriate approaches consistent with industry practice, global regulatory expectations[1,2,5,6,11,12], and sound scientific principles. Non-compendial methods used for release and stability testing are developed and validated commensurate with their intended use, whereas compendial methods are verified. As development proceeds, the suitability of

test methods is further demonstrated with additional method validation data (e.g., (b) (4) , (b) (4) (b) (4) testing approaches.

For bamlanivimab and etesevimab specifically, the methods used are phase appropriate and have been demonstrated to be stability indicating for these antibody products. Given the need to enable the rapid introduction of safe and effective products under an Emergency Use Authorization (EUA) to address the COVID-19 pandemic, some of the information that would be traditionally available in a BLA for a commercial product is still in the process of being completed for bamlanivimab and etesevimab. This approach is consistent with regulatory guidance where our experience with the analytical methods used for other monoclonal antibodies has been leveraged[11]. Even at this stage of development, the data currently generated on the test methods (e.g., (b) (4) (b) (4)) demonstrate their stability-indicating capabilities and their ability to detect differences between unaltered drug and drug product that has been (b) (4) (b) (4) using a variety of conditions (e.g., (b) (4)) thus confirming the suitability of the bamlanivimab and etesevimab methods for establishing expiry dating.

The validation data for the non-compendial bamlanivimab and etesevimab methods are provided in IND (b) (4) and IND (b) (4) , respectively, and include (b) (4) , (b) (4) . As development for these products has progressed, the suitability of test methods has been further demonstrated. For example, the results for the bamlanivimab (b) (4) method were compared to the results generated by (b) (4) . (b) (4) (b) (4)). The agreement between the (b) (4) results further confirms the suitability of the (b) (4) method for aggregate quantitation (Table 1), with apparent differences being within the expected variability of the technique.[13]

Table 1. Total Aggregates (%) Determined by (b) (4) (b) (4) and (b) (4) for Bamlanivimab (laboratory notebook c157994-2021-0009)

Sample	Total Aggregates (%)	
	(b) (4)	(b) (4)
(b) (4)	(b) (4)	

Given the results of (b) (4), and the history with the test methods used for bamlanivimab and etesevimab, these methods are scientifically sound, reliable, meaningful and specific, and the data generated using these methods support the expiry dating for the bamlanivimab and etesevimab drug substances and drug products.

Evaluation of Discrepancies in the Forced Degradation Data to Confirm the Stability-Indicating Capability of the (b) (4) Method

Lilly PR&D has reviewed forced degradation data for bamlanivimab consistently with the approach we use for other large-molecule monoclonal antibodies. Our approach to (b) (4) studies, as discussed above, is appropriate both for the type of material and the phase of development for this product. During the inspection, however, the investigator appeared to review bamlanivimab (b) (4) data through the lens of small molecule stability testing and demonstration of (b) (4) which identified greater than expected variability in the chromatographic peak areas of the main and (b) (4) (b) (4) peaks between (b) (4) samples using the (b) (4) method. As a monoclonal antibody, the bamlanivimab (b) (4) data had not been viewed in that way previously.

Although we are confident that our (b) (4) method is scientifically sound for the reasons described above, we conducted an investigation into the observed differences. Our investigation established that the observed differences were the result of (b) (4) . This latter factor impacted the investigator's calculation of (b) (4) by (b) (4) to those in an (b) (4) as this calculation assumes that all samples were prepared at the same concentration.

The scientific validity of our (b) (4) results, even with the noted sample preparation inconsistencies, remains acceptable because 1) the (b) (4) assay is an (b) (4)) method so

(b) (4)

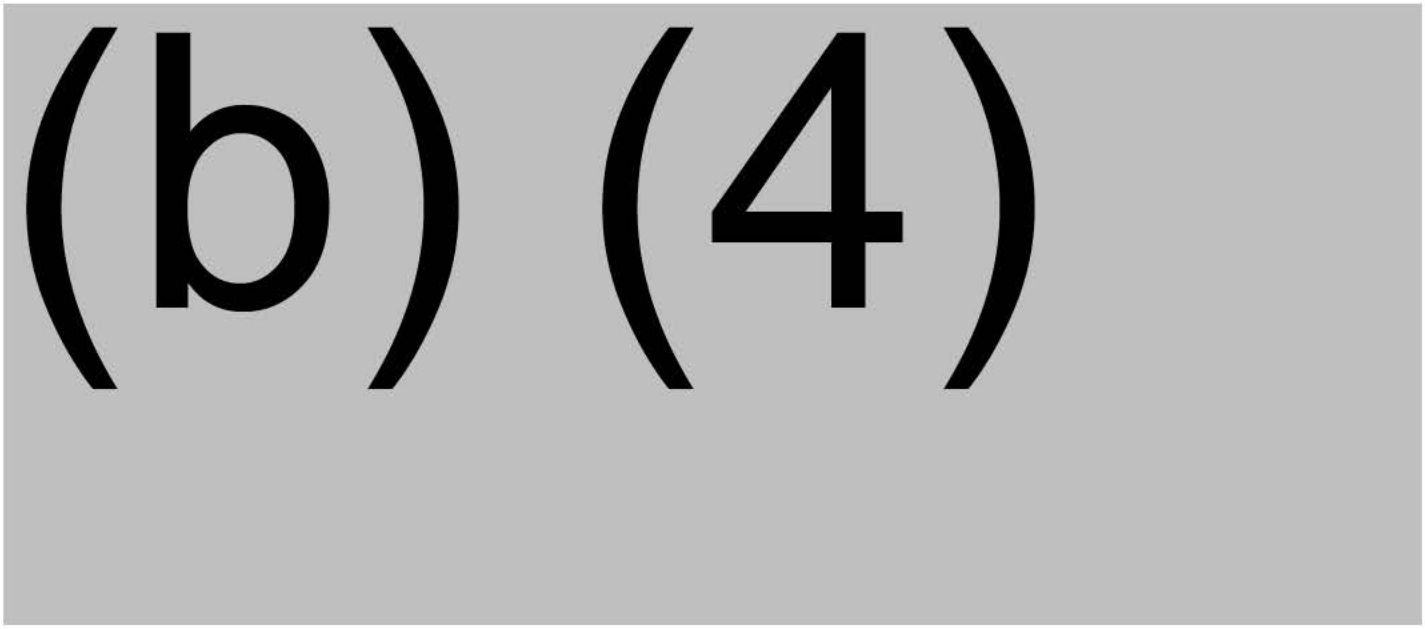
a demonstration of (b) (4) in the spirit of the approach taken by the investigator.

(b) (4) testing of the (b) (4) samples was repeated with samples prepared consistently at a target (b) (4) concentration, and calculation of (b) (4) was corrected for the measured (b) (4) sample concentration. As shown in Table 2, all (b) (4) results are within (b) (4) % of expectation, and the results further indicate no (b) (4) peaks underneath the (b) (4) peak. The (b) (4) peak areas are consistent

(b) (4)

Table 2.(b) (4) **Results for the Bamlanivimab Forced Degradation Samples**
(laboratory notebook c293526-2021-0093)

Sample[1]	(b) (4)
(b) (4)	(b) (4)
(b) (4)	



In summary, the results of method validations, (b) (4) studies, (b) (4) method assessments, and the history with the test methods used for bamlanivimab and etesevimab, demonstrate that these methods are scientifically sound, reliable, meaningful and specific. The data generated using these methods support the expiry dating for the bamlanivimab and etesevimab drug substances and drug products.

OBSERVATION 6

Representative samples are not taken of each shipment of each lot of components and drug product containers for testing or examination.

Specifically,

A. *Your firm has not qualified the process of* (b) (4) *samples). Verification of the accuracy from the vendor against samples collected in* (b) (4) *has not been performed. This applies to (but is not limited to) glass components and API used in the manufacture of Bamlanivimab, Ramucirumab, and Glucagon.*

B. *Your sample sizes are inadequate regarding discrete units such as glass vials. You pull* (b) (4) *glass vials per incoming lot when the lot size is over* (b) (4) *units. I observed* (b) (4) *samples pulled for inspection from an incoming lot of over* (b) (4) *vials. Glass vials are supplied from a high risk*

vendor. Your incoming glass vial visual inspection processes are used to inspect vial sizes ranging from approximately 3mLs – 50mLs. Glass vials in this range are used in numerous finished products filled in buildings 103, 105 and 107 including but not limited to: Cyramza, BLA 125477, approved 2014; Bamlanivimab, EUA 90/94; Portrazza, BLA125547, approved 2015.

Response to Observation 6

Introduction

Lilly has programs and systems in place to ensure that representative samples are used for quality control activities for all incoming material, including components and API.

(b) (4) samples are defined as those samples collected by the supplier (Vendor, Eli Lilly site external to the Indianapolis Technical Campus and contract manufacturing organization) on behalf of Lilly IPM for the intended use of incoming quality control activities. Supplier collected samples must be representative of the entire batch, thus the suitability of these samples is assessed through a series of controls.

For primary packaging component and excipient (b) (4) (referred to as "supplier collected samples") the sampling processes are evaluated through both Lilly quality and technical assessments of the supplier. Based on these assessments, Lilly determines whether supplier collected samples are representative of the batch and can be used for in-house testing purposes. The information associated with the process used to accept supplier-collected samples is discussed in various documents. To improve the qualification approach, all information related to the process has been compiled into an overarching strategy document, *Component and Excipient: Supplier-Collected Sampling Strategy: Indianapolis Parenteral Manufacturing (*Appendix I*)* that builds in a verification assessment of supplier collected samples against in-house collected samples. In addition, Lilly commits to the execution of a study to confirm the accuracy of supplier-collected samples against samples collected in house for primary packaging components used in commercial manufacturing.

Lilly IPM utilizes active pharmaceutical ingredients (API) or drug substances (DS) in the manufacture of the various drug products (DP) produced at IPM. For a number of API/DS materials, (b) (4) samples are supplied along with the associated batch specifically for identity testing. Sampling at API/DS sites is part of an approved process. Lilly IPM ensure API/DS (b) (4) samples are representative of the bulk API/DS material through a number of elements which include Quality oversight, API/DS site approved sampling process, controlled shipping conditions and DP batch release testing on every batch. This approach is outlined in the strategy document *Use of Active Pharmaceutical Ingredient and Drug Substance* (b) (4) *Samples: Indianapolis Parenteral Manufacturing* (Appendix J) and ensures that the API/DS (b) (4) sample is representative of the batch.

Lilly IPM understands the importance of establishing an adequate sample size for incoming testing of components to ensure we meet or exceed acceptable quality level prior to drug product manufacture. IPM's current sampling plans use a statistical approach based on the (b) (4) sampling plan standard that ensures we meet or exceed our acceptable quality level ((b) (4)% Acceptance Quality Limit (AQL)). Although our current plan (b) (4)) is statistically based and meets required quality levels, IPM commits to an increased sample size aligning with (b) (4) General Inspection Level II based on batch size range.

Actions

1. A retrospective technical assessment to confirm that existing supplier-collected sample arrangements are acceptable and are representative of the batch. *Primary Packaging Components and Excipients: IPM Supplier-Collected Sampling Retrospective Evaluation* (Appendix K) was completed on (b) (4)
2. A study protocol will be developed to directly assess the accuracy of existing supplier-collected samples against samples collected in house for each primary packaging component used in commercial manufacturing by (b) (4) . The protocol will be executed starting (b) (4) and will be completed based on supply chain timing and receipt of material batches.
3. Procedure 001-006077, *Material Supplier and GMP Service Provider Management* will be updated to specifically include expectations and required evaluations for documentation of quality approval and technical reviews during the supplier-collected sampling approval process by (b) (4) (b) (4)
4. The sampling plan will be updated to align with (b) (4) General Inspection Level II to adjust the sample size in relation to the batch size range by (b) (4)

Detailed Response to Observation 6A: Qualification of (b) (4) process

Supplier collected samples ((b) (4) apply to raw materials, components and API and are defined as those samples collected by the supplier on behalf of Lilly for Lilly's use in incoming quality control activities. Supplier-collected samples are commonly used in pharmaceutical manufacturing operations for several reasons:

- Reduction of risk to employee health and safety or to the environment due to handling of highly potent or toxic materials
- Reduction in physical handling of excipients and primary packaging components that could lead to reduced shelf life (excipient) and/or defect/contamination events and impact downstream operations.
- For "ready to sterilize" primary packaging components, it eliminates the potential introduction of particulates into/on components that will not be washed prior to sterilization at Lilly.
- For "ready to use" primary packaging components, it eliminates the potential for sterility breach events as these components are received in a sterile state for direct use in parenteral manufacturing operations after QA approval. Thus, there are no additional sterilizing activities conducted internally at Lilly.

- Identification of potential supplier issues to allow for CAPA activities and/or continuous improvement initiatives with the supplier, while minimizing potential downstream impact to the manufacturing processes
- Provision of a more streamlined, effective production operations, while ensuring quality standards are not compromised.

Supplier collected samples must be representative of the entire batch, thus the suitability of these samples is assessed through a series of controls including (b) (4) .

The supplier-collected ((b) (4) samples sent with each batch are representative of incoming batches based on both Lilly quality and technical assessments of the supplier as governed by the following global and local quality documents:

- GQS 113 *Sample Management*
- GQS 305 *Supplier Quality Management*
- CQP-305-1 *Risk Management and Periodic Performance Review of Suppliers and GMP Service Providers*
- CQP-305-3 *Supplier Certification*
- GQAAC-SOP031 *Supplier and GMP Service Provider Audit Program*
- IPM Procedure 001-006077 *Material Supplier and GMP Service Provider Management*

Currently, supplier-collected sampling processes are evaluated as a part of the supplier approval process. The quality assessment is documented in the supplier quality audit summary. The technical assessment is captured within the associated technical documents. If the supplier-collected sampling decision is made after initial approval of the supplier, the same key elements used with the supplier approval process are applied (i.e., (b) (4)) prior to acceptance of supplier-collected samples. This process is maintained via supplier monitoring through routine quality audits and supplier Periodic Performance Evaluations (PPE). The PPE is approved by QA and includes, but is not limited to, (b) (4) Also, if a supplier notifies Lilly of a change to their sampling strategy or a change is identified through a quality audit, the revised strategy is evaluated from a quality and technical perspective. The information associated with the process used to accept supplier-collected samples is included in various documents and therefore to improve the process an overarching sampling strategy document, *Component and Excipient: Supplier-Collected Sampling Strategy: Indianapolis Parenteral Manufacturing* (Appendix I) has been created that describes the process of approval and ongoing monitoring in single document. This document also details a new requirement to execute a qualification study to confirm the supplier's sampling process for new supplier-collected sampling approvals. The controls above provide Eli Lilly and

Company a high level of assurance that supplier collected samples received to date are representative of the overall batch. To continue to improve Lilly IPM commits to the following actions.

Actions

1. To confirm existing supplier-collected sample arrangements based upon the quality and technical reviews of each supplier's sampling strategy and to ensure the samples are representative of the batch, a technical assessment *Primary Packaging Components and Excipients: IPM Supplier-Collected Sampling Retrospective Evaluation* (Appendix K) has been performed for primary packaging components and excipients used in commercial manufacturing and was completed on (b) (4) .

2. A study protocol will be developed, *Primary Packaging Components: Supplier-Collected Sample Verification Protocol,* to confirm the equivalence of existing supplier-collected samples against samples collected in house for each primary packaging component used in commercial manufacturing. (b) (4)
    a. This protocol will be executed upon receipt of future batches of current approved primary packaging components where supplier-collect samples are provided, to perform visual testing on these samples and samples collected in house. Both sample populations will be compared to specifications. This will start by (b) (4) , to be completed based upon supply chain timing and receipt of material batches.

3. Procedure 001-006077, *Material Supplier and GMP Service Provider Management* will be updated to specifically include expectations and required evaluations for documentation of quality approval and technical reviews during the supplier-collected sampling approval process. In addition, the PPE process required by 001-006077 will be enhanced to require a specific statement of cumulative impact of sampling delegation strategy or process for the review period. The procedures will be updated by (b) (4)

Lilly IPM's Supplier collected sample strategy for incoming primary packaging components and excipients is achieved through a series of controls including (b) (4) . With the improvements outlined above the overall qualification process is strengthened and provides further confirmation that these samples are representative of the batch as a whole and are therefore suitable for their intended use within the IPM manufacturing operations.

API/DS (b) (4)

The IPM site utilizes active pharmaceutical ingredients (API) or drug substances (DS) in the manufacture of the various drug products (DP) produced by the site. API/DS batches are supplied to IPM from both Lilly API sites (located on the technology campus in Indianapolis and from global sites) and by external contract manufacturing partners. API/DS supplied by Eli Lilly API sites external to the technology

campus and from contract manufacturing partners require identity testing upon receipt at IPM which must be completed prior to use in a DP batch. For a number of products, (b) (4) samples are shipped along with the API/DS batch to be used for this identity test e.g. frozen DS, where we want to limit the freeze thaw cycles and mitigate any contamination. Lilly IPM ensure API/DS (b) (4) samples are representative of the bulk API/DS material through a number of elements which include Quality oversight, API/DS site approved sampling process, controlled shipping conditions and DP batch release testing on every batch.

From a Quality oversight perspective there are multiple elements that are considered. Every supplier of API or DS, whether internal or external to Lilly, must have a quality agreement in place which details the requirements that each site must meet. Lilly global quality assurance and compliance (GQAAC) ensures that an audit plan is maintained for all GMP suppliers, both internal and external to Lilly and that DS/API sites are audited for compliance with applicable regulatory requirements and the Lilly quality system. Manufactured API/DS batches are sampled according to a defined sampling plan which has been approved by quality assurance. These sampling plans define the process by which the number of samples to be taken are determined, the method of extraction, the quantity of material, and the parameters and acceptance criteria for testing. Every batch record for both internal and external sites are reviewed by quality prior to release of the resulting DS/API batch. The review is completed by an authorized quality representative (or qualified person) and ensures that the batch record has been completed and meets all GMP requirements. In addition, all changes and deviations from the validated process are reviewed by the quality assurance organization to determine any impact that could affect the (b) (4) sample as it relates to the batch.

Lilly IPM forward processes DS/API from internal and external sites for use in both pre-commercial and commercial drug product manufacturing. All sites that provide (b) (4) samples collect them during the packaging of the API/DS into the individual bulk containers for shipment via approved processes. As a part of DS/API manufacturing, unit operations are designed to ensure uniform characteristics of the material prior to sampling and packaging.

Once a manufactured DS/API batch has been approved and released, the batch is shipped to Lilly IPM. The (b) (4) sample for each batch is shipped alongside the DS/API containers. All shipments are completed in containers which are temperature controlled and monitored to ensure that the product remains within the required temperature range. Upon receipt at Lilly IPM, the data for the shipment is reviewed and any deviations from the temperature range are assessed for impact to the shipped DS/API. The DS containers and (b) (4) samples are then moved to the appropriate storage location and remain stored together until the laboratory is ready to complete the identity testing.

Prior to use of the DS/API for any DP batch, the identity test utilizing the (b) (4) must be completed and approved. Every (b) (4) ID sample is run against a reference standard to confirm its identity. As part of the release testing process of the subsequent DP batch(es), a further identity test (same assay as executed on the (b) (4) sample) confirms the identity of the batch and provides confirmation of the accuracy of the (b) (4) sample results. Drug product release testing also includes (b) (4) chemical and, where

applicable, biological assays that would also be capable of detecting identity differences between the manufactured DP batch and the associated (b) (4) sample.

The (b) (4) sampling and testing processes have sufficient quality oversight to ensure that the process meets GMP requirements and remains in control. API/DS (b) (4) samples are tested for identity prior to the start of DP batch manufacture. This subsequent DP batch(es) are then tested for identity again through the batch release process which confirms the accuracy of the (b) (4) sample. This testing process along with upstream controls confirms that the (b) (4) sample is representative of the batch and that final product meets all associated specifications to ensure quality and identity of the product. The above approach is outlined in the following strategy document *Use of Active Pharmaceutical Ingredient and Drug Substance* (b) (4) *Samples: Indianapolis Parenteral Manufacturing* (Appendix J) and ensures that the API/DS (b) (4) sample is representative of the batch.

Detailed Response to Observation 6B: Incoming Sample Size in relation to batch sizes
Lilly IPM's current sampling plans use a statistical approach based on the (b) (4) sampling plan standard. While this approach is not based on different batch size brackets, it is based on a requirement of having a titled Acceptance Quality Limit (AQL) of (b) (4)% and an accept/reject of (b) (4) for critical defects. Based on these two criteria a sampling plan of (b) (4) is used. This sampling plan has a true AQL of (b) (4)% and ensures we meet or exceed our acceptable quality level of AQL (b) (4)% and as such the current sampling size provides a high level of assurance about the quality of components used to date. The statistical rational for a sampling plan of (b) (4) is summarized in the technical report, STATS-TR-4465, *Sampling Plans for Glass Vials at Incoming/Receiving for Critical Defects* (Appendix L).

Although our current plan ((b) (4) is statistically based and meets required quality levels, Lilly IPM commits to an increased sample size aligning with (b) (4) General Inspection Level II based on batch size range, see table below.

Actions

1. For primary packaging components the sampling plan in tool (b) (4), *Sampling Plans for Defect Inspection*, will be updated to increase the sample size and adjust the batch size range. The sampling plan will be updated by (b) (4) (Note that revision of agreements with vendors are required as part of this change)

The table below outlines the proposed updated sampling plan strategy from (b) (4) Titled AQL General Inspection Level II.

(b

Inspection Type	(b) (4)
New Sampling Plan Strategy	

Note: Lilly quality standards require 0 critical defects for accepting a batch.

*Over the batch size range

The sampling plans above follow the (b) (4) General Inspection Level II regarding batch size breaks for larger batch sizes and either have the (b) (4) AQL risk as defined in the (b) (4) title AQL (b) (4)% table. The proposed action to align sample size in relation to the incoming batch size per (b) (4) titled AQL General Inspection Level II, along with maintaining an accept/reject criteria of (b) (4) for all sampling plans, provides additional confidence in the incoming inspection process for larger batch sizes.

OBSERVATION 7

The establishment of laboratory control mechanisms including any changes thereto, are not drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.

Specifically, The PR&D Development laboratory located in B314, used for lot release of clinical batches, stability testing and method validation do not perform reconciliation of injections performed in the laboratory. Only the sequences turned in for review, are evaluated.

Response to Observation 7

Lilly PR&D ensures that the data generated to support clinical trial and EUA batches are accurate, reliable, and consistent. Lilly PR&D requires that analysts who generate and review (b) (4) data are trained using both global and PR&D-specific training courses which include but are not limited to: Data Integrity and Good Documentation Practices, the use of (b) (4) to acquire, process, and report data, and technique training for HPLC/CE/ICE which covers documentation expectations that are specific to the individual methods.

The current process for verifying laboratory data for clinical trial and EUA products includes the review of injections (channels) and results within the sample set used to generate the final results as well as ensuring any additional sample sets created by the author in that (b) (4) folder are captured in the laboratory notebook. (b) (4) folders in Lilly PR&D are named using the (b) (4)

(b) (4) This process ensures that data generated as part of the experiment are reviewed even if final results were not generated (e.g., (b) (4) (b) (4)).

As an immediate action to this observation, Lilly PR&D performed a review to evaluate unlocked channels and unsigned results (RPT-324002). The purpose of this evaluation was to confirm that the practice of reviewing only sequences submitted for review had no detrimental impact to CGMP data. A query of (b) (4) was performed to include all injections/results from the analysis of clinical trial materials that were tested between (b) (4) . As the testing for bamlanivimab and etesevimab was started in (b) (4), selecting this review period ensured that all testing for those products was included in this review.

A total of (b) (4) injections were performed within the PR&D development laboratories to support the specification testing of clinical trial batches from (b) (4) . We reviewed this entire set of (b) (4) injections to identify any injections that did not follow typical processing conditions. Specifically, our criteria sought to identify any injections that were either not processed or that were processed more than (b) (4)). We identified (b) (4) sample sets for which the documentation was incomplete and one occurrence of inadvertent transfer of data between folders. There were (b) (4) instances where inadequate audit-trail documentation was found for injections processed multiple times. All (b) (4) potentially atypical processing instances that were identified amongst the (b) (4) injections reviewed have been investigated and addressed in deviation TR40227254. This deviation confirmed that there was no impact to previously reported final results associated with these atypical processing instances.

After this initial review, a further targeted review of the full data set (b) (4) injections) was performed, looking for the following situations that might be indicative of atypical processing: (b) (4) No issues were found among those reviewed for injections in multiple folders or samples with more than (b) (4) injections in the same folder. There were (b) (4) injections that were processed after signoff and not documented appropriately. (b) (4) of these were related to appropriate reprocessing of injections to calculate signal-to-noise ratio for detection limit/quantitation limit. (b) (4) injections were standards that were inadvertently reprocessed with no changes to the data as a result. These occurrences were also investigated and addressed in deviation TR40227254.

In summary, the review of all injections/results in (b) (4) from the analysis of specification testing for clinical trial materials that were tested between (b) (4) , including testing for bamlanivimab and etesevimab, concluded that there was no impact on the accuracy or reliability of the analytical results reported as a consequence of not performing reconciliation of the injections in (b) (4)

The documentation issues found during this review have been investigated and addressed in deviation TR40227254.

Lilly PR&D will implement a new procedure that expands the controls already in place for equipment, training, methods and data review to ensure full reconciliation of injections in (b) (4) We will also conduct a limited retrospective reconciliation for specification testing of clinical trial material tested from January 2019 to further confirm our initial findings that no previously reported data has been impacted by the incomplete reconciliation.

Lilly PR&D Development laboratory will implement the following actions.

Actions

1. Implement the use of locked channels and the signoff of all specification test results for clinical trial material analyses within (b) (4) In addition, Lilly PR&D will ensure that full reconciliation of these injections is performed as part of the new process. The new process will be documented in a new procedure and implemented by (b) (4)

2. Lilly PR&D will retrospectively lock channels and perform a reconciliation to confirm all (b) (4) sample sets were included in their respective notebook review for specification testing of clinical trial material tested from January 2019. Any sample sets not evaluated during the notebook review will be reconciled. This action will be completed by (b) (4)

References

1. FDA Guidance for Industry - Drug Stability Guidelines, December 9, 2008.
2. FDA Guidance for Industry - Analytical Procedures and Methods Validation for Drugs and Biologics, July 2015.
3. European Medicines Agency - Guideline on development, production, characterisation and specification for monoclonal antibodies and related products, 21 July 2016.
4. ICH Q5C, Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, section 5.3, November 1995.
5. A-Mab: A Case Study in Bioprocess Development, CASSS CMC Biotech Working Group, Version 2.1, October 2009.
6. ICH Q1A(R2), Stability Testing of New Drug Substances and Products, 6 February 2003.
7. Le Basle Y, Chennell P, Tokhadze, N, Astier A, Sautou, V. Physicochemical Stability of Monoclonal Antibodies: A Review, Journal of Pharmaceutical Sciences, 109 (2020), pp. 169-190.
8. Quality by Design - An Indispensable Approach to Accelerate Biopharmaceutical Product Development, edited by C. Campa and M. Khan, Parenteral Drug Association, March 2021.
9. Vlasak, J. and Ionescu, R. Fragmentation of monoclonal antibodies. MAbs. (2011) 3(3): 253–263.
10. Dada OO, Rao R, Jones N, Jaya N, Salas-Solano O. Comparison of SEC and CE-SDS methods for monitoring hinge fragmentation in IgG1 monoclonal antibodies. J Pharm Biomed Anal. (2017) 145:91-97.
11. FDA Guidance for Industry - Development of Monoclonal Antibody Products Targeting SARSCoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency, February 2021.
12. ICH Q2(R1), Validation of Analytical Procedures: Text and Methodology, November 2005.
13. Gabrielson JP, Arthur KK. Measuring low levels of protein aggregation by sedimentation velocity. Methods. 2011 May; 54(1):83-91.

Listing of All Actions

Observation	Actions	Date
1	All Grade A open (b) (4) interventions, regardless of criticality, will be documented in the (b) (4) and will have associated task-related personnel monitoring that is held to Grade A limits. This change will be implemented according to change control TR40223712 by (b) (4)	(b) (4)
	Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our aseptic processing operations and controls by (b) (4)	
	For the traditional aseptic filling line in B105, all Grade A environmental monitoring performed through an (b) (4) (b) (4) during active product manufacture, will have associated task-related monitoring that is held to Grade A limits. This will be documented in the environmental monitoring system, (b) (4) as detailed in change control TR40223712 effective by (b) (4) .	
	All non-EM (b) (4) aseptic manipulations will be evaluated, and associated task-related monitoring, held to Grade A limits, will be established by (b) (4)	
	The formal aseptic intervention qualification courses will be revised to include a demonstration that the trainee understands the holistic sequence of events when executing an aseptic intervention, submitting the intervention, and being task monitored. This training will ensure that all trainees understand the necessary sequence of activities as described across procedures 001-005056, 001-002046, 001-007521, and 001-001698, prior to being qualified to execute aseptic interventions. This change will be implemented according to CAPA TR40226771 by (b) (4)	
	Area-specific intervention reports (e.g., Cycle Summary Reports) will be updated to include documentation of the operator performing each intervention. In addition, all task-related monitoring will be reconciled not only to the intervention, but to the individual performing the intervention, as part of routine batch release as clarified in Local procedure 001-004754 *Environmental Monitoring Evaluation Report*	

Observation	Actions	Date
	(EMER). These changes will be implemented according to change control TR40223712 by (b) (4)	
	A series of quality stand-down meetings (department by department) will be executed across all GMP operations at the Lilly IPM site by (b) (4) .	(b) (4)
	Procedure 001-001698 *Aseptic Personnel Monitoring for Parenteral Products Operations* will be revised to clarify the requirement for task-related monitoring after each unique aseptic unit installation which includes the aseptic connection. Unit installations will no longer be grouped. These task-related samples will be held to Grade A limits. The sample plan within (b) (4) and manufacturing tickets will be updated to ensure separate (b) (4) monitoring is captured for each unique 'unit installation' including the aseptic connection. These changes will be implemented according to change control TR40223712 by(b) (4)	
	Routine personnel monitoring, which excludes task-related monitoring held to Grade A limits, will occur upon each exit from the aseptic area. These samples will be held to Grade B limits as they are not directly attributed to activity performed within the Grade A area. This action will be completed according to change control TR40223712 by (b) (4)	
	For B103, the(b) (4) differential pressure alarm delay for airlocks will be reduced to(b) (4) based on qualification data, equipment capability, operational utilization, and review of historical performance. The (b) (4) differential pressure alarm delay will be reduced to(b) (4) based on room pressure, DP measurement instrument variability, and active DP control response time. The rationale will be documented in the B103 Critical Operation Data (COD) documents. These changes will be implemented in B103 according to change control TR40224509 by(b) (4) (shutdown completion). A similar assessment will be conducted for the other aseptic manufacturing facilities, and modification to the differential pressure alarm delays will be made based on a documented rationale during the next planned facility shutdowns (b) (4) for B105A and(b) (4) for B105).	

Observation	Actions	Date
	Procedure 001-002833, *Requirements for Performing and Documenting an EMPQ*, will be revised to require all Grade A critical adjacent locations to be sampled at (b) (4) while activity is occurring in this area. This monitoring will target the critical operational activities (e.g., sterile equipment set-up) with appropriately gowned personnel present and performing those activities. The minimum number of non-viable sampling locations as recommended by ISO 14644-1:2015 will be collected at (b) (4) within the 2021 non-viable particulate requalification (PEM-231), slated for execution following the B103 (b) (4) facility shutdown ((b) (4)	(b) (4)
	Following execution of requalification sampling, task-related (b) (4) non-viable sampling locations will be selected within the Grade A critical adjacent zones and implemented into the routine Environmental Monitoring program. Sterile equipment set-up operations will be targeted for sample collection of (b) (4) particulate samples based on the nature of the operational activity. (b) (4) particulate sampling will occur as close to sterile equipment set-up operations as possible, without interference of the Grade A critical adjacent activities, to avoid potential impact to product sterility. This will be completed by (b) (4)	
2	Procedure 001-001147, *Managing Deviations* was revised to provide specific guidance to ensure investigators set an appropriate investigation scope and to require that the scope is clearly stated and justified in the record. Enhanced interview instructions are provided along with new interview templates which are designed to be more user friendly and accessible. A new trend investigation template was created to provide more specific guidance on required content and a due date of (b) (4) from creation will be applied to trend records. The revised procedure will be effective upon completion of training by (b) (4)	
	The percentage of approved records reviewed (b) (4) by the senior cross-functional team (including but not limited to quality assurance, engineering, technical services, and operations) will be increased to evaluate a greater percentage of records for completeness, robustness, adherence to new process requirements, etc. by (b) (4)	

Observation	Actions	Date
	Deviation mentor positions will be created to teach, mentor, and guide investigators, and new instructor-led training will be delivered to lead investigators with modules focused on record creation and final impact assessment by (b) (4).	(b) (4)
	Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our deviation management program by (b) (4).	
	All future (b) (4) failures will be investigated as deviations per the enhanced deviation management program, effective (b) (4). (b) (4) testing performance for the other Lilly IPM RABS filling line will be assessed based on learning from the completed B103 RABS (b) (4) management trend by (b) (4).	
	Statistically based action limits will be established for the (b) (4) management trending program and minimum timing requirements will be established for performance evaluation by (b) (4).	
	The RABS (b) (4) port design will be modified to minimize false failures during the (b) (4) test by (b) (4).	
	Both sides of RABS (b) (4) will be monitored during environmental monitoring. Detailed monitoring technique instructions have been added to procedure 001-007772, *Environmental Monitoring of the Aseptic Classified in Parenteral Manufacturing Areas* and will be effective (b) (4).	
	All reference and retention sample investigational activities must be conducted by qualified IPM QA visual inspection personnel, regardless of product type (EUA, clinical trial). Clarifications have been added to procedure 001-003526, *Reference and Retention Sample Program for Parenteral Products Operations in Indianapolis* which will be effective upon completion of training by (b) (4).	
	Procedure 001-001764, *Technical Studies* will be modified to clarify documentation requirements and the use of study data to support GMP decisions by (b) (4)	

Observation	Actions	Date
	For supplier and service provider complaints, a Lilly IPM technical approval step has been added before quality approval, to ensure that the supplier complaint responses are complete and scientifically justified. Timing expectations have been established for each step of the process and relevant metrics have been added to the supplier quality management program. Revised procedures 001-006046, *Complaints and Remarks to Suppliers*, and 001-006063, *Supplier Quality Management* will be effective (b) (4) .	(b) (4)
	All visual inspection requalification failures now trigger a deviation to investigate quality impact to previously inspected batches as of March 8, 2021, per procedure 001-005386 (version 22), *Visual Inspection Qualification*. For other qualification programs, all requalification failures will be investigated for retrospective quality impact. An annual assessment process will be added to our training and qualification program to monitor requalification failure investigation and remediation process and to assess the overall health of each qualification program. A change control to implement the program improvements will be approved by(b) (4) .	
3	A line-specific maximum intervention threshold will be established, supported by the maximum number of interventions demonstrated in the APS program. This threshold will be based on an annual review of routine production batches. Lilly IPM commits to implement this change via change control TR40223712 by(b) (4) .	
	Procedure 001-007197, *Aseptic Process Simulation Program Strategy* will be revised to require that routine interventions executed within APS will represent each functional zone of the filling line outlined in line-specific intervention risk assessments. This requirement will be implemented by(b) (4)	
	Procedure 001-007197, *Aseptic Process Simulation Program Strategy* will be revised to require that maximum fill duration is challenged by processing (b) (4) filled units and non-(b) (4) filled units to reflect continuous operations in alignment with *PDA Technical Report 22-Process Simulation for Aseptically Filled Product (revised 2011)*. Continuous operations will inherently address operator fatigue as outlined in Observation 3.A.3. This requirement will be implemented by (b) (4)	

Observation	Actions	Date
	Procedure 001-007197, *Aseptic Process Simulation Program Strategy* will be revised to require that (b) (4) units be filled for a pre-determined time-period after execution of critical interventions that occur during processing of empty units between filling orders. This requirement will be implemented by (b) (4)	(b) (4)
	Procedure 001-007197, *Aseptic Process Simulation Program Strategy* will be revised to increase the total duration of filling (b) (4) units on each individual shift. This requirement will be implemented by (b) (4) (b) (4)	
	The (b) (4) application will be revised to require decrement and increment of the number persons in the defined area to be verified. Implementation of this will be completed by (b) (4)	
	(b) (4) terminals will be installed at the aseptic area gown room (b) (4) and at the aseptic area (b) (4) airlocks. Physical location of the terminals by points of (b) (4) will help to reduce human error (i.e., forgetting to log in/out) by being placed physically in the (b) (4) pathways. This change will be implemented by (b) (4) (b) (4).	
	To further reinforce aseptic processing operational support, Aseptic Process Mentor positions will be created to mentor, coach, guide and lead aseptic manufacturing training and qualification programs. These positions will be effective by (b) (4).	
	Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our aseptic processing operations and controls and our aseptic processing simulation program by (b) (4).	
	The area-specific intervention/manipulation reports (e.g., cycle summary reports) will be updated for the other production areas to document the manipulations no later than (b) (4) according to change control TR 40205132 and TR 40180833.	
	Procedure 001-007044 *Sterility Assurance Risk Management at the IPM Site* and 7044-TEMP-03 *Aseptic Interventions and Aseptic*	

Observation	Actions	Date
	Manipulations Risk Management Template will be revised to include requirements and content specific to the comprehensive documentation of rationale for the removal or addition of coded interventions. Implementation will be completed by (b) (4)	
	Procedure 001-007997, *Parenteral Quality Manufacturing Oversight*, has been created to formalize floor walk-throughs in aseptic production areas and to define expectations, instructions and frequency for the Quality Check process in Lilly IPM. The Quality Check process applies to all operational and QC Lab areas and requires physical observation/evaluation of the area using tools and guides listed in the procedure. For example, comparing the observed area practice to the procedure for an identified task. QA is responsible and accountable for the performance, documentation, evaluation and reconciliation of the Quality Check process and outcomes as outlined in procedure 001-007997. The procedure will be effective	(b) (4)
	Additionally, effective by (b) (4), a QA for Sterility Assurance consultant role will be created to lead the quality oversight program for aseptic operations and to mentor QA floor support and Sr. QA floor specialists in aseptic processing quality and compliance attributes.	
4	The new acceptance criteria for critical (b) (4) lower limit) and major defects ((b) (4) lower limit) have been implemented, by updating procedure 001-005386 *Visual Inspection Qualification* (version 23). All inspection operators will be requalified according to these updated criteria by (b) (4) for B103 solution vial inspection operators, and (b) (4) for the other areas of the site.	
	A characterization assessment for B103 Solution Vial qualification (b) (4) using probability of detection as a consideration has been conducted (STATS-TR-4491, *103 Vial Solution Test* (b) (4) *Distribution update for alignment with* (b) (4) *and Probability of Detection (PoD)*, Appendix F). Based on this assessment, the defect distribution table for vials (b) (4) has been updated to align its defect composition, and the corresponding test (b) (4) will be improved as needed to ensure operators are capable to identify defects in worst-	

Observation	Actions	Date
	case conditions. Using these (b) (4) B103 vial operators will be requalified by (b) (4) (per response 4.A).	
	For other product presentations and platforms, a detailed characterization of the defects included in all the current test (b) (4) used for visual inspection qualification at Lilly IPM has been performed and documented in the technical report, MST08802, *Characterization of operator qualification test sets Summary Report* (Appendix G) to complement the (b) (4) composition description provided in the defect distribution tables.	N/A
	To further reinforce visual inspection operational support, a Visual Inspection Process Mentor position will be created to mentor, coach, guide and lead the visual inspection training and qualification program. This position will be effective by (b) (4)	(b) (4)
	Lilly IPM will engage qualified external consulting services to provide expertise, oversight, and independent assessment of our visual inspection process and the visual inspection qualification program by (b) (4)	
	A minimum of (b) (4) will lapse between two qualifications for the same (b) (4) by the same operator. The procedure 001-005386, *Visual Inspection Qualification,* has been revised accordingly and version 23 will be effective (b) (4) .	
	During the initial operator qualification process, different qualification test (b) (4) will be used with a single operator between two consecutive qualification tests, while adhering to the corresponding defect distribution table. Additional defect qualification (b) (4) will be implemented with the new defect qualification (b) (4) as they become fabricated. The procedure 001-005386, *Visual Inspection Qualification,* has been revised accordingly and version 23 will be effective (b) (4)	

Observation	Actions	Date
	(b) (4) fatigue assessment has been established for all visual inspection operators, by revising procedure 001-005386, *Visual Inspection Qualification.* The procedure (version 23) will be effective (b) (4) a. Operators will be challenged for fatigue (b) (4) they take (b) (4) requalification test for manual inspection, for all platforms and products. b. For the subset of operators who are also requalifying on semi-automated inspection, they will be also challenged for fatigue (b) (4) on semi-automatic equipment.	(b) (4)
	All the inspection operators will be requalified under those new conditions to address operator fatigue by (b) (4).	(b) (4)
	The training curricula on glass defects for incoming laboratory technicians (PAS0332, *Incoming Vial Inspection Qualification,* and PAS0410, *Incoming Long Syringe Barrel Inspection Qualification)* have been updated for glass defect inspection requalification to occur (b) (4). All incoming laboratory technicians trained on those two curricula have been requalified.	N/A
	A characterization assessment for vial defects has been conducted on available historical data for vial glass components, and documented in PAR-GLASS-TEC, *Assessment of Glass Vial Defects Visual Inspection* (b) (4) (Appendix H). Based on this characterization assessment, the existing vial qualification (b) (4) will be updated with the updated defect composition in type and quantity by (b) (4). All laboratory technicians will be requalified by (b) (4).	(b) (4)
	To further ensure the individual defects in the (b) (4) are representative of the defects observed through the incoming inspection process, a data collection process will be established to collect qualitative information on each found defect. This will allow the characterization assessment to remain current over time. Instructions to capture the details of each found defect (size/location) will be added to the (b) (4) vial method and implemented by (b) (4).	
	A routine review of the historical defect data will be performed to ensure the training qualification (b) (4) remain characterized accordingly. As such, an assessment will be conducted by (b) (4) to review	

Observation	Actions	Date
	the collected characterization data and to drive changes to the vial test (b) (4) Laboratory technicians will be requalified with the new test (b) (4) upon their following annual requalification. This process will be governed by a new procedure which will be implemented by (b) (4) (b) (4)	
5	An internal development guidance document (PRD-09638-TR *Forced Degradation & Stress Testing Guidance for Bioproduct Development*) will be updated to more fully ensure such discrepancies are appropriately evaluated and investigated. This will be completed by (b) (4)	(b) (4)
6	A retrospective technical assessment to confirm that existing supplier-collected sample arrangements are acceptable and are representative of the batch. Primary Packaging Components and Excipients: IPM Supplier-Collected Sampling Retrospective Evaluation (Appendix K) was completed on April 5, 2021	N/A
	A study protocol will be developed to directly assess the accuracy of existing supplier-collected samples against samples collected in house for each primary packaging component used in commercial manufacturing by (b) (4) . The protocol will be executed starting (b) (4) and will be completed based on supply chain timing and receipt of material batches.	(b) (4) (b) (4)
	Procedure 001-006077, *Material Supplier and GMP Service Provider Management* will be updated to specifically include expectations and required evaluations for documentation of quality approval and technical reviews during the supplier-collected sampling approval process by (b) (4)	(b) (4)
	The sampling plan will be updated to align with (b) (4) General Inspection Level II to increase the sample size and adjust the batch size range by (b) (4)	
7	Implement the use of locked channels and the signoff of all specification test results for clinical trial material analyses within (b) (4) In addition, Lilly PR&D will ensure that full reconciliation of these injections is performed as part of the new process. The new	

Observation	Actions	Date
	process will be documented in a new procedure and implemented by (b) (4)	
	Lilly PR&D will retrospectively lock channels and perform a reconciliation to confirm all (b) (4) sample sets were included in their respective notebook review for specification testing of clinical trial material tested from January 2019. Any sample sets not evaluated during the notebook review will be reconciled. This action will be completed by (b) (4)	(b) (4)

Listing of Appendices

Appendix A – Indianapolis Parenteral Manufacturing 3-Year Environmental Monitoring Evaluation

Appendix B – B103 Vial 3-Year Non-Zero Daily Personnel Recovery Evaluation

Appendix C – IPM 3-Year Task-Related Personnel Monitoring Data vs Intervention Data Evaluation

Appendix D - B103 Critical Alarm Delay Rationale

Appendix E - APS Intervention Retrospective Analysis (b) (4)

Appendix F – STATS-TR-4491, B103 Vial Solution Test (b) (4) Distribution update for alignment with PPN-LD-259 and Probability of Detection (PoD)

Appendix G - MST08802, Characterization of operator qualification test sets Summary Report

Appendix H – (b) (4) Assessment of Glass Vial Defects Visual Inspection (b) (4)

Appendix I - Component and Excipient: Supplier-Collected Sampling Strategy: Indianapolis Parenteral Manufacturing

Appendix J - Use of Active Pharmaceutical Ingredient and Drug Substance (b) (4) Samples: Indianapolis Parenteral Manufacturing

Appendix K - Primary Packaging Components and Excipients: IPM Supplier-Collected Sampling Retrospective Evaluation

Appendix L - Sampling Plans for Glass Vials at Incoming/Receiving for Critical Defects