Product Review

Frederick Manufacturing Center (FMC) Product Review

Fasenra
(benralizumab)

Reporting Period:
November 14, 2022 through November 13, 2023

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1 SUMMARY AND CONCLUSION

The scope of this Product Review (PR) includes Fasenra (benralizumab) Drug Substance (DS), Formulated Bulk (FB), Drug Product (DP), and associated intermediate manufacturing steps for the period 14Nov2022 through 13Nov2023 produced and/or tested at the Frederick Manufacturing Center (FMC).

This PR provides documented evidence that during this period the process to manufacture Fasenra DS, FB, and DP remained under a state of control and that the validation status has been maintained and is compliant with registered specifications. This review identified no recommendations for improvement.

Fasenra (benralizumab) Drug Substance (DS), Formulated Bulk (FB) and Drug Product (DP) are produced and/or tested at the Frederick Manufacturing Center (FMC) site. The DS is produced at two (2) scales; the 15K scale in Building 633 (B633) and the 2K scale in Building 636 (B636). DS produced at the 15K scale is approved to be formulated in B633 or in B636 to produce FB. DS produced at the 2K scale is only approved for formulation in B636. While DP is not manufactured at the FMC, release and stability testing is performed at the FMC.

Some process and facility changes were made and reported since the DS and FB manufacturing process validation at both manufacturing scales. However, the impact of these changes was low and is shown to be effective for the intended purpose with no unintended consequences.

Overall, the manufacturing processes for DS and FB are robust, well controlled, and continue to operate in a validated state (see Section 6, Analytical Data). While DP is not manufactured at FMC, release and stability testing is performed. Ten (10) DS batches were dispositioned within this period and five (05) FB batches were dispositioned within this period. Ten (10) DP batches dispositioned during this period had release testing performed at FMC. Data are collected from commercial batches as part of normal release processes as well as the Continued Process Verification (CPV) programs. These programs monitor in-process parameters, in-process attributes, and final Critical Quality Attributes (CQAs). The CQAs are monitored through the trending of the DS, FB, and DP release and stability data. These data show that the product quality is within the approved specifications and is not drifting over the course of time.

During this PR period, the CPV program reported a low process capability trend for the FB Polysorbate 20 release testing (process performance indices < 1.3). The details regarding the trend are captured in Section 6.2.

No major deviation trend was identified for DS or FB manufacturing process, demonstrating effectiveness of corrective or preventive actions (CAPAs).

A review of the prior period's PR revealed that there was one (01) adverse trend requiring follow up and reporting in this review period.

- The CPV capability analysis for FB Polysorbate 20 release testing reported a low process capability trend in the 2021 PR. CAPA 219493 and change control 222665 were initiated to revise the bulk filtration filter flushing process to reduce a potential risk that Polysorbate 20 would be lost prior to product filtration due to filter saturation. An effectiveness check, E-Check 219497, was generated to ensure that the CAPA was appropriate for future lots. As noted during the E-Check closure, while not all of the E-check requirements were satisfied, data analysis demonstrated that there was minimal variance between the Formulation and DP results. This similarity between formulation and DP results indicates the lower FB results are not related to a manufacturing process issue.

  An increase in the mean FB Polysorbate 20 release testing was observed following CAPA implementation. As process capability is the measure of all historical commercial batches, the overall process capability did not change due to the limited number of batches post CAPA implementation. There were no FB batches post process improvement with a Polysorbate 20 release test result outside the specification of 0.004-0.008%. The observed low process capability continued in the 2022 CPV observations as well as in the 2023 CPV observations. Under the CPV risk register RSKREG-000336, Quality Risk RE-002723 was generated and mitigation actions MA-001421 and MA-001750 initiated to further evaluate and mitigate the low Polysorbate 20 process capability.

The mitigation actions have closed with neither evaluation identifying additional mitigating actions. Per MA-001421, there is no evidence to suggest that the past observed PS-20 concentration excursions are the result of any manufacturing facility, process and/or sampling related factors. MA-001750 concluded that there is no evidence that the FB PS20 low process capability is the result of any sample handling related factors in the quality control laboratories.

While no mitigating actions were identified, there is no expected impact to any product quality attributes as no specification failures have occurred. RE-002723 remains active and requires periodic review. FB PS20 will continue to be monitored in the CPV program and any future events or actions will be discussed in section 6.2, Final Bulk.

The manufacturing supply chain for Fasenra covers multiple sites and is summarized in Figure 1.

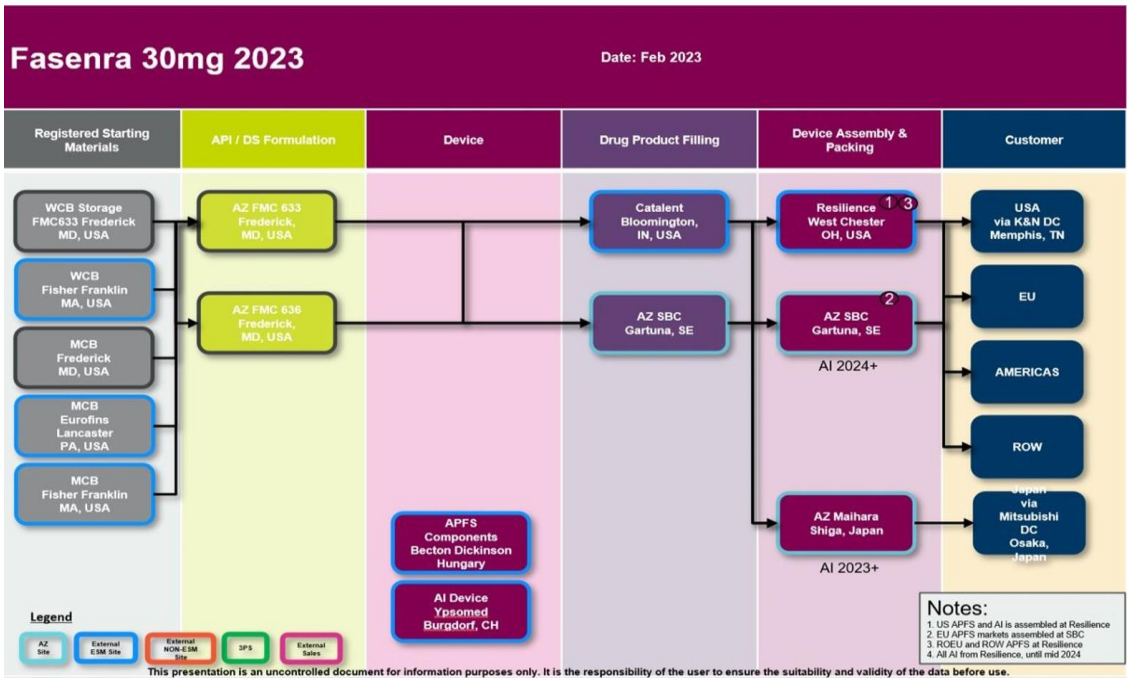

Figure 1 Fasenra Supply Chain

NOTE: AstraZeneca (AZ) sites will issue site-specific Product Review Reports. The results of those reports will be assessed in the next Product Review for Fasenra according to global procedure SOP-0034081, *Product Reviews*. An Integrated Summary Product Review (ISPR) will be issued for this product and reporting period. The ISPR will consider major trends or issues across all sites.

2 BATCHES REVIEWED (APPROVED, REJECTED AND TERMINATED)

2.1 Drug Substance Batches

Batches (with batch number) included in this report:

Batches Reviewed	Number of Batches Previous Review	Number of Batches Current Review
15K Final dispositions during the period	0	3 (PN2232, PN2271, PN2272)
2K Final dispositions during the period	2 (KN3189[a], MF3043)	7 (PT3323, PT3520, TA2010, TA2159, TA2351, TA2831, TA2833)
Batches Approved	2	10
Batches Fully Rejected	0	0
Batches Partially Rejected	N/A[b]	0
Batches Terminated (In-process)	N/A[b]	1 (TA2832[c])

[a] 2K scale process validation batches
[b] Reporting criteria was not required
[c] 2K scale

Batches rejected during the period: ☒ N/A

Batch No.	Reason	Reference

Batches terminated (in-process) during the period: ☐ N/A

Batch No.	Reason	Reference
TA2832	Contamination of the batch was discovered while in production bioreactor BRX-6151 (PN 8007258), This batch was terminated and discarded.	QE-043405

Discussion/Comments ☒ N/A

Section 2.1 Conclusion

A total of ten (10) DS batches were fully released for further manufacturing and distribution by the site during this period. Of those batches, three (03) were manufactured at the 15K scale in B633 and seven (07) were manufactured at the 2K scale in B636. There were 10 batches approved and zero batches fully rejected and zero batches partially rejected during the review period.

There were no validation batches produced during this period.

Compared with the previous period, the number of full or partial batches rejected has:

☐ Decreased ☒ Remained Unchanged ☐ Increased

Based on this review of batches reviewed, approved, and rejected:

☒ There is no evidence noted of a trend to indicate a quality or system issue.

☐ A trend indicating a quality or system issue has been identified.

2.1.1 Manufacturing In-Process Control: Upstream

Major changes, major deviations, and impact assessments for each upstream unit operation are summarized below. The major changes for the upstream operation are included below; all changes are included in Section 7 and deviations are further discussed in Section 9.

Vial Thaw:

There were no major changes implemented and no major deviations during batch execution at this stage for vial thaw.

All batches met the established in process control (IPC) acceptance criteria, and no trends were identified.

Inoculum Expansion:

There were no major changes to process controls or operational parameters implemented and no major deviations during batch execution at this stage for the batches produced.

All batches met the established IPC acceptance criteria, and no trends were identified.

Seed Bioreactors, Production Bioreactor, Harvest:

There were no major changes implemented and two (2) major deviations during batch execution at these stages for the batches produced.

QE-028045 was initiated in response to the discovery that the 100L bioreactor BRX-1009 agitator was not running and the agitator motor switch was in the “off” position during the processing of benralizumab part number (PN) 8006137 batch number (BN) PN2272. It was determined that the agitation was in the off position from 21Nov22 until 29Nov22, impacting a clean-in-place (CIP) operation and the subsequent production process of batch PN2272 until discovery on day 3 post-inoculation, when operators turned the agitator motor switch to the “on” position.

As a result of this event, the minimum cell viability at transfer (>90%) for PN2272 was not met. Following transfer, the cell culture viability recovered in the 500L bioreactor stage. The root cause of this quality event was attributed to there being no automated detectability of a failure mode in the variable frequency drive (VFD) of the agitator motor. The working state of the automation at the time of the event had no capability of notifying or preventing the process operators from proceeding with a failure mode in place. Additional contributing factors identified include a lapse in returning the equipment to the “on” state following removal of a lock out tag out (LOTO) device during preventative maintenance, as well as there being no step in the return to service process instructing a check of agitator function status.

The following corrective and preventative actions (CAPA) were initiated or implemented as a result of this event:

1. CAPA-004409: Revision of the return to service form to include a step to run agitator and visually confirm operation.
2. CAPA-004410: Revision of SOP-0106443 (Bioreactor Operations Procedure, FMC B633) to include a step to visually verify agitation operation following media addition.
3. CAPA-004412: Adjustment of VFD parameters and alarm setpoints in building 633 to enable automated detection and notification of agitator motor failure mode.
4. CAPA-004413: Adjustment of VFD parameters and alarm setpoints in building 636 to enable automated detection and notification of agitator motor failure mode.

While there was cell culture and cleaning validation impact as a result of this event, as determined by the event investigation, there was no overall impact to product quality or patient safety, as the cell culture recovered following the agitation and cell viability excursions, and all subsequent product quality testing passed required parameters. Cleaning controls were in place that ensured a proper cleaning was performed.

QE-043405 was initiated in response to a LoLo alarm for dissolved oxygen (DO) control on production bioreactor BRX-6151 during benralizumab PN 8007258 BN TA2832. As a result of the DO control excursion investigation, it was confirmed by microscopic examination and Quality Control (QC) testing that the bioreactor experienced a microbial contamination of *Bacillus toyonensis*. In response to the discovery of the bacterial contamination, BRX-6151 was placed on QA-Hold and batch TA2832 was subsequently terminated. Multiple potential contributing causes were identified including misalignment/vacuum of the media inlet lines, excess liquid condensate build-up due to multiple add line sterilization-in-place (SIP) failures and diluted caustic solution in the clean-in-place (CIP) skid following the centrifuge CIP. An additional contributing factor was the presence of *B. toyonensis* in the building 636 cell culture room P110 identified by environmental monitoring (excursion QE-041568) during the investigation. In addition to multiple ADDPORT 1 SIP improvements identified during the course of the investigation, the following corrective and preventative actions (CAPA) were initiated or implemented as a result of this quality event:

1. CAPA-006385: A CAPA resulting from EM excursion investigation QE-041568 to update SOP-0067595 (Use of Floor Drains in the Production Areas at the Frederick Manufacturing Center (FMC)) to include a 5x5 foot cleaning around floor drains with sporklenz immediately after use.
2. CAPA-009424: Installation of valve stands to allow proper alignment of the sanitary connection during preventative maintenance.
3. CAPA-009425: Implement closing of valve HV-615X-307 during Centrifuge CIP Drain All operation step.
4. CAPA-009426: Installation of air vent on centrifuge floor drain to prevent CIP solution from splashing out of P110 floor drain.

The affected batch was terminated at the production bioreactor process step. No definitive root cause was identified as a result of the investigation.

All other batches met the established IPC acceptance criteria, and no trends were identified.

2.1.2 Manufacturing In-Process Control: Downstream

Major changes, major deviations, and impact assessments for each downstream unit operation are summarized below. The major changes for the downstream operation are included below; all changes are included in Section 7 and deviations are further discussed in Section 9.

Protein A Chromatography:

There were no major changes to process controls or operational parameters implemented for the Protein A Chromatography step and no major process deviations during batch execution at this stage for batches produced.

All batches met the established IPC acceptance criteria, and no trends were identified.

Low pH Inactivation:

There were no major changes to process controls or operational parameters implemented for the Virus Inactivation step and no major process deviations during batch execution at the 15K scale for batches produced. There was one major trend deviation at the 2K scale for batches produced. QE-042077 was initiated for a trend of out-of-range (OOR) neutralized low pH treated product conductivity values. The attained conductivity values exceeded the Master Production Record (MPR) MABR-0009616 Normal Operating Range (NOR) specification of 5.0 – 9.0 mS/cm. The trend deviation was initiated for the following batches:

- TA2351; Conductivity Value: 9.1 mS/cm
- TA2831; Conductivity Value: 9.1 mS/cm
- TA2833; Conductivity Value: 9.5 mS/cm

In addition to the above batches, OOR neutralized pool conductivity values occurred during additional batches of the B636 benralizumab 2023 campaign. Neutralized pool conductivity NOR excursions of 9.1 mS/cm are documented in minor deviations QE-037658 on 02FEB23, QE-039447 on 12FEB23, and QE-040679 on 18FEB23.

QA & MFG management assessed this deviation to be a trend per SOP-0107503 "Deviation Management". Conductivity measured outside the NOR specification for six (6) out of seven (7) production batches of B636 benralizumab in the 2023 campaign.

The investigation determined the following as causal to the neutralized pool conductivity NOR excursions. Inherent process difference due to the manufacturability at different scales, contributes to a higher concentration of protein A pool, which leads to higher acid followed by higher base ratios being required for neutralization. The current NOR is not as centered as it should be considering data from 2K scale production.

There was no expected product quality impact attributed to this event as evidenced by passing lot release data and downstream performance, including product quality data. There was no patient safety risk because product quality and safety are ensured by lot release criteria that must be met to fully release the impacted lots. CAPA-006729 was initiated to facilitate a change control to update the conductivity range in the control strategy document, REP-0115041, that will be representative of both building scales. Change control QE-068524 has been initiated to update the benralizumab control strategy document (REP-0115041) for neutralized low pH product conductivity. The change recommendation will be based on process data, once gathered. Currently no changes to the range have been implemented as additional data is required to set an upper limit without impact to the performance of the subsequent cation exchange (CEX) chromatography unit operation.

All other batches reviewed during this reporting period met the established IPC acceptance criteria and no additional trends were identified.

Cation Exchange, Mixed Mode Chromatography and Virus Filtration:

There were no major changes to process controls or operational parameters implemented for the Cation Exchange, Mixed Mode Chromatography and/or Virus Filtration steps and no major deviations.

Batches reviewed during this reporting period met the established IPC acceptance criteria, and no trends were identified.

Ultrafiltration/Diafiltration:

There were no major changes to process controls or operational parameters implemented for the Ultrafiltration/Diafiltration step at either scale and no major deviations at the 15K scale. There were two (2) major deviations at the 2K scale.

QE-039406 was initiated during the 2K production of lot PT3520 for two (2) simultaneous events. Event #1: While executing UF/DF process per MABR-0009612 BN: PT3520 "636 Benralizumab Concentration/Diafiltration (8007409)" v4.0, operators observed a LoLo alarm on cross feed flow flux FIC-6227-CFF. Alarm value of 3.6L/min/m2 was below NOR range of 4.0-6.7L/min/m2. Alarm occurred approximately halfway through the Concentration 1 operation. While performing corrections, operators observed pressure indicator PI-6227-030 was increasing in pressure and held the recipe to further investigate. By the time the recipe held and the pump stopped, a high alarm occurred on PDIC-6227-030TMP. Alarm value of 32.0 psig exceeded the NOR for Concentration transmembrane pressure (TMP) of ≤30.0 psig. It was determined that single-use retentate control valve PV-6227-030 was not functioning properly. The decision was made to reinstall PV-6227-030 per SOP, clear failures in DeltaV, and resume recipe.

Upon restarting, a second NOR excursion occurred as listed in the Event #1 description. PV-6227-030 was removed and the back of the valve was observed to be damaged. The decision was made to replace the affected manifold and perform a manual prime of the system upon restarting the process. Once the system was primed, the replaced valve functioned correctly and the process resumed without further issue.

Additionally, a functionally closed system was opened to replace the malfunctioning single-use retentate control valve assembly. There was no anticipated product or process validation impact due to the event. The low cross flow flux alarm is not a classified parameter per control strategy document (CSD) REP-0115041: *MEDI-563 Downstream Control Strategy Document (Parameter Summary) for Frederick Manufacturing Center*. The TMP exceeding the NOR of ≤30.0 psig with 32 psig is classified as a key process parameter (KPP), which is a non-critical process parameter per REP-0115041 whose variability has a practically significant impact on process performance or process consistency. There was no impact to product quality as the feed pressure did not exceed the NOR and no product was detected in the permeate line. There was no process validation impact due to the TMP excursion, as there is no membrane lifetime report for this operation as the membranes are single use. CAPA-006141 was initiated as a response to this event to clarify language in the UF/DF setup SOP, SOP-0067957 to provide instructions on how to detect potential damage on the plunger component of the single use valve.

Event #2: Operators observed a product leak on the Pall KleenPak Connector II (KPC2) adapter of the retentate inlet tubing downstream of valve HV-6227-011. The leak was approximately 1mL total and occurred at the start of Concentration 1. The leak was contained when operators placed the recipe on hold due to Event #1. The leak resumed during the manual recirculation after the manifold replacement at a rate of approximately one (1) drop per second. The leak stopped when recirculation stopped and started again at the start of concentration as the pump ramped up for about twenty (20) seconds. Once the pump stabilized, the leak stopped. An approximate total volume of 50mL product leaked during mitigation of Event #1. No immediate action was taken to correct the leak. The KPC2 adapter was retained and submitted for supplier complaint under QE-039865.

The UFDF operation is not a sterile operation, however, post sanitization is constituted as functionally closed. The KPC leak on the retentate line was a breach to the functionally closed system. While there was risk to microbial ingress, the risk is highly detectable through routine testing per SPEC-0064990: *Benralizumab, FMC Building 636, Quality Control Testing Plan: Purification*. All downstream routine bioburden testing following this event did pass with all results reported as 0 CFU/10mL.

FMC Quality determined the two (2) events in combination would be included in the same deviation, under a major classification.

QE-040885 was a major trend deviation initiated due to a trend of Pall KleenPak Connector II leaks during Drug Substance manufacturing in B636 for consumables utilized during UF/DF. The trend deviation included deviations across FMC products that shared components found to contribute to the leak. Major deviation QE-039406 was the only benralizumab deviation included in this trend. There were no immediate corrective actions taken as a result of the trend of leaking components. Each leaking component was retained and submitted for supplier complaint per SOP-0040921: *Submission and Management of Supplier Complaints Discovered at Biologics Sites* and SOP-0107502: *Global Complaint Management*. CAPA-009283 was initiated to revise SOP-0068200: *Sterile Connect and Sterile Disconnect at the Frederick Manufacturing Center (FMC) Site* (v10.0) to align with manufacturer instructions when making the KPC2 connections and include a check that the foil peel strips are properly aligned prior to removal. There was no product impact as a result of this trend deviation. Lot PT3520 was the only benralizumab lot included in this deviation. All lot release testing passed, and no product quality attributes were impacted.

Batches reviewed during this reporting period met the established IPC acceptance criteria, and no additional trends were identified.

Controlled Freeze, Storage and Controlled Thaw Bulk Drug Substance:

There were no major changes to process controls or operational parameters implemented for the Controlled Freeze, Storage, and/or Controlled Thaw Bulk Drug Substance steps and no major deviations.

Batches reviewed during this reporting period met the established IPC acceptance criteria, and no trends were identified.

2.2 Final Bulk Batches

Batches (with batch number) included in this report:

Batches Reviewed	Number of Batches Previous Review	Number of Batches Current Review
B633 Final dispositions during the period	11 (PA2034, PA2035, PA2036, PA2037, PB2292, PB2293, PB2294, PH3471, PH3473, PH3474, PH3475)	5 (PB2290W, TB2315, TB3196, TB3197, TB3198)
B636 Final dispositions during the period	2 (NN2803, NN2804)	0
Batches Approved	13	5
Batches Fully Rejected	0	0
Batches Partially Rejected	0	0
Batches Terminated (In-process)	0	0

Batches rejected during the period: ☒ N/A

Batch No.	Reason	Reference

Batches terminated (in-process) during the period: ☒ N/A

Batch No.	Reason	Reference

Discussion/Comments ☐ N/A

Batch PB2290W was manufactured during the previous reporting period. The disposition was delayed due to TrackWise deviation 259401 and potential market restrictions as discussed in last year's PR. Batch PB2290W was dispositioned as approved during this reporting period with no market restrictions.

Section 2.2 Conclusion

A total of five (05) FB batches were fully released for further manufacturing and distribution by the site during this period. Of those, five (05) FB batches were formulated in B633 and zero (0) FB batches were formulated in B636. There were 05 batches approved and no batches fully rejected and no batches partially rejected during the review period.

There were no validation batches produced during this period.

Compared with the previous review, the number of full or partial batches rejected has:

☐ Decreased ☒ Remained Unchanged ☐ Increased

Based on this review of batches reviewed, approved, and rejected:

☒ There is no evidence noted of a trend to indicate a quality or system issue.

☐ A trend indicating a quality or system issue has been identified.

2.2.1 Manufacturing In-Process Control (Final Bulk)

Major changes, major deviations, and impact assessments for each upstream unit operation are summarized below. The major changes for FB are included below; all changes are included in Section 7 and deviations are further discussed in Section 9.

Formulation and Final Bulk:

There were no major changes to process controls or operational parameters implemented for the Formulation and Final Bulk steps and no major deviations.

Batches reviewed during this reporting period met the established IPC acceptance criteria, and no trends were identified.

3 REPROCESSED & REWORKED BATCHES

3.1 Drug Substance

Reprocessed and Reworked Batches	Previous Review	Current Review
Total Number of Reprocessed or Reworked Batches	1	0
Total Number of Batches Reviewed	2	10
Percentage of Batches Reprocessed and Reworked	50 %	0 %

Reprocessed and reworked batches during the period ☒ N/A

Batch No.	Reprocess/ Rework	Reason	Reference Number

3.2 Final Bulk

Reprocessed and Reworked Batches	Previous Review	Current Review
Total Number of Reprocessed or Reworked Batches	0	0
Total Number of Batches Reviewed	13	5
Percentage of Batches Reprocessed and Reworked	0 %	0 %

Reprocessed and reworked batches during the period ☒ N/A

Batch No.	Reprocess/ Rework	Reason	Reference Number

Discussion/Comments ☒ N/A

Section 3 Conclusion
There were no batches subject to reprocessing or rework during the review period.

Based on this review of batches reprocessed or reworked:

☒ There is no evidence noted of a trend to indicate a quality or system issue.

☐ A trend indicating a quality or system issue has been identified.

4 PRODUCT REVIEWS FROM PREVIOUS MANUFACTURING STAGE

This section is not applicable as an ISPR, which considers all steps and sites in the DS and DP manufacturing process, will be issued for this product and reporting period. The ISPR will consider major trends or issues across all sites.

5 STARTING AND PACKAGING MATERIALS FOR DRUG SUBSTANCE AND FINAL BULK

There were no adverse trends and the release/reject results for the critical materials are listed below.

Critical materials are defined as the working cell bank, excipients, custom blends, final containers, as well as critical processing aides, and are included in Table 5-1. Non-critical materials with possible quality concerns are included in Table 5-2. Materials rejected during the period are included in Table 5-3. All other materials, routinely released with no impacting changes or quality concerns, are excluded from this summary.

Table 5-1: Critical Materials: Excipients and Final Packaging for Drug Substance and Final Bulk ☐ N/A

Material Part Number	Material Description	Release Results Routinely Meet Specification? YES/NO	If NO, what follow-up actions needed? List other follow-up actions, if applicable	Comments on Follow-Up Actions, Results and Trends. Give Reference to Trend Charts, as applicable
563AR	Medi-563 Working Cell Bank	Yes	N/A	New Global Material Number per Standardization in Global CC QE-014406 and Local FMC CC QE-015606.
110025336	Benralizumab LQD EA WCB	Yes	N/A	New Global Material Number per Standardization in Global CC QE-014406 and Local FMC CC QE-015606.
4101095	L-Histidine USP, EP, JP (Excip) 1 kg	Yes	N/A	N/A
6001968	L-Histidine USP, EP, JP (Excip) 12 kg	Yes	N/A	N/A
6002790	L-Histidine USP, EP, JP (Excip) 10 kg	Yes	N/A	N/A
6004126	L-Histidine USP, EP/BP, JP (Excip) 50kg	Yes	N/A	N/A
4101011	Histidine HClMonohydt EP, JP Excp, 1kg	Yes	N/A	QE-059342 - FMC implementation of Japanese Pharmacopoeia 18 supplement 1, Removal of JP Heavy Metals test to Align with JP Monograph.
6001790	Histidine HClMonohydt EP, JP Excp, 12kg	Yes	N/A	QE-059342 - FMC implementation of Japanese Pharmacopoeia 18 supplement 1, Removal of JP Heavy Metals test to Align with JP Monograph.
6001792	Histidine HClMonohydt EP, JP Excp, 50kg	Yes	N/A	QE-059342 - FMC implementation of Japanese Pharmacopoeia 18 supplement 1, Removal of JP Heavy Metals test to Align with JP Monograph.

Material Part Number	Material Description	Release Results Routinely Meet Specification? YES/NO	If NO, what follow-up actions needed? List other follow-up actions, if applicable	Comments on Follow-Up Actions, Results and Trends. Give Reference to Trend Charts, as applicable
6002791	Histidine HClMonohydt EP, JP Excp, 10kg	Yes	N/A	QE-059342 - FMC implementation of Japanese Pharmacopoeia 18 supplement 1, Removal of JP Heavy Metals test to Align with JP Monograph.
4102580	a, a-Trehalose Dihydrate, NF, EP, JP 25kg	Yes	N/A	QE-059342 - FMC implementation of Japanese Pharmacopoeia 18 supplement 1, Removal of JP Heavy Metals test to Align with JP Monograph.
4102679	a, a-Trehalose Dihydrate, NF, EP, JP 50kg	Yes	N/A	QE-059342 - FMC implementation of Japanese Pharmacopoeia 18 supplement 1, Removal of JP Heavy Metals test to Align with JP Monograph.
4101390	Polysorbate 20 NF, EP, JPE	Yes	N/A	N/A
6002677	Celsius Pak, 16.6L doubleVent Filter/AC	Yes	N/A	There are Rejections reported in Table 5-3.
6002233	100L Pall Allegro Single UseSys	Yes	N/A	CC QE-012632 - Pall Duncan, SC, an already approved supplier for AstraZeneca, to manufacture materials used by AstraZeneca, Large Molecule. CC QE-015232 - AZ FMC implements use of Pall Duncan SC as supplier of Single Use Assemblies.
4100986	Cell Culture Medium DMNSO-8, 5kg	Yes	N/A	N/A
4102433	Cell Culture Medium DMNSO-8, 50kg	Yes	N/A	N/A

Material Part Number	Material Description	Release Results Routinely Meet Specification? YES/NO	If NO, what follow-up actions needed? List other follow-up actions, if applicable	Comments on Follow-Up Actions, Results and Trends. Give Reference to Trend Charts, as applicable
6000491	AACBF-A Feed Concentrate, 50kg	Yes	N/A	N/A
6000510	AACBF-A Feed Concentrate, 10kg	Yes	N/A	N/A
6000492	AACBF-B Feed Concentrate, 50kg	Yes	N/A	N/A
6000511	AACBF-B Feed Concentrate, 10kg	Yes	N/A	N/A
100061	Yeast Extract Powder - Ultrafiltered	Yes	N/A	One batch OOS described in Table 5-3.
6000662	Yeast Extract Powder - UF, Custom	Yes	N/A	N/A
6002238	Yeast Extract Powder - UF, Custom 50kg	Yes	N/A	N/A
6002963	Yeast Extract Powder - UF, Custom-II 10kg	Yes	N/A	N/A
6002965	Yeast Extract Powder - UF, Custom--II 50kg	Yes	N/A	N/A
4101797	Chromatography Media MabSelect SuRe 10L	Yes	N/A	N/A
4102160	Chromatography Media MabSelect SuRe 5L	Yes	N/A	N/A
6001979	Resin MabSelect SuRe (Benzyl Alcohol) 5L	Yes	N/A	N/A

Material Part Number	Material Description	Release Results Routinely Meet Specification? YES/NO	If NO, what follow-up actions needed? List other follow-up actions, if applicable	Comments on Follow-Up Actions, Results and Trends. Give Reference to Trend Charts, as applicable
6002000	Resin MabSelect SuRe (Benzyl Alcohol) 10L	Yes	N/A	N/A
4101780	Chromatography Media - Capto Adhere Resin	Yes	N/A	N/A
4102211	Chromatography Resin-Poros 50 HS, 40L	Yes	N/A	SIC QE-013098 and CC QE-013371: To increase capacity, Life Technologies constructed and implemented a new Chelmsford, MA facility (as well as expanded the already approved Bedford, MA facility.)
40003	Resin Poros 50 HS 10 L	Yes	N/A	SIC QE-013098 and CC QE-013371: To increase capacity, Life Technologies constructed and implemented a new Chelmsford, MA facility (as well as expanded the already approved Bedford, MA facility.)
4102503	Viresolve Pro Magnus 2.2 Device	Yes	N/A	N/A
4102531	Viresolve Pro Magnus 2.2 Shield	Yes	N/A	N/A
4102050	Filter Pellicon 3 30K Cassette, 1.14 m2	Yes	N/A	N/A
6003645	Opticap XL5 SHC 0.5/0.2 um w/ AQ-G	Yes	N/A	N/A
6002229	30" SHC Filter Manifold	Yes	N/A	N/A
6002313	Product Transfer Manifold	Yes	N/A	N/A

Table 5-2: Non-Critical Materials ☐ N/A

Material Part Number	Material Description	Release Results Routinely Meet Specification? YES/NO	If NO, what follow-up actions needed? List other follow-up actions, if applicable	Comments on Follow-Up Actions, Results and Trends. Give Reference to Trend Charts, as applicable
4102100	Chemically Defined Lipids, 5 L, Sterile	Yes	N/A	Deviation QE-054944: FMC had been manufacturing medicines using Chemically Defined Lipid Concentrate (CDLC) raw material that did not contain a certificate of suitability (CEP). No impact to product quality.

Table 5-3: Materials Rejected During the Period ☐ N/A

Material	Batch Number	Reason	Reference
Yeast Extract Powder – Ultrafiltered (PN 100061)	367966	Total Rejections: 2,830 KG (283 Containers). Incoming Internal QC testing confirmed true Bioburden OOS.	Lab Investigation QE-031416 and Supplier Deviation QE-035161
Celsius Pak, 16.6L doubleVent Filter/AC (PN 6002677)	360669 358569 354481	Total Rejections: 28 EA. All Products that failed visual inspection on the manufacturing floor (blemishes, scratches, creases, particles), but pass supplier Sartorius' Guidelines for Visual inspection of Celsius Pak since they have no impact on integrity nor functionality of the product. FMC will continue to track and trend.	Supplier deviations QE-040425, QE-042496, AZ-BIO-2022-647, and FMC Deviation QE-068929. The related Supplier Deviation for FMC Deviation QE-068929 is QE-068936 and is still under investigation.

Active Substance Supply Chain Review (performed per SOP-0069612)
For API and/or Drug Substance, a review of supply chain maps to assure all suppliers are identified and are legitimate was performed. Reference approved Supply Chain map FORM-0058735, Benra Supply Chain Map and Bill of Materials (BoM) with Suppliers. Version 4.0. ☒ Yes ☐ N/A; this product is not manufactured at this site.

Discussion/Comments ☐ N/A

There were numerous Supplier Initiated Changes (SICs) from material suppliers to add additional vendors to expand their raw materials. There were also SICs to expand new lines at already approved vendor sites, add new methods of sterilization, change the format of reports as well as make reports available online, and implement additional storage warehouses. These had no impact on AZ and were accepted.

Section 5 Conclusion

The starting materials and packaging components have all been purchased in accordance with registered specifications.

Testing of these materials by both the supplier and AstraZeneca has:

- ☐ Confirmed that all batches delivered met the registered specification; there were no rejections of materials.
- ☒ Identified that not all batches delivered met the registered specification; there were rejections of materials.

During the review period, there was a confirmed OOS with contaminated Yeast Extract Powder, however, all subsequest batches have had no quality concerns. The final containers for Benralizumab Drug Substance are 16.6 L Celsius Pak bags. Although there were rejections for 16.6 L Celsius Bags, at this time all rejections have not failed Supplier Sartorius' standard of visual inspection, and will be investigated further should the rejections meet trending criteria.

Based on this review of materials:

☒ There is no evidence noted of a trend to indicate a quality or system issue.

☐ A trend indicating a quality or system issue has been identified.

The supply chain maps for the Active Pharmaceutical Ingredient (API) included in this product review have been evaluated, and all suppliers used were approved by site QA.

6 ANALYTICAL DATA

Process Performance and Robustness

The quantifiable outputs of the CPV programs are given below for DS, FB, and DP CQAs. These data for DS, FB, and DP are presented in more detail in Table 16-1, Table 16-2, and Table 16-3. These data show that the CQAs are well controlled by the manufacturing process with respect to the specification limits and level of variability.

In the following section, process performance indices are used to track the control of product attributes (often CQAs). These data are presented for the current period as well as a comparison for the previous three periods, where applicable. Per ASTM standard E2281 "Standard Practice for Process and Measurement Capability Indices," process performance indices (hereby Ppk) are minimum process performance indices that are derived from the smaller of the upper and the lower process performance index for a given attribute. Ppk is a measurement of the historical process performance to meet the upper or lower specification limit. Ppk uses a long-term standard deviation estimate, which includes special cause variation. The Ppk indices presented in the below tables are sorted top to bottom from lowest to highest level of process performance, respectively. The accumulated individual production measurements from a process over a long period of time has an overall sample standard deviation estimated as:

$$\hat{\sigma}_{LT} = \sqrt{\frac{\sum(X_i - \bar{X})^2}{\eta - 1}}$$

This standard deviation contains the following components of variability:

- Batch to batch variability over the long term,
- Within-batch variability over the short term,
- Measurement system variability over the long term, and
- Measurement system variability over the short term.

6.1 Drug Substance

Trending for DS data is performed by FMC Manufacturing Science and Technology (MS&T). Trending for DS lots produced in the review period are included in REP-0238868, *VX-710078-PVP-R9: Continued Process Verification Stage 3a Summary Report for Benralizumab DS*. Due to the limited number of available lots for statistical analysis, benralizumab DS remains in CPV stage 3a and only run charts are provided in the CPV report. CPV trends are not applied at stage 3a. There was one major trend deviation for out-of-range (OOR) results at the low pH inactivation step: neutralized low pH treated product conductivity; refer to Section 2.1.2 for the discussion.

Based on the compiled data results, it is concluded that, following initial process validation, the routine commercial manufacturing of benralizumab remained in a state of control.

Batch Release Results

Batch release results for all commercial DS lots are shown graphically in the run charts included in Section 4 of REP-0238868 and are summarized in Table 16-1 of this product review.

Summary of OOS Results

OOS Results	Previous Review	Current Review
Total Number	0	0

All commercial DS lots dispositioned during the review period met the product specification requirements.

Drug Substance Process Performance

Benralizumab DS remains in CPV stage 3a. Per SOP-0067348, CPV trends are not applied at stage 3a. There are no significant CPV trends related to the control of DS. There was one major trend deviation for out-of-range (OOR) results at the low pH inactivation step: neutralized low pH treated product conductivity; refer to Section 2.1.2 for the discussion.

The most recent CPV study for benralizumab DS evaluated a total of twenty-five (25) lots of benralizumab manufactured from the first PPQ lot manufactured on May 2015 to November 2023. Due to the limited sample size of twenty-five (25) benralizumab DS lots, process capability (Ppk) and controls charts were not generated as part of CPV stage 3a. However, data was presented in run charts for the monitored parameters using the acceptance criteria in PRO-0099821/ VX-710078-PVP-A2. Now that a minimum of twenty-five (25) lots have been completed, a risk assessment will be performed to establish control limits and move benralizumab DS to stage 3b.

Section 6.1 Conclusion

This evaluation considered registered finished product data attributes and critical in-process attributes. A disposition decision was made for all batches meeting specification to release for further manufacturing. No CPV trends were identified to indicate a quality or system issue.

There were no batches outside of registered specification (OOS) during the review period.

The risk-based process metrics established at the site confirm that the capability of the process for the finished product and critical in-process attributes continues to operate in line with the requirements established during either initial validation or with CPV.

Real-time trending tools were deployed to assure process capability during this time period. Trending signals were identified and actioned via the Out of Trend (OOT) investigations process, as required.

Appropriate process metrics deployed as part of CPV confirm the capability and stability of the process for the product (including critical in-process parameters/attributes) to assure the process operated under control.

6.2 Final Bulk

Trending for FB data is performed by FMC MS&T; trending for FB lots produced in the review period are included in report REP-0239373, *VX-710078-PVP-R10: Continued Process Verification Stage 3b Summary Report for Benralizumab FB30*.

There were two (2) out-of-trend (OOT, out of control limit) and one (1) low process capability assessment identified for Final Bulk Polysorbate 20 batch data that are discussed in REP-0239373.

Based on the compiled data results, it is concluded that, following initial process validation, the routine commercial manufacturing of benralizumab remained in a state of control.

6.2.1 Polysorbate 20 Trend Analysis

The trend event for PB2090W was discussed in the previous PR, REP-0203683 (the lot is included here now that the batch has been dispositioned in this period). The second OOT event was for TB3198 (0.00387%) as the result was below the lower control limit of 0.004%. A review of the electronic batch record (EBR), 8004190 Benra 30mg/mL – C-Pak to MagMixer Form for batch TB3198 did not indicate that any issues occurred during the formulation unit operation that would have contributed to the observed PS-20 result which fell below the lower control limit. Dilution of the product with Trehalose Dilution Buffer (T-DB) (PN: 8002688) was completed correctly and the correct target final weight was achieved. The successful dilution is supported by the SoloVPE result following completion of the dilution operations where a final, in-specification, result of 30mg/mL was obtained.

A review of the EBR for the subsequent unit operation, Drug Substance final filtration as per 8004191 Benra 30mg/mL – MagMixer to Allegro Filt., for batch TB3198 similarly did not indicate any issues occurred during the unit operation that would have contributed to the observed PS-20 result. The minimum target flush volume for the product filter flush was successfully achieved and the overall step yield was 97%. Additionally, the final concentration result following filtration was in specification at 29.8 g/L which indicates that no further dilution of the product occurred which could have contributed the observed lower PS-20 result. No issues, exceptions, deviations or change controls were noted by Manufacturing or QC during completion of either unit operations or testing that would have contributed to the observed result. An evaluation of assay performance and trends did not indicate any abnormalities that might explain this result.

Risk RE-002723 has been initiated due to the low process capability (Ppk<1.3) for this critical quality attribute. Evaluation of historical trends indicates that there is a consistent decrease in the measured Polysorbate 20 between formulated product and bulk filtration QC release testing. Additionally, upon testing the corresponding Drug Product sample, the PS-20 result is in-line with the formulated product sample, not the bulk filtration sample (REP-0182694: 2020-2021 Fasenra Drug Product CPV Report). Mitigation Actions MA-001421 and MA-001750 were initiated to perform further evaluation on the observed Formulation, Formulated Bulk and Drug Product PS-20 concentration differences to mitigate the lack of understanding of the root cause of observed variability. Based on the evaluations, there is no evidence to suggest that the past observed PS-20 concentration excursions are the result of any manufacturing facility, process, sampling, sample handling and/or QC related factors. The mitigation actions have been closed with no additional mitigation actions identified. Polysorbate 20 will continue to be monitored as part of the CPV program.

Batch Release Results

Batch release results for all commercial FB lots are shown graphically in the control charts included in Section 4 of REP-0239373.

The batch release test results are for all commercial FB lots manufactured are summarized in Table 16-2 of this product review.

Summary of OOS Results

OOS Results	Previous Review	Current Review
Total Number	0	0

All commercial FB batches met the product specification requirements.

Final Bulk Process Performance

There are no significant changes related to the control of FB CQAs (refer to the table below within the current period or over the previous period). Although no OOS results have been observed for Polysorbate 20, quality risk RE-002723 was initiated due to the low process capability. The remaining Ppks for the FB CQAs reflect a stable and capable manufacturing process.

Assay	Component	Ppk (2022)	Ppk (2023)
Total Protein	mg/mL	1.7	1.8
pH	pH	5.2	5.3
Osmolality	mOsmo/kg	3.2	3.3
cIEF	Percent Main Peak	1.5	1.6
cIEF	Percent Total Acidic Peaks	2.5	2.5
Reducing Gel Electrophoresis	Percent Purity	1.4	1.9
Reducing Gel Electrophoresis	Percent Total Impurities	1.6	2.3
Non-Reducing Gel Electrophoresis	Major Product Peak	2.7	3.1
Non-Reducing Gel Electrophoresis	Total Impurities	N/A [a]	N/A [a]
HPSEC	Percent Major Peak	6.2	6.0
HPSEC	Percent Aggregate	8.0	8.0
HPSEC	Percent Fragments	N/A [a]	N/A [a]
Polysorbate 20	Percent	0.9	0.5 [b]
AP-1 Reporter Gene Bioassay	Relative Potency	1.5	1.6

[a] Control limits and Ppk analysis were not determined due to the low variability and operating near the limit of quantitation of the assay.

[b] Refer to section 6.2.1 for Polysorbate 20 low process capability discussion.

Section 6.2 Conclusion

This evaluation considered registered finished product data attributes and critical in-process attributes. A disposition decision was made for all batches meeting specification to release for further manufacturing.

There were no FB batches outside of registered specification (OOS) during the review period. Although there were no OOS results for Polysorbate 20, Quality risk RE-002723 has been initiated due to the low process capability. Polysorbate 20 will continue to be monitored as part of the CPV program.

The risk-based process metrics established at the site confirm that the capability of the process for the finished product and critical in-process attributes continues to operate in line with the requirements established during either initial validation or with CPV.

Real-time trending tools were deployed to assure process capability during this time period.

Any trending signals were identified and actioned via the OOT investigations process (Section 9).

Appropriate process metrics deployed as part of CPV confirm the capability and stability of the process for the product (including critical in-process parameters/attributes) to assure the process operated under control.

6.3 Drug Product

DP trending for batches produced in the review period will be presented in the ISPR. DP release testing performed by FMC during the reporting period is discussed and data provided in this product review.

Batch Release Results

The FMC batch release test results for commercial DP batches dispositioned during this reporting period where FMC performed release testing are summarized in Table 16-3. All commercial DP batches tested at FMC for lot release met the registered specification during the review period.

Section 6.3 Conclusion

This evaluation considered registered finished product data attributes and critical in-process attributes. A disposition decision was made for all batches meeting specification to release for distribution.

No DP batch release test results executed by FMC were outside of registered specification (OOS) during the review period.

Real-time trending tools assured process capability during this time period. Any trending signals were identified and actioned via the OOT investigations process (reference Section 9 for FMC deviations). The ISPR will evaluate major trends or issues across all sites.

No FMC trends were identified during this reporting period to indicate a quality or system issue.

7 CHANGES

7.1 Changes

The changes to Manufacturing (MFG) Process, Materials, MFG Equipment, and Quality Control (QC) test methods and equipment at the FMC site are summarized below from the validated Quality Management System. Administrative changes, such as formatting and rewording instructions for clarity and changes that do not apply to Fasenra/benralizumab testing, have been omitted from the summary of changes.

Changes During the Period ☐ N/A

Change Category	ID Number	Change Description	Change Level (Low, Medium, High)	Implementation Date
MFG Processing Step	QE-017007	Benralizumab 633: Virus Filtration and Re-Filtration operations conversion from paper to electronic batch record	Medium	16Nov2022
MFG Processing Step	QE-023496	Remediation of KTM Shipping Process	Medium	16Nov2022
MFG Processing Step	QE-013017	Storage of FMC Manufacturing Supplies at AZ Newark (QIMS #258922)	Low	17Nov2022
MFG Processing Step	QE-015521	New Product Introduction (NPI) of AZD7789 to Frederick Manufacturing Center	Medium	18Nov2022
Method	QE-013559	Update Polysorbate SOPs to clarify/ add DCM/IS Injection system suitability criteria. - (QIMS #255354)	Low	29Nov2022

Change Category	ID Number	Change Description	Change Level (Low, Medium, High)	Implementation Date
Material (starting material/ excipient/ packaging/ API)	QE-014531	Sartorius Implementation of Tuflux TPE	Medium	30Nov2022
QC Equipment	QE-013584	Implementation of new Osmotech Pro Multi-Sample Micro-Osmometer (OSM-500015) in Quality Control lab (4L02) - (QIMS #258006)	Medium	30Nov2022
Method	QE-018322	Removal of pH adjustment for routine bioburden testing of Benralizumab Protein A in-process samples.	Medium	06Dec2022
Material (starting material / excipient / packaging / API)	QE-012744	Implement Puritan Sodium Hydroxide 10N, 4L as a new ERP part number	Low	07Dec2022
MFG Processing Step	QE-013573	Seed and Prod Bioreactor PAS|X updates to provide cell culture sampling result summary function for data visualization - (QIMS #256887)	Medium	12Dec2022
MFG Processing Step	QE-013249	UPSTREAM - Creation and revision of GMBRs for 2022 Tech Transfers (INOCGEN, SDBRXINT, PBRXHINT, EOPCB) - (QIMS #254345)	Medium	13Dec2022

Change Category	ID Number	Change Description	Change Level (Low, Medium, High)	Implementation Date
MFG Processing Step	QE-016283	Benralizumab 633: Q4 2022 Campaign Re-Introduction Downstream/Buffer Operational Updates	Medium	13Dec2022
Material (starting material / excipient / packaging / API)	QE-013585	Implement alternate Silicone tubing on Sartorius single use assemblies - (QIMS #258110)	Medium	14Dec2022
Method	QE-013266	Fasenra APFS - combine break loose/glide force and deliverable volume methods - (QIMS #258443)	Medium	19Dec2022
Material (starting material / excipient / packaging / API)	QE-013301	Add Avantor Aurora OH as additional qualified source for Sodium Chloride SAP PN 4101063 - FMC Assessment of SIC235602 (QIMS #235607)	Low	27Dec2022
MFG Processing Step	QE-013254	DOWNSTREAM PT1 Revision of GMBRs for 2022 Tech Transfers (PACKGEN1 UNPKGEN1 PROMATE CHRMMATE VFINT UFINSTAL UFUNINST) - (QIMS #256297)	Medium	02Jan2023
MFG Processing Step	QE-012600	New Product Introduction (NPI) of AZD2936 to Frederick Manufacturing Center	Medium	06Jan2023
MFG Processing Step	QE-023673	Benra B636 Q4 Operational Readiness	Medium	10Jan2023

Change Category	ID Number	Change Description	Change Level (Low, Medium, High)	Implementation Date
MFG Processing Step	QE-013258	DOWNSTREAM PT2 Revision of GMBRs for 2022 Tech Transfers (UFDFGEN1, FRMGEN1, FLTGEN1) - (QIMS #256775)	Medium	18Jan2023
MFG Processing Step	QE-001042	Configure Limited review reporting in PASX	Low	20Jan2023
MFG Processing Step	QE-017780	Implementation of PASX w/ B636 DeltaV PCS – Rockers	Medium	24Jan2023
Material (starting material / excipient / packaging / API)	QE-034708	Alternate Carboy for Benra Unpacks	Low	27Jan2023
MFG Processing Step	QE-012931	Implementation of HTST for Durvalumab and Benralizumab in B633 (QIMS #218242)	Low	02Feb2023
MFG Processing Step	QE-012461	Implementation of HTST for Benralizumab B633 Media and Feed Preparations	Medium	02Feb2023
MFG Processing Step	QE-018735	Benralizumab B636 - 2022 Q4 Campaign Readiness	Low	01Mar2023
Material (starting material / excipient / packaging / API)	QE-023989	NMI-7693 L-Glutamine from Ajinomoto	Low	09Mar2023

Change Category	ID Number	Change Description	Change Level (Low, Medium, High)	Implementation Date
Method	QE-013568	Instron Software Upgrade for FMC QC Analytical - (QIMS #255808)	Medium	10Mar2023
MFG Processing Step	QE-040873	Restrict Benralizumab Final Bulk Batch PN2012 to Commercial US and Japan markets only	Low	18Apr2023
MFG Processing Step	QE-013561	B633 1.8m Axichrom Chromatography Column Cleaning Validation - (QIMS #255379)	Medium	20Apr2023
QC Equipment	QE-011418	Replacement of YSI 2700 SELECT with YSI 2900D at the Frederick Manufacturing Center (FMC), B633	Medium	09May2023
Material (starting material / excipient / packaging / API)	QE-042911	SAP PN 6002233 drawing format and version change	Low	17May2023
MFG Processing Step	QE-001357	Q4 2021: Internal Seed GMBR Revision	Medium	05Jun2023
Material (starting material / excipient / packaging / API)	QE-045729	Remove JP Specific Gravity test from Benzyl Alcohol, USP, EP, JP SPEC-0064416	Low	09Jun2023
Method	QE-018341	FMC: Pharmacopoeial change--update and PDG harmonization of USP <621> and Ph.Eur. 2.2.46 chromatography chapters	Low	21Jun2023

Change Category	ID Number	Change Description	Change Level (Low, Medium, High)	Implementation Date
MFG Processing Step	QE-036511	Extension of Column Packing Buffers 8005800, 8005788, 8010540, and 8005786 hold time expiry to 30 Days	Medium	26Jun2023
Method	QE-039071	Bioburden validation samples removal from Benra 20mg/mL and Benra 100mg/mL B633 QCTPs	Medium	03Jul2023
MFG Equipment	QE-056754	Addition of pressure gauge to 2,500L bioreactors at FMC B633	Medium	28Jul2023
Material (starting material / excipient / packaging / API)	QE-005135	Update Endotoxin & Bioburden spec for Excell 302 Media SAP PNs 4101645 and 6002426	High	01Aug2023
Material (starting material / excipient / packaging / API)	QE-013015	Revise the bioburden specification for MabSelect SuRE resin in ethanol RWMT000230, and in benzyl alcohol RWMT001357 (QIMS #257918)	Low	04Aug2023
Material (starting material / excipient / packaging / API)	QE-042006	Adding Biospectra, Bangor, PA (pack sizes 942.5L and 4L) as a second supplier for Sodium Hydroxide 10N	Low	08Aug2023
Method	QE-038580	Update Bioburden SOPs to Align with USP 61 and Nomenclature Change with P. acnes	Medium	24Aug2023

Change Category	ID Number	Change Description	Change Level (Low, Medium, High)	Implementation Date
Method	QE-051287	Revision of QC Micro SOPs to Include Use of Sterile Bags During Incubation and Guidance on Oasis Media Cassette Lid Closure for CAPA-006390	Low	24Aug2023
Method	QE-058056	Implementation of the Dual-Chamber Method for Anaerobic Incubation at FMC	Medium	26Aug2023
Material (starting material / excipient / packaging / API)	QE-060976	Create a new Part Number for Thermo acquired 500L bag with C-flex (4102704) as per SPEC-0064797	Low	15Sep2023
MFG Processing Step	QE-075808	B636 Sparge Algorithm Correction	Low	15Sep2023
MFG Processing Step	QE-015606	Master/Working Cell Bank Global Part Number Implementation	Medium	18Sep2023
MFG Processing Step	QE-018480	Update Benra B633 VMP for FB20 and FB100	Medium	25Sep2023
MFG Processing Step	QE-017612	Benralizumab 633: Q4 2022 Re-Introduction Viral Filtration GMBR (VFINT) Revision(s)	Medium	09Oct2023
Material (starting material / excipient / packaging / API)	QE-040152	Drawing format change for SAP PN 6001955 (200L durvalumab BDS bag), removal of Kleenpak protective bag check in SOPs	Medium	11Oct2023

Change Category	ID Number	Change Description	Change Level (Low, Medium, High)	Implementation Date
Material (starting material / excipient / packaging / API)	QE-050281	Add Sanisure as a second source for Bottle Manifolds for 125ml, 500ml and 2000mL	Medium	02Nov2023

7.2 Changes – Specifications

Changes to the global specifications are listed below. QE-017634 was implemented to mitigate future lack of vendor support for the Gyrolab® instrument required to perform current Drug Substance lot release testing by SOP QC-040639, Host Cell Protein by Gyrolab®. The current approved global acceptance criteria, ≤ 50 ng/mg protein, did not change. QE-013233 introduced a new method that combined the current beak loose/glide force and deliverable volume methods into one method reducing the number of required samples. QE-037616 was implemented to provide clarification to QE-017634 after its closure.

Specification Number	ID Number	Change Description	Level of Change (Low, Medium, High)	Implementation Date
SPEC-0123447	QE-017634	Add new ELISA test method to measure residual CHO Host Cell Proteins in benralizumab DS to benralizumab DS specification SPEC-0123447 (0409M)	High	14Dec2022
SPEC-0123449	QE-013233	Revise MS SPEC-0123449 to implement Fasenra APFS - combined break loose/glide force and deliverable volume method at SBC and FMC	Low	19Dec2022

Specification Number	ID Number	Change Description	Level of Change (Low, Medium, High)	Implementation Date
SPEC-0123447	QE-037616	Update benralizumab DS SPEC-0123447 to differentiate the Host Cell Protein test method performed using the Gyros versus a 96-Well Plate ELISA	Low	16Mar2023

7.3 Marketing Authorization Variations

This section is not applicable as an ISPR will be issued for this product and reporting period.

7.4 Post-marketing Commitments

This section is not applicable as an ISPR will be issued for this product and reporting period.

Section 7 Conclusion

A total of two (2) high-level and thirty-one (31) medium-level changes were raised, risk assessed, and managed by the site during the period of this review. In addition, there were twenty (20) low-level changes raised for manufacturing process or analytical methods that were risk assessed and managed by the site during this review period. All changes were managed in accordance with site change control procedures. Each record is individually reviewed by the impacted departments and assessed for the impact to product quality.

This level represents an increase in the number of changes compared with the previous review. This increase is not considered significantly different from previous years and is in line with expected rate of change at the site, considering process improvements implemented across the manufacturing process and for second sourcing efforts.

The impacts of these changes on the product were assessed through evaluation of compliance to registered specification and no adverse effects were observed.

The accumulation of minor/incremental changes has also been considered, and there is no additional action needed.

The regulatory compliance status for the product has been maintained through management of these changes. There was no indication of negative impact to product consistency, product quality, or the validated state of the manufacturing process as a result of the changes reviewed. Also, there was no cumulative impact of the changes to GMP and/or license requirements.

The number of changes impacting on the site is assessed during the site Management Review process, which assures that the capacity of the site to respond effectively to change is actively managed.

8 STABILITY DATA

The Fasenra/benralizumab stability program is consistent with ICH guidelines (including Q1A and Q5C) and other applicable regulatory expectations. The completed stability studies of DS, FB, and DP continue to support the shelf life claims in all current licenses. Refer to REP-0402687, *FASENRA (Benralizumab) Product Quality Review (PQR) Annual Stability Report for 2023* for a comprehensive analysis of Fasenra/benralizumab stability studies for DS, FB, and DP. This report includes a listing of all studies, their purpose and status, and graphical analyses of data.

All stability data at the recommended conditions within the scope of this report met the applicable specifications. For the recommended condition, statistical analysis identified no confirmed OOT events for DS, FB, or DP during the reporting period.

Deviations (related to stability)

Deviations related to stability during the reporting period are discussed in Section 3 of stability summary report REP-0402687. No deviations that occurred during the reporting period had an impact on product quality or the stability studies.

OOS and OOT Events (related to stability)

There were no out of specification (OOS) events within the reporting period for stability results. Statistical analysis identified no OOT events for the recommended condition for DS, FB, or DP during the reporting period.

9 QUALITY EVENTS

Quality Events	Previous Review	Current Review
Total Number	5	17
Number of Critical Reports	0	0
Number of Repeat Critical Reports	0	0
Number of Major Reports	5	17

The table below provides the total number of significant (major and/or critical) quality events (deviations, laboratory investigations), and a summary of each of those records, as applicable from the validated Quality Management System. All quality event records in this section are closed.

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
262847 (Deviation)	005H19 006H19	On 19Aug22, a Quality Control Laboratory Management Services (QCLMS) Sample Coordinator discovered a discrepancy in inventory counts for Benralizumab lots 005H19 (Process Performance Qualification (PPQ)) and 006H19 (PPQ) in 2-8C walk in cold room CR-S101A in S112 while preparing to pull for the 36 month stability time points. The count in GQCLIMS for lot 005H19 was recorded as 324 Pre-Filled Syringe Sub-Assembly (PFS-SA) Syringes, however the physical count was 301 PFS-SA syringes. The count in GQCLIMS for lot 006H19 in GQCLIMS was recorded as 278 PFS-SA syringes, however the physical count was 301 PFS-SA syringes. The event was a deviation due to the discrepancy in the counts. a Based on initial findings, there was a potential for the incorrect lot (005H19) having been pulled and tested for two additional stability CCI sample pulls during the 24 month time point for lot 006H19 and reported. Additionally, per SOP-0067829, Version 27.0, Executing Stability Studies section 4.13.4 states "Perform physical count/reconciliation of samples after each pull based on inventory off GQCLIMS stability report." Lot 006H19 and 0005H19 are both maintained by the same stability protocol SP-01300 version 2.0: *Stability Study Protocol for Benralizumab Drug Product 30 mg Injection in Support of the 2k Drug Substance Process Performance Qualificatio*n. The root cause was identified as a procedural gap where the process for additional stability pulls was not clearly defined and did not require a verification similar to the initial sample pull. There is no impact to product quality or risk to patient safety as a result of this event. The 12 month and 36 month stability timepoint CCI testing for lot 006H19 met all acceptance criteria.	Method > Procedure > No procedure/or gap in procedure	No Impact	263538

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-074762 (Lab Investigation)	LJ2067	On 15Aug23, a QC Supervisor discovered during review that benralizumab stability drug substance sample 3886388 (-40C, 48m, lot LJ2067) had an unexpected result for reduced capillary electrophoresis testing. All anomalous peaks were not present in the reference standard. There were also several smaller peaks in the sample that were not observed in the reference standard. The %purity (area purity of heavy and light chain peaks) for this sample was 95.808% and the total %impurities was 4.192%, which is within the product specification (percent purity ≥ 95.3% and percent impurities ≤ 4.7%. Results are within the specification. The root cause is identified as Method > Process > Process Design Input/Output Needs Improvement. Hypothesis testing confirms that the extra peaks observed in the original testing of sample 3886388 were due to sample preparation or lab equipment contaminant and were not true impurity peaks. The fact that the extra peaks profile was not seen in the orthogonal method Bioanalyzer further supports this profile being a sample preparation or lab equipment contaminant induced artifact. A 1X retest was performed and results were within the specification. The original reduced CE-SDS result was invalidated and the 1X retest result was authorized in GQCLIMS. Therefore, there is no product, process, or patient impact because of this event.	Root Cause: Material > Supplier / External Material Control > Material Atypical	No Impact	No CAPA required

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-039408 (Lab Investigation)	PT3323	On 09Feb23 a QC Microbiology analyst performing plate enumeration of the TSA plate in QC laboratory 4L34 for sample ID 3741913 (Process code (8007409-030, Lot PT3323) observed the aerobic count result of 2 CFU/10mL. Process code 8007409-030 sample description is Benralizumab: UF/DF Product - Pre-Filter (Post Recovery). Bioburden testing was performed on 05Feb23 for this product per procedure SOP-0106897: Bioburden Testing, v 60.0. The sample was tested in Quality Control (QC) Biological safety cabinet BSC) BSC-540106 in lab 4L34. Raw data Logbook reference L-009872 pg. 159-160 Run # BIOB_F-2023FEB05-001. The lab investigation was initiated upon completion of SDA plate incubation and disposition of final result to begin remediation/investigation activities. Per SPEC-0064990 (AzDoc0106104): Benralizumab, FMC Building 636, Quality Control Testing Plan: Purification, v 7.0 the alert limit for this step is ≤ 0 CFU/10mL and the action limit is ≤ 10 CFU/10mL. The reported result of 2 CFU/10mL exceeded the alert limit. There is no impact to product quality or risk to patient safety as a result of the bioburden alert limit result. While the sample result indicated the presence of bioburden, the investigation determined the microorganism was most likely introduced during QC testing and was not intrinsic to the product or manufacturing process. There were no issues such as leaks reported during manufacturing operations.	Method > Process > Errors Not Detectable / Recoverable	No Impact	No CAPA required

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-030446 (Deviation)	PN2272	QE-030446 was initiated to investigate a trend related to the dehydration of bioburden media plates (or cassette plates). Between the dates of 18Nov22 and 30Mar23, the Quality Control (QC) Microbiology has invalidated several bioburden results due to dehydrated media being observed upon completion of the incubation period. The dehydrated media plates have been observed across different media and sample types. All impacted media was supplied by Millipore Sigma. The root cause as per the vendor investigation, is the design of the filtration unit lid which was updated to include four (4) vents. This change in design was done in order to optimize incubation performance and allow for gas exchange during the incubation period. However, the four vents on the lid are causing air to be introduced to the media plates and become dehydrated during the incubation period. A review of the bioburden and endotoxin data was performed for sample points immediately upstream and downstream of the invalidated sample points. Overall, there is sufficient data to demonstrate microbial control of the manufacturing process for each of the impacted batches. The final Drug Substance sample for each of the impacted batches was within the specifications for bioburden and endotoxin testing. There is no impact to product quality or patient safety as a result of this event.	Root Cause: Method > Process > Process Design Input / Output Needs Improvement	No Impact	CAPA-006390

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-028045 (Deviation)	PN2272	On 29Nov22 in building 633 room 4P16, operators discovered the 100L bioreactor BRX-1009 agitator was not running and the agitator motor switch was in the “off” position. BRX-1009 was on Day 3 post-inoculation. The intended state of the system during CIP and production was for the agitator to actively run at the specified setpoint (SP). There was no impact to product quality or patient safety due to this event. There was impact to the cell culture process, however, once the agitation was restored the cell culture did recover and no impact was observed to cell culture performance. There was no license impact resulting from this event. The root cause of this event was lack of detectibility to the the incorrect motor switch position following maintenance, during return to service, and during subsequent process use. CAPA records were generated to create new alarms within automation systems to detect/notify in the event agitator motor switches are in the “off” position.	Equipment > Equipment Design > Errors Not Detectable / Recoverable	No Impact	CAPA-004409 CAPA-004410 CAPA-004412 CAPA-004413

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-054944 (Deviation)	PN2232, PN2271, PN2272, PT3323, PT3520, TA2010, TA2159, TA2351, TA2831, TA2833, TB2315, TB3196, TB3197, TB3198	On 04May2023, after a meeting between Issue Management Team Members and Frederick Manufacturing Center (FMC) site QA representatives, it was determined that a deviation was required to document the fact that FMC has been manufacturing medicines using Chemically Defined Lipid Concentrate (CDLC) raw material that does not include a Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines & HealthCare (EDQM) for the cholesterol component. The relevant regulatory filings for Anifrolumab, Benralizumab, Durvalumab, Inebilizumab, Palivizumab, and Tralokinumab indicate that this material has a CEP when used in manufacturing of products at FMC. This issue was discovered after reviewing the regulatory impact assessments of change control QE-014459, the local change control initiated to collect the impact assessments for two different changes in the source of cholesterol used in CDLC that were originally communicated under TrackWise QIMS Change Source record 238600 and EQV Global Change Control QE-011860. In scope for manufacturing not in compliance with regulatory filings are batches of Anifrolumab and Benralizumab manufactured since approximately October 2021, as these are the only products that FMC has produced since the switch to the affected CDLC lots.	Method > Documents > Inadequate Procedures / Instructions	No Impact	CAPA-008066

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-032042 (Lab Investigation)	PN2271	On 17Dec22, Conditioned Medium Prior to Final Protein A Cycle, sample ID 3682720 (Process code 8006141-090, Lot PN2271) was collected from harvest tank TK-1116 and submitted to QC for bioburden testing. On 18Dec22, QC placed the sample on test per SOP-0106897, version 60.0. The final total result was reported as 71 CFU/10mL, which exceeded the bioburden alert limit of ≤10 CFU/10mL per SPEC-0124424. . There was no impact to product quality or patient safety due to this event. There was no license impact resulting from this event. The most likely root cause of this event is attributed to a Conditioned Medium sample that was not representative due to a sampling/handling error.	Work Management > Skills & Knowledge > Knowledge-based decision required	No Impact	CAPA-006079 CAPA-006080 CAPA-006081 CAPA-006082 CAPA-006083

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-032373 QE-032472 (Lab Investigations)	PN2272	On 26Dec2022 and 28Dec2022, QC Microbiology reported two bioburden alert level excursions for Benralizumab Protein A process, batch PN2272. The excursions occurred at different steps within the same batch which were initiated under two separate EQV lab investigation records: •QE-032373, 8006152-010 “Protein A Cycle 1 Column Equilibration Effluent”, 19 CFU/10mL •QE-032472, 8006152-060 “Protein A Post-sanitization WFI Flush (final cycle)”, 61 CFU/10mL The samples were collected by manufacturing from the packed Benralizumab Protein A column CL-116816. There was no impact to product quality or patient safety due to this event. There was no license impact resulting from this event. The most likely root cause was attributed to bioburden introduction during column packing batch JF2233 in 2017. There was likely microorganism carry over to the 2022 Benralizumab Protein A column packing operations batch PN2272 as the same resin from 2017 pack was used. No additional alert excursions were reported. CAPA-004983 was created to perform the column and resin remediation of the Benralizumab Protein A column CL-116816 associated with the events. CAPA-005093 was created to identify resin at FMC that meets the remediation criteria as outlined per GUID-0020031.	Method > Process > Process Design Input / Output Needs Improvement	No Impact	CAPA-004983 CAPA-005093

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-039406 (Deviation)	PT3520	On 10Feb23 in Formulation Suite P140, while executing Ultrafiltration / Diafiltration (UFDF) process per MABR-0009612 BN:PT3520 "636 Benralizumab Concentration/Diafiltration (8007409)" v4.0, operators observed Low Cross feed flow flux and High Transmembrane Pressure alarms; while performing corrections and resuming the process, a leak was observed. There was no impact to product quality or patient safety due to this event. There was no license impact resulting from this event. The root cause of the alarm events was attributed failing to visually inspect and identify a damaged component per SOP-0067957 v15.0 “Setup & Breakdown of Pall Allegro UF/DF System at FMC B636 “. The root cause of the leak was attributed to a material defect at the KPC-2 single-use connector o-ring.	Work Management > Skills & Knowledge > Post Training Knowledge Proficiency Material > Supplier / External Material Control > Material Atypical	No Impact	CAPA-006141

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-040885 (Deviation)	N/A	This trend deviation was initiated on 20Feb2023 per SOP-0067360 for nine minor and one major deviation associated with leaks at KleenPak™ II Sterile Connectors (KPC2) from a period of 02Jun2022 to 10Feb2023. There was no product impact or risk to patient safety due to this event. There was no license impact from this event. The investigation identified the following root causes: • Operator execution variability - The design of the KPC2 requires operators to manually pull the foil tabs from both the male and female connections in a perpendicular fashion. There is task execution variability in the way an operator pulls the tabs and tears can happen in several ways. • Supplier quality variability - Variability in the strength of the foil welds may affect the amount of force required from operators to remove the foil tabs resulting in tears. As long-term degradation can occur following gamma radiation, the radiation and age of the component can operate in conjunction to result in weakened welds and torn foil. • Inadequate procedure - Visuals within the site SOP do not align with the vendors instructions. There are additional visuals and instructions provided in the instruction packet that ships with the KPC2s which are not in the SOP instructions.	Work Management > Skills & Knowledge > Post Training Knowledge Proficiency Equipment > Equipment Performance > Instrument Drift Method > Documents > Inadequate Procedures / Instructions	No Impact	CAPA-009283

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-042077 (Deviation)	TA2351 TA2831 TA2833	This trend deviation was initiated for OOR neutralized pool conductivity values during the benralizumab Q1 2023 campaign. While performing product closeout step of building 636 benralizumab neutralized low pH treated product (Virus Inactivation) Part Number: 8007405 for the following batches in Purification (Room: P180), operators received an out-of-range (OOR) value for the neutralized low pH treated product (neutralized pool) conductivity value: •TA2351; Conductivity Value: 9.1 mS/cm •TA2831; Conductivity Value: 9.1 mS/cm •TA2833; Conductivity Value: 9.5 mS/cm The attained conductivity values exceeded MABR-0009616 NOR specification of 5.0 – 9.0 mS/cm. In addition to the above batches, Neutralized pool conductivity NOR excursions are documented in minor deviations QE-037658 on 02FEB23, QE-039447 on 12FEB23, and QE-040679 on 18FEB23. QA & manufacturing management assessed this deviation to be a trend per SOP-0107503 "7-P38 Deviation Management". Conductivity measured outside the NOR specification for 6 out of 7 production batches of B636 benralizumab Q1 2023 campaign. There was no impact to product quality or patient safety due to this event. Each batch met passing disposition criteria. There was no license impact resulting from this event. The root cause of this event was attributed to the neutralized pool conductivity NOR not being representative of the process at the 2000L scale due to inherent process differences from the 15000L scale.	Method > Process > Process Design Input / Output Needs Improvement	No Impact	CAPA-006729

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-043405 (Deviation)	TA2832	On 06Mar23, Bldg 636 in cell culture, a LoLo alarm was triggered for dissolved oxygen (DO) control on the production bioreactor BRX-6151 which was batched with Benra (PN 8007258), BN: TA2832. Microscopic examination confirmed a contamination; the organism was identified as Bacillus toyonensis. There was product impact, but no risk to patient safety due to this event; the batch was terminated and all cell culture material discarded. There was no license impact resulting from this event. Although no definitive root cause was discovered, several potential contributing factors were identified, including a non-integral media transfer line, excess liquid holdup in CIP/SIP header, and recovery of isolate from environment.	Equipment > Equipment Maintenance Program Equipment > Equipment Performance Environment > Internal Environmental Conditions	Fully Impacted	CAPA-009424 CAPA-009425 CAPA-009426
QE-055982 (Deviation)	PT3520 TA2351 TA2831 TA2833	On 07MAY23, while performing an 18-month Preventative Maintenance (PM) on BRX-613101, in Cell Culture (Room: P110 of Building 636), per SAP work order (WO) 51475552, a Facilities Process Technician identified the two (2) non-identical spray balls in the vessel were installed in the incorrect locations. There was no impact to product quality or risk to patient safety from this event. It was determined any residual protein would be below the detection limit and far below the lowest dose of product. Steam exposure further reduces the risk. All product batches impacted were forward processed without issue. There was no license impact resulting from this event. The root cause of this event was a technician error that occurred during a process that relies on human performance and has limited controls to ensure proper execution.	Environment > Internal Environmental Conditions > People	No Impact	CAPA-007680 CAPA-007681

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-069966 (Deviation)	PT3520 TA2159 TA2831	On 11Jul23 level transmitter LIT-6191-109 on Harvest Tank TK-619101 was found Out of Process Tolerance during a scheduled calibration by I&C Technician. The level was found with the following deviations: -23.4 liters at the 250-liter nominal set point; -15.2 liters at the 2500-liter nominal set point. The approved process tolerance in the PROCAL (calibration database) system for this level transmitter is ±14 liters. LIT-6191-109 was taken out of service. There was no product impact or risk to patient safety due to this event. There was no license impact from this event. The root cause of this event is a damaged antenna within the level transmitter most probably caused due to non-integral O-rings which allowed steam into the antenna housing.	Equipment > Equipment Performance > Part Failure	No Impact	CAPA-012017

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-020893 (Deviation)	N/A	On 17Oct22 it was identified by manufacturing personnel that a method 2 cleaning using 1% SporKlenz was not performed after dispensing of Chemically Defined Lipid Concentrate (CDLC) (PN 4102100) during a raw material weigh out. As CDLC is an animal derived raw material, a method 2 cleaning using SporKlenz should have been performed after dispensing. The immediate correction updated Symphony for all future animal derived raw material weigh outs to include a visual indicator on the scheduled operation to alert operators to request a method 2 cleaning of the area. There was no impact to product or patient safety, validation, cGMP, regulatory/license or compliance drift as a result of this event. In-process testing and manufacturing controls were in place during the effected period. Therewas impact to process as the cleaning agent that is to be use for Method 2 cleanings after animal derived raw material weigh outs is not clear. The root cause of the eventwas Method -> Documents -> Inadequate Procedures/Instructions. Procedural gaps in SOP-0067369 and0067369 and SOP-0106918 were identified for Method 2 cleanings after animal derived raw material weigh outs.	Method > Documents > Inadequate Procedures / Instructions	No Impact	CAPA-005312 CAPA-005313 CAPA-005314 CAPA-005315

Record ID	Batch	Event Description	Cause (Root / Contributing)	Impact (product / regulatory)	CAPA Record ID
QE-023505 (Deviation)	N/A	During a Protein A ELISA run performed on 21Oct22 it was determined by the analyst that the SoftMax template used for the run was not validated. Upon further investigation it was discovered that calculations for results and system suitability generated previous on un-validated SoftMax templates were not manually verified by the analysts and reviewers. This event was a deviation as SoftMax templates were not introduced to the site per SOP-0067823 (Introduction or Modification of Equipment and Computerized Systems at FMC) to determine whether validation was/was not required, and the templates were used for testing and GxP decisions. Verification activities confirmed here was no impact to product quality or patient safety because of this event.	Method > Documents > Inadequate Procedures / Instructions	No Impact	CAPA-005815 CAPA-005816 CAPA-005817 CAPA-006391 CAPA-006398

Comment on any trend within the review period and from previous review period.

There were zero (0) critical and seventeen (17) major quality events for the review period. Sixteen (16) major events were determined to have no product impact, one (1) major event had product impact resulting in discard during processing and zero (0) major events were determined to have license impact. Zero (0) major events were determined to be repeat events, which supports the effectiveness of corrections and preventative actions implemented during the deviation investigation and/or CAPAs. There were no trends identified among the major events.

No minor events were determined to have license impact.

Corrective and Preventive Actions Taken for Major and Critical Quality Events

There were zero (0) critical events for the review period.

The seventeen (17) major events generated thirty-two (32) CAPAs. Thirty (30) of the CAPAs are closed, including CAPA-009424 which closed outside the reporting period on 20Dec2023 and is reported in this PR, and two (2) remain in-progress. CAPA-009425 is due 17Apr2024 and CAPA-012017 is due 08Mar2024. There were no in-progress CAPAs from the previous review period that remain open or have closed in this review period.

Record ID	Description	Parent Record ID	Status
263538	Correct documents for CCI result for Benra lot 006H19 at the 24 month time point per stability protocol SP-01300/REP-0102523	262847	Closed
CAPA-006390	Revision of QC Micro SOPs to Include Sterile Bags During Incubation and Update Lid Instructions in Applicable QC Microbiology SOPs	QE-030446	Closed
CAPA-004409	Agitator check step on RTS form	QE-028045	Closed
CAPA-004410	Agitator check step post-media addition on SOP-0106443 Bioreactor Operations Procedure, FMC B633	QE-028045	Closed
CAPA-004412	633 CAPA Enable VFD Capability to Detect Loss in Agitator Functionality	QE-028045	Closed

Record ID	Description	Parent Record ID	Status
CAPA-004413	636 CAPA Enable VFD Capability to Detect Loss in Agitator Functionality	QE-028045	Closed
CAPA-004983	Benra Pro A empty Column CL-116816 and Resin Remediation	QE-032373	Closed
CAPA-005093	Identify & Remediate Resin at FMC that Meets the Bioburden Remediation Criteria per AZDoc0199403 stored at FMC	QE-032373	Closed
CAPA-006079	B633 Upstream, revise SOP-0068243, create system to inspect crimping tool/replace blades	QE-032042	Closed
CAPA-006080	B633 Buffer hold, create system to inspect crimping tool/replace blades	QE-032042	Closed
CAPA-006081	B633 Downstream, revise SOP-0106932, create system to inspect crimping tool/replace blades	QE-032042	Closed
CAPA-006082	B636 Upstream, revise SOP-0069244, create system to inspect crimping tool/replace blades	QE-032042	Closed
CAPA-006083	Refresher training -address the sampling order stated in SOP-0068243 and good sampling practices	QE-032042	Closed
CAPA-006141	Update SOP-0067957 v15.0 “Setup & Breakdown of Pall Allegro UF/DF System at FMC B636”	QE-039406	Closed
CAPA-006729	Initiate Change Control to Update PN: 8007405 Neutralized Pool Conductivity NOR	QE-042077	Closed
CAPA-007680	Update checklists that require spray ball inspection.	QE-055982	Closed
CAPA-007681	Create and deliver an on-the-job training about spray ball installation.	QE-055982	Closed
CAPA-008066	Update GUID-0020022 to increase robustness for regulatory assessment of animal-derived raw materials and excipients	QE-054944	Closed
CAPA-009283	Revise SOP-0068200 (v10.0) Sterile Connect and Sterile Disconnect at the Frederick Manufacturing Center (FMC) Site	QE-040885	Closed

Record ID	Description	Parent Record ID	Status
CAPA-009424	Install Valve Stands under HV-615X-015 for All Production Bioreactors in Building 636	QE-043405	Closed
CAPA-009425	Close HV-615X-307 during Centrifuge CIP	QE-043405	In-Progress
CAPA-009426	Install Vent Line in Tech Core Space and Connect to CG-6182 Floor Drain in P110	QE-043405	Closed
CAPA-012017	Create an SOP for the Guided Wave Transmitters	QE-069966	In-Progress
CAPA-005815	Perform Validation of the Identified Un-validated SoftMax Pro Templates	QE-023505	Closed
CAPA-005816	New NIA will be created specifically for SoftMax Pro template	QE-023505	Closed
CAPA-005817	Implement engineering control to ensure no un-validated templates available in the QC folders in SoftMax Pro 7.1.1	QE-023505	Closed
CAPA-006391	Update SoftMax Pro 7.1 Role Permission	QE-023505	Closed
CAPA-006398	Correct the "IL-13 Dose Response Template"	QE-023505	Closed
CAPA-005312	Create risk in GPQS: Method 2 SporKlenz cleaning is not performed after use/sampling of animal derived RMs	QE-020893	Closed
CAPA-005313	Create Global Hazard Statements for all animal derived raw materials to indicate that a method 2 cleaning/wipe down is required after weigh out	QE-020893	Closed
CAPA-005314	Update SOP-0067369	QE-020893	Closed
CAPA-005315	Update SOP-0106918	QE-020893	Closed

Effectiveness of Corrective and Preventive Actions Taken for Major and Critical Quality Events

Twelve (12) CAPAs generated during this reporting period required effectiveness checks, of which nine (9) remain in-progress. Effectiveness checks 260399, 262145, and 263539 were generated in the previous reporting period and 260399 and 262145 closed during this reporting period. Effectiveness check 263539 closed outside the reporting period on 06Dec2023 and is being reported in this PR.

Record ID	Description	Parent Record ID	Status
260399	Effectiveness of CAPA 260397 to replace aged bioassay multichannel pipettes	260397	Closed
QE-054820 (previously 261974)	Effectiveness check for CAPA 263538	263538	Closed
262145	Ensure EndoScan-V version update is effective for preventing file corruption	261587	Closed
EFF-005460 (previously 263539)	QIMS 263539 E-Check for SOP-0067829 updated under CAPA 262740 per Deviation 262847. SOP-0067829 was updated with instructions to require secondary analyst verifications at the time of additional pulls for the stability samples. Successful e-check will include 100% of verified additional stability pulls (minimum 3 pulls) with no discrepancy between the physical count and the count documented in GQCLIMS.	262740	Closed
EFF-005058	After implementation of the CAPA-006390, dehydrated plate deviations will be evaluated after 6 months. Successful e-check will include no more than 2% of total plates used over the next 6 months are identified as dehydrated after the CAPA has been implemented.	QE-030446	Work in Progress (Due 24Apr24)
EFF-006439	After implementation of the CAPA-006390, dehydrated plate deviations will be evaluated after 3 months (interim check). Successful e-check will include no more than 0.3% of total plates used over the next 3 months are identified as dehydrated after the CAPA has been implemented.	QE-030446	Work in Progress (Due 30Dec23)
EFF-004823	E-check to – CAPA-006079, CAPA-006080, CAPA-006081, CAPA-006082, CAPA-006083.	QE-032042	Work in Progress (Due 22Mar2024)
EFF-004864	Effectiveness Check for CAPA-006141	QE-039406	Work in Progress (Due 31Jan2024)

Record ID	Description	Parent Record ID	Status
EFF-005699	CAPA- 007680 and CAPA-007681 Effectiveness Check – Spray ball inspection	QE-055982	Work in Progress (Due 22May2024)
EFF-006505	Effectiveness Check for CAPA-009283	QE-040885	Work in Progress (Due 12Jul2024)
EFF-006598	Effectiveness Check for CAPA-009424 to Install Valve Stands under HV-615X-015	QE-043405	Work in Progress (Due 28Feb2024)
EFF-006599	Effectiveness Check for CAPA-009426 to connect a vent to the Centrifuge Floor Drain in P110	QE-043405	Work in Progress (Due 17Apr2024)
EFF-005059	E-Check for CAPA-005817	QE-023505	Work in Progress (Due 05Apr2024)
EFF-004446	Evaluate effectiveness of addition of GHS to animal derived RMs in PAS|X and updates to SOP-0067369	QE-020893	Closed
EFF-004447	Evaluate effectiveness of updates to SOP-0106918	QE-020893	Closed

Effectiveness checks EFF-004446 and EFF-004447 were both generated under CAPAs from Deviation QE-020893. Both of these effectiveness checks failed because the required cleaning agent was not used.

In the effectiveness check assessments, it was identified that all requests for cleanings post dispensing animal derived materials from March 2023-September 2023 were completed but the required cleaning agent was not used (EFF-004446) or did not include enough details to support use of the required cleaning agent (EFF-004447). Deviation QE-071235 “GMP cleanings after animal derived raw material weigh-outs not executed per SOP-0106918 v32” was initiated to investigate the missed cleanings and ineffective CAPAs. The investigation generated five (5) CAPA’s, all of which are closed, and two (2) effectiveness checks, which are in-progress.

Section 9 Conclusion

There were zero (0) critical and seventeen (17) major quality events raised, risk assessed, and managed by the site during the review period. These events were managed in accordance with site procedures.

Compared with the previous review the number of quality events has:

☐ Decreased ☐ Remained Unchanged ☒ Increased

There were ten (10) Drug Substance batches included in the current review period, compared to two (2) Drug Substance batches included in the previous review period. The seventeen (17) major quality events raised during this review period represents a raw increase in the number of events, but a reduced rate of events per batch.

The number of quality events impacting on the site, together with trend analysis, is assessed during the Site Management Review process. This assures the site actively manages the capability to respond to quality events.

Based on this review of quality events:

☒ There is no evidence of a trend to indicate a quality or system issue.

☐ A trend(s) indicating a quality or system issue has been identified.

10 COMPLAINTS (PRODUCT QUALITY)

This section is not applicable as an ISPR will be issued for this product and reporting period.

11 RECALLS, STOCK RECOVERIES, FIELD ALERTS REPORTS (FAR)/BIOLOGICAL PRODUCT DEVIATION REPORTS (BPDR)

Record Type	Previous Review	Current Review
Recall	0	0
Stock Recovery	0	0
FAR/BPDR	0	0

Recalls, Stock Recoveries, FARs, BPDRs ☒ N/A

Record Type	Batch No.	Reason

Discussion/Comments ☒ N/A

Section 11 Conclusion

Recalls:

☒ No recalls of product released for distribution have been made during the period of the review.

☐ Recalls of product released for distribution were undertaken during the period of the review.

Stock Recoveries:

☒ There have been no stock recoveries undertaken on product released for distribution during the period of the review.

☐ There have been stock recoveries undertaken on product released for distribution during the period of the review.

FARs/BPDRs:

☒ There have been no FARs/BPDRs (FDA) or contact with National Competent Authorities via alerting processes during the period of the review.

☐ There have been FARs/BPDRs (FDA) or contact with National Competent Authorities via alerting processes during the period of the review.

12 RETURNED AND SALVAGED GOODS

Returned and Salvaged Goods	Previous Review	Current Review
Total Number of Returned Batches	0	0
Total Number of Returns Related to Product Quality Deficiency	0	0
Total Number of Salvaged Batches	0	0

All returns received and investigated during the PR period are listed below: ☒ N/A

Batch No.	Reason for Return	Date Received	Final Disposition

Discussion/Comments ☒ N/A

Section 12 Conclusion

☒ There were no returned products or salvaged good in the period of the review.

☐ There were returned products or salvaged goods in the period of the review.

13 CONTRACTUAL AGREEMENTS / ARRANGEMENTS

Below is a list of contractual agreements that were active at the FMC site during the reporting period.

Name	City	Region	Contract – Effective Date
Accugenix	Newark	DE	25Apr2022
Advanced Scientifics	Millersburg	PA	27Apr2021
Ajinomoto do Brasil Industria	Limeira	Brazil	29Jul2022
Ajinomoto North America	Raleigh	NC	29Jul2022
Atlantic Analytical	Lebanon	NJ	29May2020
Avantor Performance Materials, LLC	Paris	KY	18Sep2019

Name	City	Region	Contract – Effective Date
Avantor Performance Materials, LLC	Phillipsburg	NJ	18Sep2019
Avantor Performance Materials, LLC	Aurora	OH	18Sep2019
Becton Dickinson	Columbus	NE	23Feb2017
Biospectra	Bangor	PA	29Nov2021
Charles River	Malvern and Wayne	PA	08Feb2022
Corning	Oneonta	NY	12Jul2022
Corning Sciences Mexico	Parque Industrial Del Norte Reynosa	Mexico	12Jul2022
Cytiva	Logan	UT	12Apr2023
Cytiva	UPPSALA	Sweden	12Apr2023
Cytiva US LLC	Duncan	SC	27Jul2022
Element	Santa Fe Springs	CA	31Oct2023
EMD Millipore Corporation	Danvers	MA	11Feb2021
Eurofins	Lancaster	PA	05Apr2022
Freudenberg Medical (formerly Helix	Carpinteria	CA	18Jan2021
Greenfield Global USA Inc.	Brookfield	CT	29Mar2023
ILC Dover LP	Frederica	DE	28Oct2023
Life Technologies	Bedford	MA	16Sep2020
Life Technologies	Chelmsford	MA	16Sep2020
Life Technologies (Invitrogen)	Grand Island	NY	20May2021
Life Technologies (Invitrogen)	Paisley	UK	20May2021
Life Technologies Corporation	Miami	FL	12Jul2022
Life Technologies Corporation	Logan	UT	27Apr2021
Merck KGaA	Darmstadt	Germany	11Feb2021
Merck Life Science Technologies	Nantong, Jiangsu	China	11Feb2021
Millipore Corporation	Jaffrey	NH	11Feb2021
Millipore Corporation	Burlington	MA	11Feb2021
Millipore SAS	Molsheim	Germany	11Feb2021
Novo Nordisk Pharmatech A/S	Koege	Denmark	16Oct2023
Pall	Ilfracombe	UK	27Jul2022
Pall Puerto Rico Incorporated	Fajardo	Puerto Rico	27Jul2022
Pfanstiehl, Inc. [Formerly Ferro	Waukegan	IL	04May2022
Puritan Products	Bethlehem	PA	27Apr2023
Quality Chemical Laboratories	Wilmington	NC	23Mar2020
SAFC Biosciences	Cleveland	OH	10Sep2019
SAFC Biosciences	Lenexa	KS	10Sep2019
Saint-Gobain	Taunton	MA	14Mar2023
Saint-Gobain	Akron	OH	14Mar2023

Name	City	Region	Contract – Effective Date
Sanisure	Camarillo	CA	30Jul2020
Sartorius Stedim Bioprocess SARL	Bourbiaa, Mohamdia	Tunisia	19Sep2023
Sartorius Stedim Biotech	Beijing	China	19Sep2023
Sartorius Stedim Biotech, Inc.	Goettingen	Germany	19Sep2023
Sartorius Stedim Filters Inc.	Yauco	Puerto Rico	19Sep2023
Sartorius Stedim FMT S.A.S	Aubagne	France	19Sep2023
Sartorius Stedim NA, Inc.	New Oxford	PA	19Sep2023
Sartorius Stedim Switzerland AG	Tagelswangen	Switzerland	19Sep2023
Sigma Aldrich	Sheboygan Falls	WI	10Sep2019
Sigma Aldrich	St. Louis	MO	10Sep2019
Sigma Aldrich Chemie GMBH	Steinheim	Germany	10Sep2019
Sigma Aldrich Company LLC	Milwaukee	WI	10Sep2019
Sigma Aldrich Company LLC (Dekalb)	Saint Louis	MO	10Sep2019
Sigma-Aldrich	Buchs	Switzerland	10Sep2019
Techno Plastics	Trasadingen	Switzerland	23Jan2013
ThermoFisher ASI	Matamoros	Mexico	27Apr2021
ThermoFisher Scientific	Rochester	NY	09Mar2020 (expired and being incorporated into Global)
Watson Marlow Bredel Pumps, Inc.	Falmouth	CO	06May2020

Discussion/Comments ☒ N/A

Section 13 Conclusion

The Standard Internal Quality Assurance Agreement (QAA) governs the responsibilities between AZ manufacturing/supply sites/functions within Operations. The Standard Marketing Company (MC) QAA serves as an Internal QAA between AZ manufacturing/ supply sites/functions within Operations and AZ Marketing Companies. Reference SOP-0033724 current version.

Based on this review of Contractual Agreements/Arrangements:

☐ All contractual agreements between the site and customers or suppliers are current and the service provided is aligned to the requirements established in the agreements.

☒ Not all contractual agreements between the site and customers or suppliers are current and are under development or revision.

ThermoFisher Rochester is being incorporated into the Global QAA.

14 QUALIFICATION STATUS OF RELEVANT EQUIPMENT AND UTILITIES

Qualification and validation activities performed at the FMC site have been reviewed and demonstrate that the systems are operating in a state of control.

All critical equipment involved in the production and QC testing of DS, FB, DP and intermediate materials, as applicable, is properly installed and qualified. All qualification/ requalification studies for critical equipment and revalidation/ maintenance studies for associated cleaning and sterilization/ sanitization processes were completed per approved procedures.

For the data review period, the classified clean rooms and utility systems were assessed against performance criteria and found to be functioning within a state of control.

Continuous process validation results demonstrate that the process is within a state of control.

Sub-sections below summarize the completed installation and qualification activities of new equipment or modifications to existing Manufacturing and QC equipment, cleaning/sterilization/sanitization revalidation activities and utilities/clean room requalification activities performed during the review period as defined in site Validation Master Plans (VMPs), procedures, and change controls (CCs). Refer to Sections 14.1 and 14.2 for qualification activities performed for cleaning/sanitization/sterilization processes, manufacturing and QC equipment, classified clean rooms, and utilities. Process validation, method validation, and computerized system validation are performed as required when new processes or methods are implemented, or changes are made to existing processes and/or methods. Refer to Sections 14.3 to 14.5 for validation activities performed for processes, methods, shipping, and computerized systems.

14.1 Qualification Status of Relevant Equipment and Cleaning/ Sterilization/ Sanitization Processes

Qualification and validation activities performed at the FMC site for relevant equipment and cleaning/sterilization/sanitization processes during the review period have been identified in Table 14-1 through Table 14-6.

Table 14-1 and Table 14-2 list the cleaning and sterilization/sanitization validation studies completed to support requirements defined in site VMPs, procedures, and change controls. Revalidation/maintenance (on-going monitoring program) studies were performed per VMPs [PLAN-0113023, VMP-X-033: *Cleaning Validation Master Plan for the Frederick Manufacturing Center (FMC) Facility* and PLAN-0057047*: VMP-X-090: Validation Master Plan for Equipment, Facilities and Utilities at the Frederick Manufacturing Center (FMC)* and procedures (e.g., SOP-0068010, Steam in Place (SIP) Validation Program at the Frederick Manufacturing Center and SOP-0068589, *Cleaning Validation Program at Frederick Manufacturing Center*)] providing documented evidence that the validated state of cleaning and sterilization/sanitization processes remain in a state of control.

Table 14-3 and Table 14-5 list the manufacturing and QC equipment qualification/ requalification studies completed to support requirements defined in site VMPs, procedures, and change controls. Qualification/requalification studies were performed per VMPs [PLAN-0057047, *VMP-X-090: Validation Master Plan for Equipment, Facilities and Utilities at the Frederick Manufacturing Center (FMC)* and PLAN-0057086, *VMP-X-087: Validation Master Plan for Computerized Systems at Frederick Manufacturing Center (FMC) Site*], pre-approved protocols, and procedures (e.g., SOP-0069424, *Preparation and Qualification of Controlled Temperature Units (CTUs) at the Frederick Manufacturing Center (FMC)*) providing documented evidence that the validated state of manufacturing and QC equipment remain in a state of control.

Table 14-6 lists the QC equipment decommissioned following requirements defined in SOP-0106401, *Equipment and Systems Decommissioning at Frederick Manufacturing Center (FMC)* and provide documented evidence that the validated state of retired equipment/systems remained in a state of control up to the end of equipment/system lifecycle. There was no manufacturing equipment decommissioned during the review period as shown in Table 14-4.

Table 14-1 FMC Cleaning Maintenance Activities

Validation Report Number	Completion Date	Validation Report Title
REP-0199343	Nov 2022	VX-110100-TER-R6: Technical Report for the Cleaning Validation Maintenance for Column Packing Equipment Matrix Located at Frederick Manufacturing Center (FMC) Building 633 for Calendar Year 2022
REP-0202691	Jan 2023	VF-106992-TER-R6: Summary Technical Report of the Cleaning Processes at the Frederick Manufacturing Center (FMC), Building 636 for Calendar Year 2022
REP-0101461	Jan 2023	VF-105942-TER: Technical Report for the Cleanability Assessment of Buffer Solutions prepared at the Frederick Manufacturing Center (FMC)
REP-0200611	Feb 2023	VF-101240-RV2-R1: Summary Report for the Cleaning Revalidation of the Buffer Contact Equipment Matrix at the Frederick Manufacturing Center (FMC) B636

Validation Report Number	Completion Date	Validation Report Title
REP-0205875	Mar 2023	VX-104192-TER-R9: Summary Technical Report of the Cleaning Processes at the Frederick Manufacturing Center (FMC), Building 633 for Calendar Year 2022
REP-0215201	Oct 2023	VF-101241-TER-R4: Technical Report for the Cleaning Validation Maintenance of the Downstream Purification and Formulation Equipment at the Frederick Manufacturing Center (FMC) Building 636 for the Calendar Year 2023

Table 14-2 FMC Sterilization/ Sanitization Revalidation/ Maintenance Activities

Validation Report Number	Completion Date	Validation Report Title
REP-0205425	Mar 2023	VX-804180-TER-R10: Summary Report for the SIP Processes at the Frederick Manufacturing Center (FMC), Building 633 for Calendar Year 2022
REP-0212514	Jul 2023	VX-501447-RV11-R1: Final Report for the Revalidation of the Production Autoclave AUT-144701 at the Frederick Manufacturing Center (FMC) Building 633, for Calendar Year 2023
REP-0223588	Sep 2023	VX-704016-TER-R2 Autoclave Hold Technical Report
REP-0214828	Sep 2023	VX-501445-RV12-R1: Final Report for the Revalidation of the Production Autoclave AUT-144501 at the Frederick Manufacturing Center (FMC) Building 633, for Calendar Year 2023

Table 14-3 FMC Equipment Qualification/ Requalification Activities (Manufacturing Equipment)

Validation Report Number	Completion Date	Validation Report Title
REP-0196355	Nov 2022	VX-820037-TER-R2: Summary Report for the Periodic Review of the CTU – Freeze / Thaw Units Located at Frederick Manufacturing Center (FMC) for Calendar Year 2022
REP-0198838	Nov 2022	VW-300013-IOQ-A1-R1 Summary Report for Addendum to IOQ for the Freeze/Thaw Skid Automation System Unit PK-220501 at FMC
REP-0199264	Dec 2022	VX-220071-OQP-R2 Summer OQ Report for Intra Campus Transit of BDS-DS Using the Refrigerated Truck at the Frederick Manufacturing Center (FMC)

Validation Report Number	Completion Date	Validation Report Title
REP-0200171	Jan 2023	VW-300013-IOQ-A2-R1: Summary Report for Addendum to IOQ for the Freeze-Thaw Unit PK-220502 at the Frederick Manufacturing Facility (FMC)
REP-0202456	Feb 2023	VX-710078-PVP-R8: Continued Process Verification Stage 3b Summary Report for Benralizumab Formulated Bulk Manufactured at the 15,000L and 2,500L scales at FMC for Review Period of November 2021 through November 2022
REP-0202581	Feb 2023	VX-105012-PQP-A1-R2: Final Report for the Cleaning Validation of the 1.8m GE Axichrom Chromatography Column (CL-156302) Located at Frederick Manufacturing Center (FMC), Building 633
REP-0203506	Mar 2023	VX-504324-IOQ-A4-E1: Summary Report for the Addendum IOQ for the SoloVPE Spectrometer
REP-0211883	Jun 2023	VF-507123-IOQ-E1: Summary Report to the Installation and Operational Qualification for the 80cm Stainless Steel AxiChrom Chromatography Column (CL-620010) at FMC B636
REP-0212424	Jun 2023	VX-820048-TER-R2: Summary Report for the Periodic Review of the Tube Sealers Located at Frederick Manufacturing Center (FMC) B633 and B636 for Calendar Year 2023
REP-0212425	Jun 2023	VX-820049-TER-R2: Summary Report for the Periodic Review of the Tube Welders Located at Frederick Manufacturing Center (FMC) B633 and B636 for Calendar Year 2023
REP-0212952	Jun 2023	VX-820041-TER-R2: Summary Report - Periodic Review of the B630 LN2 Freezers Located at FMC (2023)
REP-0213271	Jul 2023	VX-820036-TER-R3: Summary Report for the Periodic Review of the Cold Rooms Located at FMC B633 & B630 for the Calendar Year 2023
REP-0223127	Aug 2023	VW-504444-TER: Technical Report of Airflow Visualization Test for Sampling Booths BTH-220102 and BTH-220101 in Rooms 1W35B AND 1W35C, respectively, at FMC B630
REP-0222182	Sep 2023	VX-505605-IOQ-A2-E1: Summary Report for the Addendum to the IOQ of the Walk-In Cold Room CR-6P24
REP-0213984	Sep 2023	VX-820038-TER-R3: Summary Report for the Periodic Review of the Freezer Units Located at Frederick Manufacturing Center (FMC) for Calendar Year 2023
REP-0226257	Sep 2023	VW-502112-IOQ-A1-E1: Summary Report for the Requalification for Cold Room CR-1W26D B630 at the Frederick Manufacturing Center (FMC)
REP-0222661	Oct 2023	VF-501132-IOQ-A2-E1: Summary Report for the Addendum to the IOQ of the -35°C to -45°C Walk-in Freezer (CR-S101B) at the FMC B660 Per QE-041429

Validation Report Number	Completion Date	Validation Report Title
REP-0233125	Oct 2023	VF-500043-IOQ-A2: Summary Report for the Addendum to the IOQ of the 2°C to 8°C Walk-In Cold Room (ER-6) at FMC (B636) Per QE-045233
REP-0226127	Oct 2023	VF-501152-IOQ-A2-E1: Summary Report for the Addendum of the Panasonic 2°C to 8°C Refrigerator (REF-610004) at the FMC B636 Per QE-028297
REP-0234103	Oct 2023	VW-502111-IOQ-A1-E1: Summary Report for the Requalification for Cold Room CR-1W26C B630 at the Frederick Manufacturing Center (FMC)
REP-0232804	Nov 2023	VX-505604-IOQ-A4-E1: Summary Report for the Addendum of the 2°C to 8°C Walk-in Refrigerator (CR-1P36) at the FMC B633 Per QE-041429
REP-0233389	Nov 2023	VF-501207-IOQ-A2-E1: Summary Report for the Addendum of the IOQ of the Walk-In Cold Room CR-S101C at FMC B660

Table 14-4 FMC Equipment Retirement Activities (Decommissioned Manufacturing Equipment)

Change Control Number	Completion Date	Decommissioning Change Summary
N/A		

Table 14-5 FMC Equipment Qualification/ Requalification Activities (Quality Control Equipment)

Validation Report Number	Completion Date	Validation Report Title
REP-0199689	Nov 2022	VX-520084-IOQ-E1 Summary Report for the IOQ for the OsmoTECH Pro Osmometer at FMC
REP-0203309	Mar 2023	VF-500899-IOQ-A1-E1: Summary Report for the Addendum IOQ for Bio-Rad Laboratories GS-900 Calibrated Densitometer
REP-0203495	Mar 2023	VX-504308-IOQ-A1-E1: Summary Report for the Addendum IOQ for the Fourier-Transform Infrared Spectroscopy (FTIR)
REP-0203503	Mar 2023	VF-501058-IOQ-A3-E1: Summary Report for the Addendum IOQ for PA800 Plus
REP-0203506	Mar 2023	VX-504324-IOQ-A4-E1: Summary Report for the Addendum IOQ for the SoloVPE Spectrometer

Validation Report Number	Completion Date	Validation Report Title
REP-0203867	Mar 2023	VX-502603-IOQ-A3-E1: Summary Report for the Addendum IOQ for Metrohm 905 Titrando and TiamoTM Software
REP-0204014	Mar 2023	VX-504185-IOQ-A3-E1: Summary Report for the Addendum IOQ for Agilent 2100 Bioanalyzer
REP-0203336	Mar 2023	VF-300953-IOQ-A1-E1: Summary Report for the Addendum IOQ for the Beckman Coulter Vi-Cell XR Cell Counter Cell Viability Analyzers
REP-0203535	Mar 2023	VF-300954-IOQ-A2-E1: Summary Report for the Addendum IOQ for the Envision Multilabel Plate Reader
REP-0203892	Mar 2023	VX-502566-IOQ-A4-E1: Summary Report for the Addendum IOQ for MicroSEQ Genetic Analyzer
REP-0203317	Mar 2023	VF-500997-IOQ-A1-E1: Summary Report for the Addendum IOQ for Agilent UV-Visible Spectrophotometers
REP-0203894	Mar 2023	VX-504292-IOQ-A2-E1: Summary Report for the Addendum IOQ for Agilent UV-Visible Spectrophotometer
REP-0206232	Mar 2023	VX-504350-IOQ-A1-E1: Summary Report for the Addendum IOQ for Agilent Chromatography Standalone Systems
REP-0204010	Mar 2023	VX-504423-IOQ-A3-E1: Summary Report for the Addendum IOQ for BioTek Microplate Reader
REP-0206415	Mar 2023	VX-504090-IOQ-A3-E1: Summary Report for the Addendum IOQ for Molecular Devices Microplate Readers
REP-0203233	Mar 2023	VX-504360-IOQ-A3-E1: Summary Report for the Addendum IOQ for e-Scan 625 High Voltage Leak Detector
REP-0203312	Mar 2023	VF-500990-IOQ-A1-E1: Summary Report for the Addendum IOQ for the Beckman Coulter Liquid Particle Counter (HIAC 9703+)
REP-0206234	Mar 2023	VX-502633-IOQ-A3-E1: Summary Report for the Addendum IOQ for Gyrolab XP Work Station
REP-0208641	Apr 2023	VF-500202-IOQ-A3-E1: Summary Report for the Addendum of the Hot Pack 2°C to 8°C Walk-in Refrigerator (ER-13) at the FMC B660 Per QE-010449
REP-0209683	May 2023	VX-520073-IOQ-A2-E1: Summary Report for the Addendum IOQ for the YSI2900 Series Biochemistry Analyzer

Validation Report Number	Completion Date	Validation Report Title
REP-0213722	Jul 2023	VX-820039-TER-R3: Summary Report for the Periodic Review of the Incubators / Photostability Chambers Located at FMC B633 & B660 for the Calendar Year 2023
REP-0222815	Sep 2023	VX-504284-IOQ-A2-E1: Summary Report for the Addendum of the IOQ of the Walk-In Cold Room CR-4L04 at FMC B633
REP-0233382	Oct 2023	VX-530006-IOQ-E1: Summary Report for the Installation and Operational Qualification (IOQ) of the Ultra-Low Temperature (-80°C) Freezer (FZ-500222) at the FMC B633 Per QE-057064
REP-0233383	Oct 2023	VX-530005-IOQ-E1: Summary Report for the Installation and Operational Qualification (IOQ) of the Ultra-Low Temperature (-80°C) Freezer (FZ-500223) at the FMC B633 Per QE-057064
REP-0233384	Oct 2023	VF-530004-IOQ-E1: Summary Report for the Installation and Operational Qualification (IOQ) of the Ultra-Low Temperature (-80°C) Freezer (FZ-500224) at the FMC B660 Per QE-057064
REP-0234836	Oct 2023	VX-505277-IOQ-A1-E1: Summary Report for the Revalidation of the Bahnson Stability Chamber (SI-500005) in Room S112 Building 660 at the FMC Per QE-057064
REP-0234630	Nov 2023	VX-504629-PQP-A3-R1: Final Report for the Addendum to EMPQ of Quality Control Biological Safety Cabinet BSC-500000 for Relocation to Room 4L36 and BSC-540108 to Room 4L34 – Per CC QE-054081
REP-0226128	Nov 2023	VX-530012-TER: Technical Report of Airflow Visualization Test Results Performed for BSCs Located in FMC B633, Room 4L34 and 4L36 per QE 054081
REP-0225723	Nov 2023	VF-501037-IOQ-A2-E1: Summary Report for the Addendum of the Panasonic 2°C to 8°C Refrigerator (RF-500119) at the FMC B660 Per QE-028297

Table 14-6 FMC Equipment Retirement Activities (Decommissioned Quality Control Equipment)

Change Control Number	Completion Date	Decommissioning Change Summary
QE-017594	Mar 2023	Decommissioned Refrigerator RF-500011
QE-011418	May 2023	Decommissioned YSI 2700 Select Biochemistry Analyzer BA-500007
QE-020106	Aug 2023	Decommissioned Agilent 7890A Gas Chromatography System GC-500000

14.2 Qualification Status of Relevant Classified Clean Rooms and Utilities

Requalification activities performed at the FMC for relevant classified clean rooms and utilities during the reporting period have been identified in Table 14-7 and Table 14-8.

Table 14-7 lists the requalification studies completed during the reporting period to support requirements defined in PLAN-0057047, *VMP-X-090: Validation Master Plan for Equipment, Facilities and Utilities at the Frederick Manufacturing Center (FMC)* and to provide documented evidence that the qualification state of classified clean rooms remains in a state of control. Environmental Monitoring Performance Qualification (EMPQ) studies were performed and demonstrated that the cleanrooms are capable of consistently maintaining environmental conditions that meet acceptance criteria for the established room classification. Table 14-7 includes the EMPQ studies that were completed for B633 and B636 clean rooms.

There were no utilities requalification studies completed during the reporting period as shown in Table 14-8.

Table 14-7 FMC Clean Room Requalification Activities

Validation Report Number	Completion Date	Validation Report Title
REP-0197289	Nov 2022	VF-406988-TER-R4: Technical Report for the Periodic Cleanroom Classification per ISO 14644-2 for the Classified Areas in B636 at the Frederick Manufacturing Center (FMC) During Calendar Year 2022
REP-0198272	Dec 2022	VX-804567-TER-R4: Technical Report for the Periodic Cleanroom Classification per ISO 14644-2 for Classified Cleanrooms in B633 at the Frederick Manufacturing Center (FMC) During Calendar Year 2022
REP-0198405	Nov 2022	VX-404028-PQP-A20-R1: FINAL REPORT FOR THE ADDENDUM EMPQ OF B633 HARVEST ROOM 3P10 - PER CC 257868
REP-0199718	Dec 2022	VF-406016-PQP-A2-R1: Final Report for the Addendum EMPQ for Media Prep and Buffer Prep Fume Hoods Located in Building 636 at FMC – Per CC QE-003146
REP-0206344	Apr 2023	VF-406019-PQP-A3-R1: Final Report for the Addendum to the Environmental Monitoring Performance Qualification (EMPQ) of B636 Column Packing P170 per QE-018103
REP-0212775	Aug 2023	VX-404028-PQP-A21-R1: Final Report for the Addendum EMPQ of B633 Harvest Room 3P10 - Per CC QE-020837

Validation Report Number	Completion Date	Validation Report Title
REP-0224178	Sep 2023	VW-500012-IOQ-A1-E1: Summary Report for the Addendum Installation and Operational Qualification (IOQ) for B630 ISO 8 Zone (1W35A) at the Frederick Manufacturing Center (FMC) B630

Table 14-8 FMC Utilities Requalification Activities

Validation Report Number	Completion Date	Validation Report Title
N/A		

QC trending reports for FMC critical utilities and environmental monitoring results from 2022 to 3Q2023, within the PR review period, are listed in Table 14-9.

Table 14-9 FMC Environmental Monitoring/Utilities Monitoring Testing and Trending Activities

Report Number	Quality Control Trending Reports (EM/Utilities Monitoring)
REP-0206254	Annual 2022 Environmental Monitoring Building 633, Building 636, and Quality Control Biological Safety Cabinets Trending Report
REP-0205507	Annual 2022 Trending Report Water/Steam Systems, Oil Free Compressed Air, Clean Air, and Specialty Gas Systems at FMC Building 633, Building 636, and Building 630
REP-0211487	1Q2023 Environmental Monitoring Building 630, Building 633, and Building 636 Trending Report
REP-0223974	2Q2023 Environmental Monitoring Building 630, Building 633 and Building 636 Trending Report
REP-0237418	3Q2023 Environmental Monitoring Building 630, Building 633, and Building 636 Trending Report
REP-0209263	1Q2023 Trending Report Water/Steam Systems Building 633 and Building 636
REP-0223151	2Q2023 Trending Report Water/Steam Systems Building 633 and 636
REP-0236959	3Q2023 Trending Report Water-Steam Systems Building 633 and 636
REP-0205507	Annual 2022 Trending Report Water/Steam Systems, Oil Free Compressed Air, Clean Air, and Specialty Gas Systems at FMC Building 633, Building 636, and Building 630
REP-0205876	Annual 2022 Microorganism Recovery Trending Report for Building 633, 636, and 630

Discussion/Comments ☐ N/A

The qualification status of the equipment and critical utilities/systems with direct product impact were reviewed.

Equipment and Facilities:

Equipment and facilities at the site having direct impact on product quality are subject to appropriate quality oversight described in PLAN-0057087, *VMP-X-089: Site Validation Master Plan for the Frederick Manufacturing Center (FMC)* and SMF-0000249, *Frederick Manufacturing Center (FMC) Site Master File*.

Calibration and Maintenance are carried out in accordance with approved procedures.

Where requalification has been identified, this have been undertaken within the PR period.

Where deviations have occurred from the VMP or procedures, these have been managed through the deviations process (see section 9.0).

Review of data from Process Capability (Section 6) or relevant utilities has not identified any trends caused by qualification of equipment.

Utilities:

Direct impact utilities are described in the site master file.

Site Water Systems (Generation and Delivery):

The Water for Injection (WFI), laboratory water, pre-treatment, and pure steam systems at FMC B633 and B636 were in a state of overall control from 14Nov2022 to 13Nov2023 and continued to produce a consistent and acceptable quality of water and steam.

Refer to quarterly and annual trending reports REP-0205507, REP-0209263, REP-0223151, and REP-0236959 for details. Review of control procedures and records, combined with independent monitoring of water quality by Quality Control, provides documented evidence that the site water systems produce water of an appropriate Pharmacopeia Quality. Review of all relevant alert-level excursion investigations showed no impact to either the product or the water system; corrections were effective.

Any major changes to the site water system during the period of this review have been applied through change control to the water system.

Review of deviations relating to water production did not identify any trends.

Review of the control procedures and records, combined with independent monitoring of water quality by QC, provides documented evidence that the site water systems produce water of an appropriate pharmacopeial quality.

The combination of these review activities provides assurance that the site water generation and distribution systems operated in a state of control during the period of this review.

HVAC & Environmental Monitoring:

The environmental conditions of classified clean rooms at FMC B633 and B636 were in a state of overall control from 14Nov2022 to 13Nov2023 and continued to maintain a state of control. Refer to quarterly and annual environmental monitoring reports REP-0206254, REP-0211487, REP-0223974, and REP-0237418. Reports for the fourth quarter and 2023 annual report will be included in the next PR. Review of control procedures and records, combined with independent monitoring of environmental monitoring by Quality Control, provides documented evidence that the site clean rooms maintain an appropriate environment for pharmaceutical production. Review of all relevant alert-level excursion investigations showed no impact to either the product or clean room capabilities to maintain environmental conditions; corrections were effective.

Any major changes to the site HVAC system during the period of this review have been applied through change control to the HVAC system.

Review of deviations relating to HVAC did not identify any trends.

Review of control procedures and records, combined with independent environmental monitoring of HVAC air quality by QC, provides documented evidence that the site HVAC systems maintains an appropriate environment for pharmaceutical production.

The combination of these review activities provides assurance that the site HVAC system operated in a state of control during the period of this review.

Compressed Gases System (Generation and Delivery):

The Oil-Free Compressed Air (OFCA) and specialty gas (nitrogen, carbon dioxide, and oxygen) systems at FMC B633 and B636 were in a state of overall control from 14Nov2022 to 13Nov2023 and continued to produce a consistent and acceptable quality of OFCA and specialty gases. Refer to annual trending report REP-0205507 for details. Sample results and any associated excursion investigations from 01Jan2023 through 13Nov2023 were reviewed, and no adverse trends were identified. The 2023 annual report will be included in the next PR. Review of control procedures and records, combined with independent monitoring of OFCA and specialty gases by Quality Control, provides documented evidence that the site OFCA and specialty gases systems maintained under control. Review of all relevant alert-level excursion investigations showed no impact to either the product or the systems; corrections were effective.

Any major changes to the compressed gas system during the period of this review have been applied through change control to the compressed gas system.

Review of deviations relating to compressed gases did not identify any trends.

Review of the control procedures and records, combined with independent monitoring of compressed gases by QC, provides documented evidence that the site compressed gas system was maintained under control.

The combination of these review activities provides assurance that the site compressed gases system operated in a state of control during the period of this review.

14.3 Validation Status of Process and Methods

Process validation and method validation are performed as required when new processes or methods are implemented or changes are made to existing processes and methods. Table 14-10 summarizes process validation completed during the review period as defined in site VMPs, procedures, and change controls. There were no method validation studies during the review period as shown in Table 14-11.

Table 14-10 FMC DS and FB Process Validation Activities

Validation Report Number	Completion Date	Validation Report Title
REP-0234210	Nov 2023	VF-717012-PVP-R2: Benralizumab Process Validation Mixed Mode Column Resin Lifetime
REP-0215622	Nov 2023	VF-717013-PVP-R2: Benralizumab 636 Process Intermediate Hold Times
REP-0238868	Jan 2024	VX-710078-PVP-R9: Continued Process Verification Stage 3a Summary Report for Benralizumab DS
REP-0239373	Jan 2024	VX-710078-PVP-R10: Continued Process Verification Stage 3b Summary Report for Benralizumab FB30

Table 14-11 FMC DS, FB and DP Method Validation Activities

Validation Report Number	Completion Date	Validation Report Title
N/A		

14.4 Validation Status of Relevant Shipping Process

Shipping qualification activities are performed per VMP-X-056, *Validation Master Plan for Benralizumab (01P003, MEDI-563) at the Frederick Manufacturing Center (FMC) Building 633*. There were no shipping qualification studies completed in the review period as shown in Table 14-12.

Table 14-12 FMC Shipping Validation Activities

Validation Report Number	Completion Date	Report Title
N/A		

14.5 Validation Status of Computerized Systems

Validation activities executed during the review period that support computerized systems associated with the manufacture of benralizumab are listed in Table 14-13 as defined in PLAN-0057086, *VMP-X-087: Validation Master Plan for Computerized Systems at Frederick Manufacturing Center (FMC) Site*, procedures, and change controls. These activities include projects, such as PAS-X implementation, for which only the reports approved during the review period are listed. Table 14-13 summarizes validation activities performed for computerized system validation.

Table 14-13 FMC Computerized System Validation Activities

Validation Report Number	Completion Date	Report Title
REP-0199112	Dec 2022	VX-304594-IOQ-E4: Installation and Operational Qualification (IOQ) Test Report for the B636 Site Historian Asset Framework Batch Context for SIMCA-Online Process Models at the Frederick Manufacturing Center (FMC)
REP-0200802	Dec 2022	VX-304572-PQP-E6: Performance Qualification (PQ) Test Report for Building 633 (B633) the Inoculum Generic Master Batch Record (GMBR) in the Werum Information Technology (IT) Solution PAS-X Manufacturing Execution System (MES)
REP-0200805	Dec 2022	VX-304637-PQP-E5: Performance Qualification (PQ) Test Report for the Virus Filtration (VF) Generic Master Batch Record (GMBR) in the Werum Information Technology (IT) Solution PAS-X Manufacturing Execution System (MES)
REP-0199031	Dec 2022	VX-304643-OQP-E3: Operational Qualification (OQ) Test Report for the Building 633 Process Control System (PCS) Virus Filtration Setup and Transfer Recipes
REP-0201092	Dec 2022	VX-304687-PQP-E1: Performance Qualification (PQ) Test Report for Celsius-Pak (C-Pak) Filtration Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0201095	Dec 2022	VF-304572-PQP-E2: Performance Qualification (PQ) Test Report for the Building 636 (B636) Inoculum Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)

Validation Report Number	Completion Date	Report Title
REP-0200999	Jan 2023	VX-304652-PQP-E2: Performance Qualification (PQ) Test Report for Ultrafiltration/Diafiltration (UF/DF) Membrane Install Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0201000	Jan 2023	VX-304650-PQP-E3: Performance Qualification (PQ) Test Report for Ultrafiltration/Diafiltration (UF/DF) Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0201098	Jan 2023	VF-304574-PQP-E1: Performance Qualification (PQ) Test Report for the Building 636 (B636) Rocker Bag Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0201300	Jan 2023	VF-304573-PQP-E2: Performance Qualification (PQ) Test Report for the Building 636 (B636) Inoculum Suite Readiness Equipment Related Specification (ESP) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0196917	Jan 2023	VX-304435-PQP-E2: Performance Qualification (PQ) Test Report for the Building 633 (B633) Media Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0196919	Jan 2023	VF-304435-PQP-E1: Performance Qualification (PQ) Test Report for the Building 636 (B636) Media Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0200998	Jan 2023	VX-304653-PQP-E2: Performance Qualification (PQ) Test Report for Ultrafiltration/Diafiltration (UF/DF) Membrane Uninstall Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0201928	Jan 2023	VF-306954-IOQ-A9-R1: Summary Report for Addendum to Installation and Operation Qualification of the Building 636 Utilities Process Control System (PCS) at the Frederick Manufacturing Center (FMC) - WFI EM Classes and Harvest Phase

Validation Report Number	Completion Date	Report Title
REP-0197854	Jan 2023	VX-304655-PQP-E4: Performance Qualification (PQ) Test Report for the Column Packing Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0197858	Jan 2023	VF-304434-PQP-E1: Performance Qualification (PQ) Test Report for the Building 636 (B636) Buffer Preparation Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0202556	Jan 2023	VX-320076-OQ-A1-E1 Summary Report for the Addendum OQ for the QA Lot Disposition Power BI Dashboards at FMC
REP-0196204	Jan 2023	VX-304632-PQP-E1: Performance Qualification (PQ) Test Report for the Production Bioreactor and Harvest Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0196915	Jan 2023	VX-304588-PQP-E3: Performance Qualification (PQ) Test Report for the Seed Bioreactor Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0198478	Jan 2023	VX-304418-CVR-R7: Final Summary Report for Building 636 Solution Preparation Operations in the Manufacturing Execution System (MES) Domain
REP-0201758	Jan 2023	VX-304656-PQP-E4: Performance Qualification (PQ) Test Report for the Column Unpacking Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0196547	Feb 2023	VX-304594-CVR2: FMC Site Historian DeltaV Interface Validation Summary Report
REP-0201757	Feb 2023	VX-304418-CVR-R8: Final Summary Report for Building 636 Rocker Bag Operations in the Manufacturing Execution System (MES) Domain
REP-0203515	Mar 2023	VF-306952-IOQ-A32-R1: Summary Report for Addendum to Installation and Operation Qualification of the Building 636 Upstream Process Control System (PCS) at the Frederick Manufacturing Center (FMC) – Rockers Epic Q

Validation Report Number	Completion Date	Report Title
REP-0204072	Mar 2023	VX-304572-PQP-E7: Performance Qualification (PQ) Test Report for Building 633 (B633) the Inoculum Generic Master Batch Record (GMBR) in the Werum Information Technology (IT) Solution PAS-X Manufacturing Execution System (MES)
REP-0204809	Mar 2023	VX-304632-PQP-E4: Performance Qualification (PQ) Test Report for the Production Bioreactor and Harvest Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0206385	Mar 2023	VF-306954-IOQ-A9-R1: Summary Report for Addendum to Installation and Operation Qualification of the Building 636 Downstream Process Control System (PCS) at the Frederick Manufacturing Center (FMC) - BHOLD Tanks Temperature Alarms
REP-0203570	Mar 2023	VX-304655-PQP-E5: Performance Qualification (PQ) Test Report for the Column Packing Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0204084	Mar 2023	VX-304588-PQP-E4: Performance Qualification (PQ) Test Report for the Seed Bioreactor Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0205472	Mar 2023	VX-304637-PQP-E6: Performance Qualification (PQ) Test Report for the Virus Filtration (VF) Generic Master Batch Record (GMBR) in the Werum Information Technology (IT) Solution PAS-X Manufacturing Execution System (MES)
REP-0205418	Mar 2023	VX-304652-PQP-E3: Performance Qualification (PQ) Test Report for Ultrafiltration/Diafiltration (UF/DF) Membrane Install Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0205419	Mar 2023	VX-304653-PQP-E3: Performance Qualification (PQ) Test Report for Ultrafiltration/Diafiltration (UF/DF) Membrane Uninstall Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0206893	Apr 2023	VX-304605-OQP-E4: Operational Qualification (OQ) Test Report for Building 633 Process Control System (PCS) 400L Bioreactor Recipes

Validation Report Number	Completion Date	Report Title
REP-0206896	Apr 2023	VX-304606-OQP-E4: Operational Qualification (OQ) Test Report for Building 633 Process Control System (PCS) 2000L Bioreactor Recipes
REP-0207467	Apr 2023	VF-306952-IOQ-A33-R1: Summary Report for Addendum to IOQ of the Building 636 Upstream Process Control System (PCS) at FMC – B636 Bioreactor, Media, and Harvest Automation Modifications
REP-0207990	Apr 2023	VX-304625-OQP-E7: OQ Test Report for B633 Process Control System (PCS) Production Bioreactor Recipes
REP-0208403	Apr 2023	VX-304647-OQP-E3: Operational Qualification (OQ) Test Report for Building 633 Process Control System (PCS) POD Filtration Recipes
REP-0208407	Apr 2023	VX-304645-OQP-E3: Operational Qualification (OQ) Test Report for Building 633 Process Control System (PCS) Multi-Functional Filtration (MFF) Virus Filtration (VF) Recipes
REP-0208684	Apr 2023	VX-304695-PQP-E2: Performance Qualification (PQ) Test Report for the B633 Room Cleaning and Solution Preparation Equipment Related Specification (ESP) in the PAS-X Manufacturing Execution System (MES)
REP-0199171	Apr 2023	VX-304418-OQR-A1: Addendum to the Operational Qualification (OQ) Test Report for the Limited Review Report in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0205833	May 2023	VX-304650-PQP-E4: Performance Qualification (PQ) Test Report for Ultrafiltration/Diafiltration (UF/DF) Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0206688	Jun 2023	VX-304626-OQP-E3: Operational Qualification (OQ) Test Report for Building 633 Process Control System (PCS) Harvest Recipes
REP-0208002	Jun 2023	VX-304658-OQP.02-E5: Operational Qualification (OQ) Test Report for Building 633 Process Control System (PCS) UF1209 Process Recipes
REP-0208400	Jun 2023	VX-304643-OQP-E4: Operational Qualification (OQ) Test Report for Building 633 Process Control System (PCS) Virus Filtration Setup and Transfer Recipes

Validation Report Number	Completion Date	Report Title
REP-0211779	Jun 2023	VF-306953-IOQ-A48-R1: Summary Report for Addendum to Installation and Operation Qualification of the Building 636 Downstream Process Control System (PCS) at the Frederick Manufacturing Center (FMC) - Buffer Prep Automation Improvements
REP-0212234	Jun 2023	VF-306952-IOQ-A34-R1: Summary Report for Addendum to Installation and Operation Qualification of the Building 636 Upstream Process Control System (PCS) at the Frederick Manufacturing Center (FMC) - Media Prep Automation Improvements
REP-0207996	Jun 2023	VX-304661-OQP-E6: Operational Qualification (OQ) Test Report for Building 633 Process Control System (PCS) Column Packing Recipes
REP-0208121	Jun 2023	VW-304689-PQP-E1: Performance Qualification (PQ) Test Report for Building 630 (B630) Thaw Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0211847	Jun 2023	VF-304434-PQP-E2: Performance Qualification (PQ) Test Report for the Building 636 (B636) Buffer Preparation Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0212123	Jun 2023	VF-304436-PQP-E2: Performance Qualification (PQ) Test Report for the Building 636 (B636) Carboy Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0211567	Jun 2023	VX-304638-PQP-E2: Performance Qualification (PQP) Test Report for the Methotrexate (MTX) Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES)
REP-0211566	Jul 2023	VF-304435-OPQ-E1: Operational and Performance Qualification (OPQ) Test Report for Building 636 (B636) Media Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0211849	Jul 2023	VX-304435-PQP-E3: Performance Qualification (PQ) Test Report for the Building 633 (B633) Media Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)

Validation Report Number	Completion Date	Report Title
REP-0212729	Jul 2023	VX-304431-PQP-E2: Performance Qualification (PQ) Test Report for the Polysorbate Generic Master Batch Record (GMBR) in the Werum Information Technology (IT) Solution PAS-X Manufacturing Execution System (MES)
REP-0221614	Aug 2023	VX-304632-PQP-E5: Performance Qualification (PQ) Test Report for the Production Bioreactor and Harvest Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0222159	Aug 2023	VX-305016-IOQ-A2-E23-R1: Summary Report for Addendum to IOQ of FMC Campus EMS—Points
REP-0222146	Aug 2023	VX-305016-IOQ-A2-E22-R1: Summary Report for Addendum to IOQ of FMC Campus EMS - Points Group A
REP-0222231	Aug 2023	VX-304694-PQP-E3: Performance Qualification (PQ) Test Report for the Benralizumab (Benra) Bag to Bag Filtration Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0208126	Aug 2023	VW-304688-PQP-E1: Performance Qualification (PQ) Test Report for Building 630 (B630) Freeze Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0208145	Aug 2023	VX-304418-CVR-R9: Final Summary Report for Building 630 Freeze/Thaw Operations in the Manufacturing Execution System (MES) Domain
REP-0234736	Oct 2023	VX-305016-IOQ-A2-E24-R1- Summary Report for Addendum to IOQ of FMC Campus EMS - Points Group B
REP-0214949	Nov 2023	VF-304703-PQP-E1: Performance Qualification (PQ) Test Report for the Building 636 (B636) Downstream Equipment Related Specification (ESP) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0214959	Nov 2023	VX-304703-PQP-E1: Performance Qualification (PQ) Test Report for the Building 633 (B633) Downstream Equipment Related Specification (ESP) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0233106	Nov 2023	VF-306952-IOQ-A35-R1- Summary Report for Addendum to Installation and Operation Qualification of the N+1 Harvest Centrifuge for the B636 Automation Implementation

Validation Report Number	Completion Date	Report Title
REP-0236003	Nov 2023	VX-304691-CVR: Final Summary Report for the Nymi Enterprise Authentication Service at the Frederick Manufacturing Center (FMC)
REP-0234791	Nov 2023	VF-304435-PQP-E2: Performance Qualification (PPQ) Test Report for Building 636 (B636) Media Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)
REP-0234806	Nov 2023	VF-304436-PQP-E3: Performance Qualification (PQ) Test Report for the Building 636 (B636) Carboy Generic Master Batch Record (GMBR) in the PAS-X Manufacturing Execution System (MES) at the Frederick Manufacturing Center (FMC)

Section 14 Conclusion

The qualification status of the equipment and critical utilities/systems with direct product impact were reviewed. All changes to equipment/facility/utilities are managed through the change management system with the appropriate qualification/validation activities performed.

The conclusion from this review is that the qualification status of relevant equipment and critical utilities/systems with direct impact on product quality has:

☒ Been maintained in a state of control and meets the requirements for the review period.

☐ Has not been fully maintained.

15 OTHER

15.1 Visual Examination of Reserve Samples

The Annual visual check of reserve samples was performed in Oct2022 per SOP-0067949, Quality Control Sample Management of Reserve (EU: Reference) Samples, and inspection of reserve samples. Reference REP-0204409, *2022 QC Reserve Inspection at Frederick Manufacturing Center (FMC)*, section 2.1 for benralizumab reserve sample inspection details. The 2022 annual reserve inventory successfully documented the physical reconciliation of reserves at Frederick Manufacturing Center (FMC) in Laboratory Information Management System (GQLIMS). There were no leaks or damages discovered during the inspection of the reserve lots. No samples were assessed for disposal.

Section 15.1 Conclusion

The annual visual check of reserve samples was completed, and inspection of reserve samples has confirmed that all batches delivered continue to meet the licensed specification.

15.2 Transportation Quality Events

Transportation quality events that occurred during this reporting period were evaluated. The tables below provide the total number of significant (major or critical) quality events and a summary of each of those records, as applicable, from the validated Global Pharmaceutical Quality System (GPQS). All quality records in this section are closed.

Quality Events	Previous Review	Current Review
Total Number	0	3
Supply & Logistics	0	0
Temperature Excursions	0	3
Defect Category/Defect Type	N/A	Transport > Temperature Range Exceeded

Quality Events During the Period ☐ N/A

Batch Number	Description	Date Detected/ Reported	Root Cause	Reference Number
LA2735S2	When SBC received frozen Benralizumab (batch LA2735S2, quantity 23,8 kg) from FMC the temperature was out of range according to the temp records. 2 pieces of Weblogger II Dry Ice were in this shipment and they both had a high alarm, with temperatures over -15°c. One weblogger was over alarm value during 3hours and 20 minutes, with a highest temperature of -8.58°c. The other weblogger was over alarm value for 10 minutes with a highest temperature of -14.66°c	28 Sep 2022	Method > Process > Operator used instructions for Temperature recorder placement using an SSM Shipper rather than a KTM shipper	QE-017769
LA2735S3	SBC received frozen Benralizumab (art.nr 110021395, batch LA2735S3, quantity 23,9 kg) from FMC the temperature was out of range according to the temp records. 2 pieces of Weblogger II Dry Ice were in this shipment and they both had a high alarm, with temperatures over -15°c. One weblogger was over alarm value during 10 minutes, with a highest temperature of +20.83°c. The other weblogger was over alarm value for 10 minutes with a highest temperature of +20.22°c A third weblogger was attached outside the shipper, and the print from this weblogger was attached along with the 2 prints from the webloggers inside the shipper.	27 Oct 2022	Method > Process > Loading excursion during pack out as per process. FedEx unable to determine root cause for excursion during transit	QE-022373

Batch Number	Description	Date Detected/ Reported	Root Cause	Reference Number
TA2010 PT3520	SBC received frozen Benralizumab (art.nr 8007340, batch TA2010 quantity 32kg and batch PT3520 quantity 33,8kg) from FMC in 2 KTM shippers and the temperature was out of range according to the temp records. It appears to have occurred when the Webloggers was started during the start up phase. 2 pieces of Weblogger II Dry Ice were included per KTM in this shipment and one weblogger for each KTM had a high alarm and one weblogger was within range. For batch TA2010, weblogger with ID D111661242442997 was out of range for 20 minutes with a high extreme of -13,81. Weblogger with ID D111661241644994 was within range for the whole shipment. For batch PT3520, weblogger with ID D111661241955214 was out of range for 20 minutes with a high extreme of -14,30. Weblogger with ID D111661241875971 was within range for the whole shipment. Goods receive and downloading the temperature records are executed according to WI-0010164. Temperature excursion was not raised immediately because of an internal communication error at SBC.	29May2023	Material -> Internal Product / Material Controls -> Product / Material Handling Controls	QE-059329

Conclusion:

There were three (3) Major transportation events:

QE-017769 was for a temperature excursion of Fasenra (Benralizumab) Drug Substance (DS) from FMC to Sweden Biomanufacturing Center in Sodertalje, Sweden (SBC). The shipment experienced temperatures > -15° C for 3 hours and 20 minutes with a maximum temperature of -8.58°C. The average temperature was -46.49°C and the Mean Kinetic Temperature (MKT) was -28.5°C. The shipment was visually inspected and appeared frozen upon receipt and was immediately put into a freezer. Product Impact Fasenra DS has undergone 3X freeze thaw testing. That data from the regulatory stability submission section shows that three freeze thaw cycles do not impact product quality. It is unlikely that this event had any impact on product quality.

Partial thawing and re-freezing can result in the formation of concentration gradients within the DS which are mitigated upon mixing prior to DP fill. The maximum temperature reached was -8.58°C. This temperature is not high enough to denature proteins and alter tertiary structure. The DS was released for further processing as this event was unlikely to have impact the product quality of the DS or DP.

QE- 022373: A temperature excursion occurred during the routine shipment of Fasenra (benralizumab) Drug Substance (DS) batch LA2735S3 from FMC to SBC. At the very beginning of the shipment of the batch, there was a temperature spike. The shipment took less than three (3) days (longest weblogger recorded time of 2 days, 17 hours and 32 minutes), which is one (1) day shorter than the expected four (4) day duration. The temperature monitoring devices recorded temperatures of 20.83 °C and 20.22°C.

The shipment was packed out per SOP-0106498: *Storage and Shipment of Frozen Bulk Drug Substance (BDS) in Bags*, which requires that the product load is retrieved from the storage location and moved to the KTM shipper in ≤ 25 minutes. As per the Frozen BDS Material Transfer Sheet, the time removed from-40°C for labeling occurred at 1536, 24Oct2022 and was back in the -40°C storage at 1546, 24Oct2022. Therefore, it was recommended that Fasenra (benralizumab) Drug Substance (DS) batch LA2735S3 be released for forward processing. The 10 minute (worst case) recorded temperature spike is expected as part of the product load packaging process and was well within the allowable time (≤ 25 minutes) outside of -40°C storage.

QE-059329: DS shipped from FMC, during this reporting period. Based on the investigation, the root cause was determined to be Material -> Internal Product / Material Controls -> Product / Material Handling Controls as the temperature excursion was caused by the SSM being removed from the -40°C cold room to be placed in the KTM shipper during the shipping process.

There was no expected impact to the product quality or patient safety related to Fasenra (benralizumab, MEDI-563) 130 mg/mL DS batches TA2010 and PT3520, as the temperature excursions were 20 minutes each. Although there was no supportable data in S Life (Storage Life Management System), the excursion is supportable per REP-0075640 “Time Out of Frozen (TOF) for benralizumab Bulk Drug Substance in Celsius Pak Bags,” which has the recommended TOF parameter defined for frozen benralizumab (Fasenra, MEDI-563 and 01P003) BDS as ≤ 25 minutes. In conclusion the batches were concluded to have no impact due to this temperature excursion.

16 REFERENCES AND ENCLOSURES

References:

REP-0238868, *VX-710078-PVP-R9: Continued Process Verification Stage 3a Summary Report for Benralizumab Drug Substance Manufactured at the 15,000L and 2,500L scales at FMC During the Review Period of November 2022 through November 2023*

REP-0239373, *VX-710078-PVP-R10*: *Continued Process Verification Stage 3b Summary Report for Benralizumab Formulated Bulk Manufactured at the 15,000L and 2,500L scales at FMC for Review Period of November 2022 through November 2023*

REP-0402687: *FASENRA (Benralizumab) Product Quality Review (PQR) Annual Stability Report for 2023*

Enclosures:

16.1 Appendix 1: 16-1 Appendix 1 – Drug Substance Release Data

16.2 Appendix 2: 16-2 Appendix 2 – Final Bulk Release Data

16.3 Appendix 3: 16-3 Appendix 3 – Drug Product Release Data

VERSION HISTORY

Version	Comments
1.0	New document

16.1 Appendix 1 - Drug Substance Release Data

Table 16-1 Release Testing and Results for Commercial Drug Substance Batches

		Batch Date of Manufacture									
Test (unit)		**PT3323 05Feb2023**	**TA2833 19Mar2023**	**TA2159 23Feb2023**	**PN2232 19Dec2022**	**PN2271 24Dec2022**	**PN2272 29Dec2022**	**PT3520 11Feb2023**	**TA2010 17Feb2023**	**TA2351 01Mar2023**	**TA2831 07Mar2023**
Appearance - Clarity		Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets
Appearance - Color		Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets
Appearance – Visible Particles		Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets
Osmolality (mOsm/kg)		372	368	379	357	365	352	372	378	380	379
pH		5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9
Total Protein (mg/mL)		132	131	129	134	143	128	131	130	132	132
HPSEC	% Major product peak	99.6	99.7	99.7	99.7	99.7	99.8	99.7	99.7	99.7	99.7
	% Aggregate	0.3	0.2	0.3	0.2	0.2	0.2	0.3	0.3	0.3	0.3
	% Fragment	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	0.1	<0.1	<0.1
Peptide Mapping		Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563

		Batch Date of Manufacture									
Test (unit)		**PT3323 05Feb2023**	**TA2833 19Mar2023**	**TA2159 23Feb2023**	**PN2232 19Dec2022**	**PN2271 24Dec2022**	**PN2272 29Dec2022**	**PT3520 11Feb2023**	**TA2010 17Feb2023**	**TA2351 01Mar2023**	**TA2831 07Mar2023**
cIEF – Charge Heterogeneity	% Main peak	66	68	69	69	69	69	67	66	67	67
	% Total acidic peaks	20	17	17	17	17	17	19	19	17	18
	% Total basic peaks	14	15	14	14	13	14	14	16	16	15
Reducing Gel Electrophor-esis	Area % purity of heavy + light chain peaks	97.3	97.9	98.0	97.4	97.5	96.9	97.5	97.4	97.4	97.7
	% Total Impurities	2.7	<2.2	<2.2	2.7	2.5	3.1	2.5	2.7	2.7	2.4
Non-Reducing Gel Electrophor-esis	% Major product peak	98.7	98.8	98.6	98.8	98.7	98.7	98.6	98.5	98.4	98.5
	% Total impurities	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5
Reduced CE-SDS	Area % purity of heavy + light chain peaks	97.1	97.0	97.2	96.8	97.0	97.0	97.0	96.9	97.0	97.0
	% Total impurities	2.9	3.0	2.8	3.2	3.0	3.0	3.0	3.1	3.0	3.0

		Batch Date of Manufacture									
Test (unit)		**PT3323 05Feb2023**	**TA2833 19Mar2023**	**TA2159 23Feb2023**	**PN2232 19Dec2022**	**PN2271 24Dec2022**	**PN2272 29Dec2022**	**PT3520 11Feb2023**	**TA2010 17Feb2023**	**TA2351 01Mar2023**	**TA2831 07Mar2023**
Non-Reduced CE-SDS	% Major product peak	97.5	97.4	97.6	97.5	97.5	97.5	97.6	97.4	97.2	97.2
	% Total impurities	2.5	2.6	2.4	2.5	2.5	2.5	2.4	2.6	2.8	2.8
Reporter Gene Bioassay (% Reference Standard Activity)		89	99	89	95	89	88	86	96	83	84
Host Cell Proteins by 96-well (ng/mg protein)		<4	<4	<4	<4	<3	<4	<4	<4	<4	<4
Host Cell Proteins by Gyrolab (ng/mg protein)		<11	<11	<12	<11	<10	<12	<11	<12	<11	<11
Endotoxin (LAL) (EU/mg protein)		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Bioburden (CFU / 10 mL)		0	0	0	0	0	0	0	0	0	0

Results have been reviewed against Master Specification SPEC-0123447 (0409M). All results met acceptance criteria.

16.2 Appendix 2 - Final Bulk Release Data

Table 16-2 Release Testing and Results for Commercial Final Bulk Batches

		Batch Date of Manufacture					
Test (unit)		**[1]PB2290 18Feb2022**	**[1]PB2290W 18Feb2022**	**TB2315 18Feb2023**	**TB3196 19Feb2023**	**TB3197 20Feb2023**	**TB3198 21Feb2023**
Appearance - Clarity		Meets		Meets	Meets	Meets	Meets
Appearance - Color		Meets		Meets	Meets	Meets	Meets
Appearance - Visible Particles		Meets		Meets	Meets	Meets	Meets
Osmolality (mOsm/kg)		310		313	316	319	319
pH		6.0		5.9	5.9	5.9	5.9
Total Protein (mg/mL)		29.2		29.8	29.8	29.8	29.8
HPSEC	% Major product peak	99.8		99.8	99.8	99.8	99.8
	% Aggregate	0.2		0.2	0.2	0.2	0.2
	% Fragment	< 0.1		0.1	0.1	0.1	0.1
Lateral Flow Identity		Positive for MEDI-563		Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563	Positive for MEDI-563

		Batch Date of Manufacture					
Test (unit)		**[1]PB2290 18Feb2022**	**[1]PB2290W 18Feb2022**	**TB2315 18Feb2023**	**TB3196 19Feb2023**	**TB3197 20Feb2023**	**TB3198 21Feb2023**
cIEF – Charge Hetero-geneity	% Main peak	70		70	69	69	69
	% Total acidic peaks	17		17	17	17	17
	% Total basic peaks	13		13	14	14	14
Reducing Gel Electro-phoresis	Area % purity of heavy + light chain peaks	97.8		97.8	97.9	97.4	96.8
	% Total impurities	2.2		2.3	< 2.2	2.6	3.2
Non-Reducing Gel Electro-phoresis	% Major product peak	98.8		98.4	98.4	98.5	98.6
	% Frag-ment	< 2.5		< 2.5	< 2.5	<2.5	<2.5
Reduced CE-SDS	Area % purity of heavy + light chain peaks	96.9		97.0	96.9	97.0	97.0
	% Total impurities	3.1		3.0	3.1	3.0	3.0

		Batch Date of Manufacture					
Test (unit)		**[1]PB2290 18Feb2022**	**[1]PB2290W 18Feb2022**	**TB2315 18Feb2023**	**TB3196 19Feb2023**	**TB3197 20Feb2023**	**TB3198 21Feb2023**
Non-Reduced CE-SDS	% Major product peak	97.5		97.7	97.8	97.6	97.7
	% Total impurities	2.5		2.3	2.2	2.4	2.3
Reporter Gene Bioassay (% Reference Standard Activity)		87		94	92	94	102
Polysorbate 20 (%)		[1]0.003	[1]0.006	0.005	0.004	0.004	0.004
			[1]0.006				
			[1]0.006				
			[1]0.006				
			[1]0.006				
Endotoxin (LAL) (EU/mg protein)		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Bioburden (CFU/10 mL)		0	0	0	0	0	0

[1]Note: Refer to deviation TW 259401 (reference the previous PR).

Results have been reviewed against Master Specification SPEC-0123513 (0410M). All results met acceptance criteria.

16.3 Appendix 3 – Drug Product Release Data

Table 16-3 Release Testing and Results for Commercial Drug Product – PFS-SA Batches

		Batch Date of Manufacture									
Test (unit)		**010F22 18Sep2022**	**017J22 19Sep2022**	**006C23 13Apr2023**	**007C23 15Apr2023**	**008C23 23May2023**	**009F22 19Nov2022**	**011F22 11Dec2022**	**012F22 17Nov2022**	**029E23 24May2023**	**030A23 21Feb2023**
Appearance - Clarity		Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets
Appearance - Color		Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets
Appearance – Visible Particles: Beginning		Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets
Appearance – Visible Particles: Middle		Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets
Appearance – Visible Particles: End		Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets	Meets
Osmolality (mOsm/kg)		311	313	315	311	319	326	314	312	318	309
pH		5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9
Total Protein (mg/mL)		29.7	29.1	29.5	29.3	29.5	29.8	29.8	29.4	29.5	29.1
Sub-Visible Particles (particles/ container)	Particles per container ≥ 10µm	29	21	39	12	32	87	54	15	11	172
	Particles per container ≥ 25µm	<4	<4	<4	<4	<4	<4	4	<4	<4	<4

		Batch Date of Manufacture									
Test (unit)		**010F22 18Sep2022**	**017J22 19Sep2022**	**006C23 13Apr2023**	**007C23 15Apr2023**	**008C23 23May2023**	**009F22 19Nov2022**	**011F22 11Dec2022**	**012F22 17Nov2022**	**029E23 24May2023**	**030A23 21Feb2023**
HPSEC	% Major product peak	99.7	99.7	99.6	99.6	99.7	99.6	99.7	99.7	99.7	99.7
	% Aggregate	0.2	0.2	0.3	0.3	0.2	0.3	0.2	0.2	0.2	0.3
	% Fragment	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
cIEF – Charge Hetero-geneity	% Main peak	69	71	64	65	66	63	70	69	67	70
	% Total acidic peaks	18	17	20	20	18	21	17	19	18	17
	% Total basic peaks	13	12	16	15	16	16	13	13	16	13
Reducing Gel Electrophor-esis	Area % purity of heavy + light chain peaks	97.6	97.4	96.9	97.5	97.1	97.8	97.6	97.6	97.1	96.9
	% Total Impurities	2.4	2.7	3.1	2.6	2.9	2.3	2.5	2.5	2.9	3.2
Non-Reducing Gel Electrophor-esis	% Major product peak	98.7	98.7	98.2	98.2	98.6	98.0	98.7	98.1	98.6	98.4
	% Total impurities	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5
Reduced CE-SDS	Area % purity of heavy + light chain peaks	96.8	96.9	96.9	96.9	96.9	96.8	96.9	96.9	96.8	97.0
	% Total impurities	3.2	3.1	3.1	3.1	3.1	3.2	3.1	3.1	3.2	3.0
Non-Reduced CE-SDS	% Major product peak	97.4	97.3	96.9	97.1	97.3	96.9	97.3	97.2	97.4	97.2
	% Total impurities	2.6	2.7	3.1	2.9	2.7	3.1	2.7	2.8	2.6	2.8
Reporter Gene Bioassay (% Reference Standard Activity)		99	96	99	103	99	98	102	97	93	93

	Batch Date of Manufacture									
Test (unit)	**010F22 18Sep2022**	**017J22 19Sep2022**	**006C23 13Apr2023**	**007C23 15Apr2023**	**008C23 23May2023**	**009F22 19Nov2022**	**011F22 11Dec2022**	**012F22 17Nov2022**	**029E23 24May2023**	**030A23 21Feb2023**
Polysorbate 20 (%)	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Endotoxin (LAL), Beginning (EU/mg protein)	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Endotoxin (LAL), Middle (EU/mg protein)	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03
Endotoxin (LAL), End (EU/mg protein)	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03

Results have been reviewed against Master Specification SPEC-0123448 (0411M). All results met acceptance criteria.

Document Approvals

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