Medicines & Healthcare products Regulatory Agency

MHRA

INSPECTION REPORT

ADVENT BIOSERVICES LTD

SAWSTON BUSINESS PARK

SAWSTON

CAMBRIDGE

CB22 3JG

UNITED KINGDOM

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: First routine inspection and MIA application

Licence or Reference Number: MIA 54923, MIA(IMP) 54923, MS 54923

Licence Holder/Applicant: ADVENT BIOSERVICES LTD

Details of Product(s)/ Clinical trials/Studies: [redacted]

Activities carried out by company:	**Y/N**
Manufacture of Active Ingredients	N
Manufacture of Finished Medicinal Products – Non sterile	N
Manufacture of Finished Medicinal Products - Sterile	Y
Manufacture of Finished Medicinal Products - Biologicals	Y
Manufacture of Intermediate or Bulk	Y
Packaging – Primary	Y
Packaging – Secondary	Y
Importing	N
Laboratory Testing	Y
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	Y
Broker	N
Other: *Specials and Advanced Therapy Medicinal Products*	Y

Name and Address of site(s) inspected (if different to cover):

ADVENT BIOSERVICES LTD
SAWSTON BUSINESS PARK
SAWSTON
CAMBRIDGE
CB22 3JG
UNITED KINGDOM

Site Contact: [redacted]

Date(s) of Inspection: 11 to 13 October 2022 and remote inspection 07 February 2023

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

Case Folder References: Insp GMP/IMP 54923/21898763-0003

Section B General Introduction

B1 Background information

Advent Bioservices Ltd occupies a site on the Sawston Business Park and currently employs approximately 58 staff to manufacture Advanced Therapy Medicinal Products (ATMPs) and "Specials". The site currently manufactures [redacted] product. The MIA(IMP) and MS licences were granted in December 2021. The site also holds an HTA licence for the import, storage and distribution of tissues and cells.

Previous Inspection Date(s): 11 to 14 October 2021

Previous Inspectors: [redacted]

B2 Inspected Areas

Introductions, site overview, changes.
Quality Systems: Deviations, CAPAs, Change Control, Validation, Product Recall, batch record review and QP release
Training, Self-inspection, Distribution
Supplier assurance, TSE compliance, outsourced activities
QC analytical controls.
Environmental monitoring and sterility assurance
Facility Tours: warehouse, cryogenic storage, manufacturing suites.
Remote inspection 07/02/23: QP release of licensed products, secondary packaging controls, distribution

Limitations / exclusions to inspected areas

Self-inspection

B3 Key Personnel met/contacted during the inspection

Name	Position
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	Version [redacted] / 04 October 2022	Y
Compliance Report	03 October 2022	Y
Comments: It was noted that the site master file had not been updated to reflect intended MIA activities.		

Section C Inspector's Findings

C1 Summary of significant changes

Detailed changes are recorded in the pre-inspection compliance reports held in the case folder.

Changes since previous inspection which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

Introduction of [redacted] for aseptic vial filling.

The site had launched a biobanking service, but this was managed as part of the site HTA licence.

Future planned changes which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

[redacted]

[redacted]

C2 Action taken since the last inspection

Actions from the previous inspection had been completed but were not sufficiently effective. For example, the steps taken to improve processes to protect medicinal products from contamination; this led to a major deficiency.

C3 Starting Materials

General

Supplier approval was governed by [redacted] and [redacted] and controlled via [redacted] Issues were found with supplier management; this was raised as major deficiency D2.2 and was a continuation of issues found in the last inspection. The data within [redacted] was not accurate and the list of suppliers/vendors did not contain sufficient detail such as the actual materials or services provided. The procedure did not consider risks to final product. Deficiencies with specific suppliers are documented in section D2.2.

Autologous starting materials (i.e. human tissues and cells) were obtained from a third party HTA licensed establishment which held a licence for procurement of tissues and cells under the HTA Quality and Safety Regulations.

Compliance with TSE Guidelines

All materials were assessed for TSE risks as required by the site policy [redacted]

API Compliance

Not applicable.

C4 Pharmaceutical Quality System (PQS)

The site undertook quarterly reviews of the PQS including a summary of activities, review and trending of non-conformances, review of change controls, review of risk assessments, document control and audits. There was no evidence that the reviews had been formally accepted and approved. There was no formal process in place for the management of regulatory updates despite this being highlighted in the previous inspection report. A Major deficiency for the PQS was raised.

Deviations

Deviations were managed according to [redacted] and supported by the [redacted] The deviation procedure required the investigation of non-conformances (NCON) to be completed within 30 days, however, this was routinely missed. The procedure lacked guidance on the management of target date extensions and check criteria used during assessment. [redacted] was used to document PQS elements including NCONS but this was not always completed contemporaneously. Several examples of NCON were reviewed during the inspection:

[redacted] related to a pressure drop in the cleanrooms over a weekend. Appropriate actions had been taken and this was linked to a CC for the implementation of a BMS system.

[redacted] related to identical ID labels on two sets of operator broth samples. Appropriate actions were taken; however, no effectiveness check criteria had been defined.

[redacted] related to equipment issued beyond expiry, which was considered acceptable.

[redacted] related to empty final product vials; appropriate investigation and CAPA were not completed.

Change control

Change controls (CC) were managed according to [redacted] The following changes were reviewed:

[redacted] or the removal of sterile welders from [redacted] and [redacted]

[redacted] for the introduction of flow cytometry methodology for [redacted] nto Sawston. Included the flow methods validation report [redacted] Three-month post-implementation review was passed with no issues detected. FMEA in place covering reasonable risks on brief review.

[redacted] for the introduction of the [redacted] into [redacted] grade B cleanroom. Included Installation and qualification of a controlled rate freezer. Change not yet completed.

[redacted] for the creation of additional storage in the Warehouse Controlled temperature area using containers stored on the floor beneath the bottom shelves. Items were already being stored despite an incomplete change control.

[redacted] for the application for an MIA. A gap analysis had been carried out against Eudralex Volume 4 Part 1, Annexes 8, 11,15,16 and 19 and Part 4. An action plan was produced however not all actions had been completed. Further gaps in the requirements for QP release, secondary packaging and control of distribution. This was actioned and a further remote inspection was carried out see section C7.

C5 Personnel

There were 58 personnel employed by Advent Bioservices. Some of these staff were based at [redacted] and did not routinely work at the Sawston site.

Induction training was carried out according to [redacted] with ongoing Training as per [redacted] There were no specified timelines in place for the completion of induction training and no records to confirm that induction had been completed. The site carried out GMP training as part of the induction process; annual GMP training was not any different to the induction GMP and did not include any site specifics or have any assessment of effectiveness.

Deficiencies cited in D2.1.1 suggested that training in operator deportment and gowning was not sufficiently robust. Operators were not required to carry out annual Microbiological training.

Operators were required to be qualified for gowning, transfer of items into the cleanroom and a universal broth test on a 6-monthly basis. In the case of failure staff would re-train and repeat the initial qualification with 3 consecutive runs. A repeat failure should be considered by the line manager, however, in the case of a failed training plan for an operator [redacted] the operator was only retrained and allowed to retake the assessment. The retraining consisted of the same training and questions as the previous retraining.

C6 Premises and Equipment

The site at Sawston comprised a single building containing two separate GMP suites with grade D/C/B classified and unclassified areas and a QC laboratory. In addition, there was a warehouse, a room containing -80°C freezers, a cryogenic storage unit and general office area.

The site generated its own liquid nitrogen; this system was not reviewed during the inspection.

The site maintained a list of critical equipment indicating the equipment's impact and risk to product along with current validation status. Details of required servicing and maintenance were managed through the asset module on [redacted]

Equipment calibration and maintenance records were not always detailed enough to allow confirmation of the checks carried out. The calibration record for pipette [redacted] carried out on 10 November 2022 was reviewed without comment.

The site validation master plan [redacted] described the approach to qualification and validation.

The qualification of the facility that had been outstanding at the previous inspection in October 2021 was reviewed. PQ Environmental Monitoring (EM) [redacted] did not ensure that all recommended EM points were included into routine sessional plates within [redacted] or production forms such as [redacted] The report included averaging of results, 2 and 3 standard deviation calculations for Grade B and A EMs, which were not applicable or appropriate for consideration. The Validation Report [redacted] for the Hotel Suites [redacted] cleanrooms including AHU set-back had not been formally reviewed or approved by appropriate personnel, for example, the Head of Production.

The qualification of freezer [redacted] was reviewed and it was found that the alarm delay had been set at 20 minutes, longer than the documented recovery time of 13 minutes. This was a repeat deficiency showing there remained a failure for qualification activities to direct operational procedures.

There was no process in place to carry out routine physical assessments of any frost or ice build-up within the Ultra-Low freezers, to ensure that door seals and probes were not impacted.

The most recent temperature mapping records for fridge [redacted], used to store reagents for manufacturing, were reviewed. The loaded configuration used during the mapping did not match the actual use of the fridge seen during inspection in that several hard plastic crates were within the fridge. The crates had been put in place to protect specific media from the light, however,

two bottles of medium requiring protection were located outside of the crates. There was no comment on the suitability of routine monitoring sensors in the equipment based on the mapping data. A sign on the front of the fridge stated that there were 2 monitoring sensors in place but there was only actually one sensor within the fridge.

Smoke studies carried out in grade B and C cleanrooms in January 2022 were reviewed. The video recordings were not clear enough to allow a clear assessment but had been accepted. There were no comments made on apparent air travelling upwards in grade C or evidence of airflows being impacted or blocked by trolley tables next to air extracts.

C7 Documentation

Documentation was controlled via [redacted] the site's electronic QMS, and the quality of documentation was generally acceptable.

There were several data integrity issues highlighted particularly in the quality control laboratory. These are listed in D3.1.2 and demonstrated a lack of control of data on electronic equipment and PCs.

Quality review and release of IMPs were assessed, a deficiency was raised.

There were some gaps in the documentation of processes to support MIA activities in particular in QP release, secondary packaging control and distribution oversight for licensed medicinal products, a Major deficiency was raised. The responses to these findings were covered in a remote inspection carried out on 07 February 2023 as follows:

<u>QP release of licensed products</u>

The updated procedure [redacted] and associated QP Certificate [redacted] were reviewed and found to be satisfactory.

<u>Secondary packaging</u>

The procedure [redacted] and associated procedures did not provide sufficient control over secondary packaging. For example, they did not consider all aspects required to ensure that artwork and proofing processes (inc. version controls) would be managed appropriately, and that receipt checks for components would be carried out correctly (inc. against appropriate standards).

<u>Distribution</u>

The site had carried out a gap analysis against GDP requirements. A new SOP [redacted] had been put in place.

C8 Production

Activities in production were viewed during the inspection either by direct observation from the grade C areas or by the viewing of CCTV.

The production of [redacted] comprised 3 steps; [redacted]

Processing steps that required aseptic manipulation were carried out in microbiological safety cabinets monitored to grade A within a grade B surround room.

Activities that should have been designed and carried out to minimise the risk of contamination were found to be lacking and a major deficiency was raised in D2.1. Specifically gowning procedures were not appropriately designed as they included the donning of sterile gowns in grade C increasing the risk of contamination of the gowns. Operators did not wear goggles and gloves in a manner that reduced opportunities for contamination and glove sanitisation was poor. The transfer of materials into the cleanroom and cabinets did not ensure contamination risks were sufficiently reduced; improvements in the approach to spray and wipe techniques were required.

Separate media fills were carried out for the [redacted] process and the generation of [redacted] through to final product process. Each type of media fill had an associated justification document to determine the appropriate way to mimic the production process. The media fill procedure for [redacted] had not been increased from a maximum fill of [redacted] cryovials in light of a released batch that produced [redacted] cryovials.

The batch review and release procedures were reviewed. The QP release activities did not have an associated checklist or similar mechanism to demonstrate that the QP had fulfilled all of their responsibilities.

C9 Quality Control

The site carried out a number of QC activities including measurements such as cell counting, cell viability, cell surface marker expression and cell identity by flow cytometry and sterility by [redacted] Samples were logged into the laboratory and given a unique id. Testing required was documented onto a test request form.

The use of equipment was generally well controlled, however, some areas for improvement were identified, including data management (see deficiency). The procedure for the flow cytometer did not consider the tests on samples run between a QC pass and a QC failure to ensure all results were valid. Although a backlit colony counter had been purchased it was not yet being used to enumerate microbial counts.

Deviation [redacted] related to a failed Spreadsheet validation linked to Endotoxin testing was reviewed. This did not clearly define why the failure occurred or what actions had been taken, but did include confirmation that all issues were corrected prior to formal implementation.

The Out of Specification (OOS) and atypical results [redacted] was the same as noted in the previous inspection. No analytical OOS reports had been raised, with only [redacted] elated to a growth promotion test failure; this was not appropriately detailed.

C10 Outsourced Activities

Oversight of contract laboratory [redacted] for [redacted] was assessed during the review of supplier and vendor management. Deficiencies were noted, refer to the Major deficiency.

C11 Complaints and Product Recall

The site had a [redacted] and had received no complaints to date. The recall part of the procedure was deficient as it did not describe the procedure required to communicate with Clinical Trial Sponsors in case of a recall or require that the company contact all receiving facilities of products. The last mock recall was found to be incomplete in terms of reconciliation and communication.

C12 Self Inspection

Self-inspection was not covered in detail during this inspection, but the site did have an audit schedule in place.

C13 Distribution and shipment

The site had not released any IMPs yet but had released [redacted] batches under the MS licence since the last inspection.

C14 Questions raised by the Assessors in relation to the assessment of a marketing authorisation

None

C15 Annexes attached

Annex 1 site risk rating

Section D

Note section D has been listed as part a and b to cover the findings at the onsite inspection on 11-13 October 2022 and the remote inspection on 07 February 2023.

Section D a List of Deficiencies from onsite inspection 11-13 October 2022

D1 Critical

None

D2 Major

2.1 Systems and processes to maintain appropriate sterility assurance of aseptically prepared products were deficient as evidenced by:

2.1.1 Operator gowning and deportment were deficient in that:

2.1.1.1 Sterilised clothing was not worn in such a way as to protect the product from contamination, as sterile gowning was donned in the Grade C change; hence it was not handled in such a way that it did not gather additional contaminants that could later be shed.

2.1.1.2 Operators were observed, via CCTV footage, in the grade B area with goggles resting on their foreheads rather than covering their eyes and exposed skin.

2.1.1.3 Operators did not sanitise their gloved hands with sufficient frequency nor consistently prior to reaching into the Grade A laminar airflow cabinet.

2.1.1.4 Operators were observed to be wearing ill-fitting gloves when in the grade B area, where the gloves were not extended up the arms and were gathered in folds on the operator's arms.

2.1.1.5 Clean area clothing and contamination controls were inappropriate, as evidenced by sterile outer gloves being changed in the grade B manufacturing area rather than the change area.

2.1.2 The transfer of materials into the cleanroom and laminar airflow cabinets was not carried out in a manner to minimise the risk of contamination:

2.1.2.1 Polythene bags and sleeves were used without any consideration of contamination on the inner surface of the bags; this included bagged pipettes from the warehouse and [redacted] ransport boxes from external sites, as well as batch paperwork from the offices.

2.1.2.2 There was no justification for the lack of sporicidal treatment of various surfaces such as the boxes used to transport [redacted] material and caps/necks of reagent bottles covered in shrink wrap.

2.1.2.3 Non-aseptic items such as general office-supply ballpoint pens and batch record paperwork, were not sterilised prior to entry into the grade B area.

2.1.2.4 Materials and components were transferred from cabinet [redacted] in [redacted] into the adjacent cabinet [redacted] for further processing without any sanitisation linked to the transit through the Grade B area.

2.1.3 There was no clearly defined process for the use of wipes (sporicidal or IPA); operators were observed to use individual wipes for extended periods and did not ensure sufficient wetting or use techniques such as folding to ensure different sections of the wipes were used.

2.1.4 Activities in clean areas were not kept to a minimum, as evidenced by the inspections and controls that were not conducted outside the clean areas.

2.1.5 Surface sanitisation within the Grade B area was seen via CCTV to be carried out at excessive speed, increasing the risk of introducing contamination from the operators.

2.1.6 Environmental Monitoring plates were not consistently opened at an appropriate time to cover the set up operations and initial stages of processing within the grade B and A areas.

2.1.7 Smoke studies carried out in January 2022 were deficient in that:

2.1.7.1 The results were accepted despite the fact that the video recordings did not allow a clear assessment of airflow patterns.

2.1.7.2 Evidence of air travelling upwards in grade C had not been appropriately assessed.

2.1.7.3 Evidence of airflows being impacted or blocked by trolley tables next to air extracts had not been appropriately assessed.

2.1.8 Operator qualification was deficient in that:

2.1.8.1 No extra measures were taken in the case of a repeat failure for a gowning qualification process.

2.1.8.2 There was no robust system to ensure that operators who were not qualified for gowning or failed gowning qualification did not access the cleanrooms, for example use of the access control systems.

2.1.8.3 Qualification for transfer of items via environmental monitoring (EM) assessment did not ensure that samples used were exposed to an applicable level of bioburden to ensure that the transfer process challenge was appropriate, e.g. pre-EM results were 0 CFU.

Reference: EU GMP Part 4: 3.15, 3.16, 3.23, 3.24, 3.25, 3.27, 3.29, 3.30, 3.31, 4.57, 4.58, 4.62, 9.32, 9.36, 9.37, 9.50, 9.52.

The supply of unlicensed medicinal products 'specials', MHRA guidance note 14. https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials

2.2 Supplier and Vendor Management was deficient in that:

2.2.1 The overall Quality Risk Management (QRM) approach to supplier and vendor management was not consistently defined and recorded, which was a continuation of a deficiency raised during the MHRA inspection in October 2021.

2.2.2 There was no formal system in place to manage and ensure appropriate oversight of status of suppliers and vendors, with data within [redacted] not accurate and not reflective of actual assessment details.

2.2.3 The procedure did not appropriately assess the risk to final product from the suppliers of products or services; for example, the sterilisation status of cryovials, and hence criticality was not considered.

2.2.4 The Supplier / Vendor Management list did not define the materials or services provided in appropriate detail to ensure that non-approved material types would not be sourced.

2.2.5 Records for [redacted] contract testing laboratory, were deficient in that:

2.2.5.1 The 2018 supplier assessment record did not clearly identify that this record was from [redacted] quality system (current CMO site) and there was no justification for acceptance of the negative responses for GAMP 5 / EU GMP Annex 11 compliance, Business Continuity or Disaster Recovery processes.

2.2.5.2 The AdventBio Supplier Evaluation from June 2021 was focused on consumables and reagents and did not include relevant sections or focus on contract testing services.

2.2.5.3 The audit report from December 2021 did not include any detail to confirm testing check processes or data retention or integrity.

2.2.6 Records for [redacted] did not clearly define the relationship with the company, with respect to materials supplied and business ownership of [redacted] (which was part of the larger [redacted] organisation).

2.2.7 No actions or change controls were raised following the Supplier Requalification Self Inspection report [redacted] completed in March 2022, where multiple discrepancies were noted with respect to questionnaire and audit requirements, as well as technical agreements for suppliers and vendors.

2.2.8 The management of TSA plate supplies via CC [redacted] elating to transitioning to an alternative TSA plate supplier was deficient in that:

2.2.8.1 There was no justification for the continued use of a batch of [redacted] plates following multiple QC OOS growth promotion testing results for subsequent batches,

2.2.8.2 There was no justification for a 6-month implementation period for the associated update to the Environmental Monitoring SOP and withdrawal of Material Specifications for [redacted] supplied TSA plates.

Reference: EU GMP Part 4: 1.24 (iii), 1.24 (vi), 2.31, 6.16, 7.10, 7.14, 7.15, 9.75, 13.11.

The supply of unlicensed medicinal products 'specials', MHRA guidance note 14. https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials

2.3 Pharmaceutical Quality Systems (PQS) were deficient in that:

2.3.1 No quarterly quality reports which covered all aspects of the PQS had been formally accepted and approved.

2.3.2 Management of Non-Conformances (NCONs) [redacted] and [redacted] processes were deficient in that:

2.3.2.1 There was no oversight to ensure that NCONs were raised and investigated in a timely manner within the procedural requirement of 30 days; over 50% of NCONs were not completed in 30 days, and site reviews only assessed records against a 60-day timeline.

2.3.2.2 There was no process to manage deadline extensions.

2.3.2.3 There was no formal requirement to define when effectiveness checks were required, nor define check criteria prior to any assessment.

2.3.2.4 Details within [redacted] entries were retrospectively completed, with no contemporaneous record keeping.

2.3.2.5 [redacted] relating to empty final product vials was deficient in that:

2.3.2.5.1 Actions or full assessments for each potential root cause were not defined or recorded; for example, those linked to time pressures and crowded laminar airflow cabinet

2.3.2.5.2 Actions linked to updates to the Master BMR template were 6 weeks overdue, and the draft document submitted for approval did not ensure a consistent and robust approach to product reconciliation.

2.3.3 There was no formal process in place to manage regulatory updates.

2.3.4 The systems and [redacted] to manage recall of defective product was deficient in that:

2.3.4.1 The SOP did not address communication of recall requirements with Clinical Trial Sponsors.

2.3.4.2 The SOP did not require that the company contact all receiving facilities of products.

2.3.4.3 The mock recall challenge carried out in November 2021 did not provide any details of the reconciliation of the cryovials defined as non-sterile and did not provide any confirmation or compliance that receiving sites could be contacted.

Reference: EU GMP Part 4: 1.23, 1.24 (vii), 1.25, 9.14, 14.15, 14.20, 14.22, 14.26.

2.4 Validation controls were deficient in that:

2.4.1 Qualification activities did not automatically direct operational procedures. For example, there remained an arbitrary alarm delay on the -80°C freezers of 20 minutes however, freezer [redacted] for example, was demonstrated to recover from an out of limit temperature within 13 minutes during the qualification activities.

2.4.1.1 This was a repeated deficiency, despite site reassessment after the October 2021 inspection, which did not address this matter appropriately.

2.4.2 The PQ Environmental Monitoring (EM) [redacted] process was deficient in that:

2.4.2.1 The report did not ensure that all recommended EM points were included into routine sessional plates within [redacted] or production forms such as [redacted] for example, the Grade B change was not included in sessional requirements.

2.4.2.2 The report included averaging of results, 2 and 3 standard deviation calculations for Grade B and A EMs, which were not applicable or appropriate for consideration.

2.4.3 The Validation Report [redacted] for the Hotel Suites [redacted] & [redacted] cleanrooms including AHU set-back had not been formally reviewed or approved by appropriate personnel, for example, the Head of Production.

2.4.4 The [redacted] media fill procedure was not amended from a maximum fill of [redacted] cryovials despite the manufacture and release of a batch of [redacted] product under the MS licence in July 22 that was manufactured from a [redacted] that produced [redacted] cryovials.

2.4.5 Results which did not meet the pre-defined acceptance criteria in qualification activities were not recorded as deviations and investigated appropriately. For example, failures in the operational qualification of the [redacted] vial filling equipment.

2.4.6 There was no formal procedure in place to use temperature mapping data to ensure the correct siting of routine sensors.

Reference: EU GMP Part 4: 1.24(iii), 4.43, 4.44, 4.59, 4.67, 9.55, 10.10, 10.16

The supply of unlicensed medicinal products 'specials', MHRA guidance note 14. https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials

2.5 Processes to support MIA activities were not in place as evidenced by:

2.5.1 There was no process or system in place to demonstrate that the Qualified Person had fulfilled all their responsibilities.

2.5.2 There was no QP certificate template for licensed medicines.

2.5.3 There were no procedures in place for the control of secondary packaging.

2.5.4 There were no procedures in place to ensure appropriate distribution oversight and control the supply of licensed medicinal products.

Reference: EU GMP Part 4: 12.12(iii), 6.20(x), 11.27, 11.30, 11.34,

EU GMP C1.4(xvi), 1.8 (ix).

D3 Others

3.1 Quality Control processes and Data Integrity controls were deficient in that:

3.1.1 The Out of Specification report [redacted] relating to a growth promotion test failure and associated records were deficient in that:

3.1.1.1 The Phase 1 report was not generated in a timely manner (two months after the issue) and the Phase 1B report did not provide any justification for the hypothesis testing approach relating to increased temperature exposure,

3.1.1.2 No final disposition was recorded for impacted batches of TSA plates within the OOS report, the material receipt records for TSA batch [redacted] were not completed with any disposition information and there was no information on the final physical disposition.

3.1.2 Data integrity controls within the QC laboratory were deficient in that:

3.1.2.1 There was no justification for monthly manual back-ups

3.1.2.2 No restore challenges were periodically carried out to ensure that backed up data remained accessible

3.1.2.3 QC PCs included the software [redacted] which has the potential to be used to change or adapt pdf reports

3.1.2.4 It was not clear if test record files that were directly saved to server locations could be overwritten or deleted.

3.1.2.5 Equipment date and time were not locked such that users could not alter these.

3.1.2.6 There was no check on the transfer of environmental monitoring raw data to the spreadsheet used for trending purposes.

3.1.2.7 QC-Check reports for the [redacted] were not consistently annotated and were not all printed out and filed as required.

3.1.3 Annual calibration and maintenance records were not reflective of detail or checks carried out and did not provide confirmation of e.g. linearity, accuracy or range.

3.1.4 There was insufficient monitoring in place to ensure appropriate performance of equipment used in the QC laboratory. For example, there were no procedural requirements to run positive controls during routine testing on the [redacted] machine.

3.1.5 There was no consideration of the validity of tests run between a QC pass and a QC failure on the flow cytometer.

3.1.6 Opened expiry dates were not applied to reagents as required by [redacted]

3.1.7 There was no justification for the failure to use a backlit colony counter for the accurate enumeration of microbial counts from EM plates.

Reference: EU GMP Part 4: 1.24(iii), 5.17(i), 6.13, 6.27, 6.28(iv), 12.10, 12.31, 12.33.

3.2 The controls and maintenance of temperature-controlled storage areas were deficient in that:

3.2.1 In the case of fridge [redacted] used to store reagents for manufacturing:

3.2.1.1 The label on the front of the fridge indicated that there were two monitoring sensors in place when there was only a single sensor in the fridge.

3.2.1.2 The fridge was not loaded in keeping with the temperature mapping study carried out in Jan 22. The mapping activity only included tissue culture flasks whereas the fridge was loaded with large, lidded plastic crates containing media.

3.2.1.3 There were bottles of media stored in the fridge that were not protected from the light as required by the Material Specification (MTS).

3.2.2 There was no process in place to carry out routine physical assessments of any frost or ice build-up within the Ultra-Low freezers, to ensure that door seals and probes were not impacted.

3.2.3 No deviation had been raised to record or address the one-hour time discrepancy on the monitoring system for the freezers and fridges.

3.2.4 Items were stored in crates on the warehouse floor despite the fact that [redacted] to facilitate this change had not been approved.

Reference: EU GMP Part 4: 1.24(ii), 4.67, 5.17(i), 6.27

3.3 The processes to manage the release of investigational medicinal products (IMPs) were deficient in that:

3.3.1 The QP certificate template for IMPs was not in accordance with EU GMP Annex 13, nor referenced the correct UK legislation.

3.3.2 There was no process or system in place to demonstrate evidence that the Qualified Person had fulfilled all their responsibilities, via the QP release procedure nor associated checklist.

Reference: EU GMP Part 4: 11.27, 11.29, 11.30

3.4 Training was deficient in that:

3.4.1 There were no records to reflect that all induction training had been completed as per [redacted] and there were no specified timelines for the completion of this stage of training.

3.4.2 There was no difference between Induction GMP training and Annual GMP training, and no assessment of the effectiveness of this training.

3.4.3 Training records for the new Warehouse Technician were not set to ensure that GMP training was marked as a renewable (annual) requirement.

3.4.4 There was no requirement to carry out annual Microbiological training

Reference: EU GMP Part 4: 1.24(1), 3.11, 3.12, 3.14, 3.19

D4 Comments

4.1 The site may be subject to a further inspection, that may be conducted remotely as an office-based inspection, before approval of the MIA licence application.

Section D b List of Deficiencies from remote inspection 07 February 2023

D1 CRITICAL

None

D2 MAJOR

None

D3 OTHERS

D3.1 The procedures in place for the control of secondary packaging were not sufficiently robust. For example, they did not consider all aspects required to ensure that artwork and proofing processes (inc. version controls) would be managed appropriately, and that receipt checks for components would be carried out correctly (inc. against appropriate standards).

Reference: EU GMP Part 4: 6.16, 9.15, 9.16, 12.12(iii)

Section E Site Oversight Mechanism

Site referred or to be monitored by:	Tick (✓)	Referral date	Summary of basis for action
Risk Based Inspection Programme			
Compliance Management Team	✓	November 2022	Referred to CMT
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The deficiencies were presented verbally to those personnel identified in Section B3 and were accepted as presented.

F2 Assessment of response(s) to inspection report

Onsite inspection 11-13 October 2022:
The post inspection letter was sent on 25/10/22. Acceptable responses were received on 01/12/22.

Remote inspection 07/02/23:
The post inspection letter was sent on 08/02/23. Acceptable responses were received on 10/02/23.

F3 Documents or Samples taken

None

F4 Final Conclusion/Recommendation, Comments and Evaluation of Compliance with GMP and GDP

The site operates in general compliance with the requirements of:

Compliance statement	Tick all statements that apply
GMP as required by the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	✓
The Medicines for Human Use (Clinical Trials) Regulations 2004	✓
Regulation 5 of the current Veterinary Medicines Regulations	
Regulation C17 of the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	

and is acceptable for the products in question.

Name of Inspector (s):

Lead Inspector: [redacted] **Date:** 06 March 2023

Accompanying Inspector: [redacted] **Date:** 06 March 2023

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	5	Last inspection:	3
Other deficiencies this inspection:	5*	Last Inspection:	5

*** 1 other deficiency was as a result of the remote inspection carried out on 07/02/23**

(b). Provisional Rating based on Inspection Output (✓ applicable box)

Risk rating level	**Input from current Inspection Findings** (last inspection findings applicable to rating V only)	**Provisional rating – this assessment**	**Final rating last assessment**
0	Serious triggers outside the inspection cycle	[redacted]	
I	Critical finding		
II	>/= 6 Major findings		
III	<6 Major findings		
IV	No critical or Major findings		
V	No critical or Major findings from current or previous inspection and <6 other findings on each.		

(c). Risk Assessment Inputs – discriminatory factors (✓applicable box)

[redacted]	None relevant (default)
	Significant concern over robustness of quality system to retain adequate control
	Significant failures to complete actions to close previous deficiencies raised at the last inspection
	Complex site
	Significant changes reported in Compliance Report
	Significant mitigating factors applied by the site
	Higher risk rating identified by other GxP and considered relevant to the GMP site
	Relevant site cause recalls, notifications to DMRC or rapid alerts since last inspection
	Nature of batch specific variations submitted since the last inspection give concern over the level of control
	Regulatory action related to the site
	Failure to submit interim update and/or failure to notify MHRA of significant change or slippage in commitments from post inspection action plan
	First Inspection by MHRA (does not require counter-signature for RR II)
	Other discriminatory factor (record details and justify below)

(d). Inspectors Comments Related to Discriminatory Factors

[redacted]

(e). Risk Rating Result Incorporating Discriminatory factors (✓ applicable box)

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (✓)
0	Immediate (as soon as practicable)	[redacted]
I	6 monthly	
II	12 months	
III	24 months	
IV	30 months	
V	30 months with 50% reduction in duration of the next inspection	

(f). Basis for risk-based acceptance of specific matters arising during the inspection

[redacted]

(g). GMP or GDP certificate conditioning remarks required as a result of risk-based decisions

[redacted]

(h). Conclusions

[redacted]

(i). Expert/ Operations Manager / Compliance Management Team (CMT) Comments

[redacted]

(j). Confirm Agreed Risk rating following this inspection:

Risk Rating:	Next Inspection target date:
[redacted]	

Notes regarding re-inspection and GMP certificate validity

1. The inspection schedule is based upon risk and resource. This date may change at any time due to factors not pertaining to your site.
2. The GMP certificate does not 'expire' it is provisionally assigned 3 year validity date. For external questions regarding your validity thereafter; please advise that this can be confirmed by contacting the inspectorate at gmpinspectorate@mhra.gov.uk