Medicines & Healthcare products Regulatory Agency

MHRA

INSPECTION REPORT

PHARMARON MANUFACTURING SERVICES (UK) LTD

WINDMILL INDUSTRIAL ESTATE

SHOTTON LANE

CRAMLINGTON

NE23 3JL

UNITED KINGDOM

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine re-inspection against EU GMP Part II

Licence or Reference Number: API 22857

Licence Holder/Applicant: PHARMARON MANUFACTURING SERVICES (UK) LTD (previous site name Aesica Pharmaceuticals Ltd)

Details of Product(s)/ Clinical trials/Studies: Manufacture of APIs by chemical synthesis

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

Name and Address of site(s) inspected (if different to cover):
PHARMARON MANUFACTURING SERVICES (UK) LTD
WINDMILL INDUSTRIAL ESTATE
SHOTTON LANE
CRAMLINGTON
NE23 3JL
UNITED KINGDOM

Site Contact: [redacted]

Date(s) of Inspection: 21st and 22nd Feb 2022 on site and 24th Feb 2022 remotely

Lead Inspector: [redacted]

Accompanying Inspector(s): N/A

Case Folder References: Insp GMP 22857/36790-0008

Section B General Introduction

B1 Background information

The Cramlington site has a long history and through time changed ownership several times.

It was acquired by Boots the Chemist in late 1970's with the first plant [redacted] commissioned in 1983 for [redacted] production. [redacted] plant was commissioned in 1987 for multiproduct production. Boots Pharmaceuticals division was acquired by BASF in 1995 and Cramlington integrated into Knoll Pharmaceuticals as part of acquisition. However, Knoll Pharmaceuticals sold by BASF, Cramlington transferred to BASF Plc, UK Division in the late 90's. Cramlington Site Business was sold as a business to Aesica Pharmaceuticals Limited in September 2004. Cramlington being the original Aesica site. Other manufacturing sites were in the UK (Aesica Queenborough – API and dosage forms site), Germany and Italy. Aesica Business was Acquired by Consort Medical in 2014 and Consort Medical Acquired by Recipharm in 2020. The latest change was acquisition of Cramlington Site (Aesica Pharmaceuticals Limited) by Pharmaron in 2022. The site name changed into Pharmaron Manufacturing Services (UK) Limited. The other Pharmaron sites in the UK were in Hoddesdon and Rushden and held MIA(IMP) 47794.

The Cramlington site manufactured [redacted] for supply as a commercial API and was the holder of CEP for this. Number of other APIs were manufactured under contract. The site presentation contains information which active substance was manufactured in which plant [redacted] and when.

The site holds the [redacted]

Previous Inspection Date(s): 23-24 May 2018

Previous Inspectors: [redacted]

B2 Inspected Areas

Quality Risk Management Policy/systems
Management Review
Product Quality Review
Deviations
Change Control system
Complaints, Returns
Reprocessing
Site Inspection
Goods receipt system, sampling, storage – inc. solids, drums, tankers,
Manufacturing facilities, inc. arrangements for IPCs
Filling, labelling and packaging
Plant cleaning, utilisation log system
Examples of equipment IDs to check calibration/ maintenance
Qualification – equipment, facilities and services
Batch record review
Validation systems and records - process and cleaning
Quality Control
Laboratory Out of Specification system
Sample management
Systems and documents for testing and approval of raw materials, intermediates and finished products, packaging materials

Reference standards Stability testing and retention samples Equipment calibration and daily/weekly checks Retesting QA batch review and release including C of As Maintenance, calibration and service contracts Internal audit procedure and program Training Document control systems Supplier approval and technical agreements TSE/BSE compliance

Limitations / exclusions to inspected areas

There was no manufacture taking place in [redacted] and [redacted] at the time of inspection, preparation in progress. Recall CAPAs Outsourced activities Method validation Environmental monitoring - programme and results Purified Water Distribution and transport – this could be of interest for the next inspection (consider GDP certificate)

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[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	[redacted] Oct 2021	Y
Compliance Report	28 Jan 2022	Y
Comments: The SMF required revision following the recent change of the site name.		

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:

Staff changes; redundancy in 2021

[redacted] introduced for deviations, change controls, complaints, CAPA and audit in 2019

New contract laboratory [redacted] introduced for endotoxin testing on purified water and [redacted] API.

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

None confirmed, but due to acquisition changes are anticipated.

C2 Action taken since the last inspection

The actions arising from the previous inspection had been completed

C3 Starting Materials

General

Previously the supplier assessment was governed by corporate procedure, but it was updated for the site process. It already considered that only if onsite audit was not possible, it could be replaced by the distant assessment. Reassessment of suppliers was done every 3 or 4 years.

The approved supplier list, latest update from 18/02/2022 was reviewed. It contained also contracted services and contracted laboratories such as [redacted] for HPLC, GC, UV/VIS, FTIR; [redacted] used for some specific test. [redacted] was introduced via change control [redacted] raised 24/08/2021, considered minor change. Assessment was done according to the questionnaire for service provider and procedure [redacted] Reassessment required every 3 year (tolerance 25% of that period), monitoring in the meantime via deviation system. See section C9 for deviation.

Compliance with TSE Guidelines

TSE statements were required as part of vendor approval, and thereafter were reviewed during periodic supplier requalification; this was on a sliding scale based on the criticality of the material (e.g. API, registered starting material). If older than 3 years, a new version was requested.

API Compliance

Not applicable for this inspection.

C4 Pharmaceutical Quality System

The site introduced [redacted] in 2019 to cover deviations, CAPA, change control, complaints, and audit management.

Management Review

Records of the Management review were reviewed for December 2021 and annual for year 2021 which included Minutes of Meeting held. Quality trend data was reviewed by the Head of Quality every week, and a monthly report was produced for the management team. The KPI reports per quarter indicated minor issues in delay in closing some records on time during Q3 2021, but Q4 indicated improvement.

Change Control

Change control was managed according to procedure [redacted] dated 21/02/2022. The SOP covered permanent and temporary changes. Temporary instruction could be used only for limited number of batches (usually 3 to 5). Post implementation review was embedded in the process.

Examples reviewed included [redacted] – change to the validation batches of [redacted] and [redacted] – re-introduction of [redacted] – change in progress.

Deviations

Deviations were managed according to the procedure [redacted] dated 06/12/2021. It contained flowchart and was revised following [redacted] implementation. Deviations/ quality events were categorised as atypical, minor, major or critical and full root cause analysis was required for all major and critical.

Examples inspected included:

[redacted] after milling at [redacted] Investigation at [redacted] included also testing and comparison of retained samples from the validation batch, per drums parameters were within qualification and validated range; adjustment done and two drums rejected (for reprocessing), Other passed IPC and final testing on composite sample. [redacted] concluded it is [redacted] material. Investigation at [redacted] couldn't prove the same or find the cause. Investigation was coordinated with the customer who ordered the material.

[redacted] – product shipped to customer in China which was not aware that import couldn't been done from Beijing port, so material had to be sent back and then to Shanghai. Checks done there was no impact or damages, and material was shipped in line with required (no required) temperature conditions.

[redacted] – Batches of product failing EP appearance of solution. Initially OOS recorded on 4 batches but during the investigation of the root cause and bracketing exercise 5 batches were found impacted and rejected. The cause was determined as failure of baffle type, but the further investigation with equipment manufacturer didn't detect cause of this failure. CAPA was determined to replace with different type of baffle on glass reactors. However, the investigation failed to record review of impact to other equipment with the potentially same baffle considering also the usage period and maintenance. CAPA was assigned to person left from E&I and due date 24/01/2022 without extension recorded. This was discussed and management aware of this and need to allocate new person responsible to replace left one.

Corrective and Preventative actions

This was not inspected in detail than via other quality elements such as deviations, complaints,

Product quality reviews

Product quality reviews were prepared according to the procedure [redacted] for all APIs and split by process stages, at the end of each manufacturing campaign or after 12 months of manufacture for extended campaigns. Review had been prepared even if there was no manufacture of API in the period.

Product annual review [redacted] in [redacted] Dec 2018 to Nov 2019 and [redacted] in [redacted] Dec 2019 to Nov 2020 were reviewed. The 2019 PQR was shorter as there was no batch manufactured in this period, but it covered all applicable sections e.g., stability, complaints, change controls, recall, returns. There was one complaint received 2019/1 – [redacted] for black particles. Investigation summary was appropriate. Last re-validation/ re-qualification during the campaign 2018, but conclusion was that it remains in validated state all products Hydrochloride, medium grade and fine grade.

The PQR for 2020 covered one primary campaign 23 batches including 2 heel scrapes, one reprocessing campaign of 6 batches including heel scrapes. Results trending, including stability was appropriate and no adverse trend identified. Any action arising from PQR would be recorded in CAPA system or other quality records under QMS.

The list of authorised personnel to release the product was part of the procedure [redacted] SOP dated 02/02/2022 and currently there were 6 qualified staff.

C5 Personnel

The API facilities operated a 4-shift system covering 24/7/365 production. The site presented new organigrams as part of the opening meeting presentation. [redacted] reported to [redacted] responsible for both UK sites. The Production was restructured into 3 business units: [redacted] and [redacted]

Training was not inspected in detail. All staff met during the inspection were knowledgeable about their roles. The training records for QC technician [redacted] and analyst [redacted] related to [redacted] were reviewed. [redacted] was trained twice on Controlled Drugs in Feb and Oct 2020, but this was due to [redacted] change in responsibilities and training update.

A deficiency was raised because there was no GDP training refresher since 2017.

C6 Premises and Equipment

Detailed description of the facilities is available in the SMF, as well as layout and photos in the site presentation stored in the inspection case folder.

Warehouse

The warehouse of solid raw materials, intermediates and APIs had controlled access to the building and additional authorisation by electronic card was needed for CD storage area. There were two main storage areas, namely for solid raw materials and for intermediates and APIs, with a dividing wall separating the two areas. Material status was managed by SAP computerized system. Temperature within the warehouse was monitored with a computerised system with alarm limits set at 25 ºC with a messages and telephone calls being sent upon being triggered. At the time of the inspection no materials required cold chain storage.

The sampling was done in sampling booth under LF by warehouse staff. Risk based sampling programme was covered in the procedure [redacted] 25/01/2022 and was developed [redacted] Activities were recorded in log books. Dedicated sampling tools were clearly labelled with the material for which they were to be used and with the clean hold date stored in dedicated closet.

Drums of liquid raw materials were stored in a solvent store. Bulk liquids were stored in outdoor bulk tanks. There were materials where the sample was taken by the supplier/ manufacturer. Example reviewed HCl, batch [redacted], delivered by [redacted] tankers. There was statement of dedicated tank [redacted] CoA and analytical worksheet for internal testing done and release.

Production Unit [redacted]

The [redacted] building was a computer-controlled multi-product facility. One equipment train was dedicated to [redacted] manufacture, which ran on a 24/7 basis. The other two equipment trains were used to manufacture campaigns (short campaign up to 10 batches) of [redacted] Solvent toluene recovery same stage process didn't require sampling according to the validation and DMF approved.

During the inspection of facility various records were reviewed. [redacted] SOP cleaning record was lacking the instruction if swab result at step 67 was out of limits. The operator interviewed explained that re-clean should be done and swabbed again. The results after this were satisfactory. Deficiency was raised due to incomplete ambiguous instruction.

In [redacted] cleaned parts (cleaned 21/02/2022) in preparation for commissioning were located on trolley labelled as clean, but several issues were noticed. For details see section D3.

Production Unit [redacted]

[redacted] was also a computer-controlled multi-product facility and was used to manufacture the intermediate stages of [redacted], and various APIs ([redacted] with three ISO Class 8 discharge suite for final API. The upgrades in computerised system were planned in the future first in [redacted] plant. Audible alarm was triggered if something was wrong, and if it was during process with potential impact to CPP, a deviation was raised. QA could review all records in the computerised system, as well as the printout at the end of production.

Pilot Plant [redacted]

The pilot plant was a manually operated multi-product plant capable of manufacturing 10-40 kg batches. There was no change in the equipment since the previous inspection. Products manufactured were [redacted] and the plant was in preparation for the [redacted] (first after 2018). The glove box for final API had to be commissioned with dedicated parts.

Scale Up Lab [redacted]

The scale up laboratory was used for the manufacture of early phase clinical trial materials. There was no switch between intermediates of different products, one product was manufactured at the time. New introduced product was [redacted]

Equipment Maintenance and Calibration

All maintenance activities were scheduled in [redacted] Number of records were reviewed indicating the equipment criticality/ quality related parts, without any issue identified. Unplanned maintenance was also recorded in [redacted] system and paper; Work order for repair to [redacted] was raised in [redacted] performed activities recorded on paper and following user's acceptance of the equipment work order was closed in [redacted] by [redacted]

C7 Documentation

Documentation procedures were regularly reviewed and revised when required, although some were still in the Aesica Pharma layout. Records were made in paper as well as in electronical systems.

A deficiency was raised due to inadequate documentation practice evidenced by the record of quantity in drum of [redacted] Fine Seed stored in warehouse, where the quantity was changed on the label from 5 kg into 2 kg without signature, date and reason provided. Records of usage from [redacted] evidenced that 1 kg of seed was used in December 2019 for crystalisation of each of 3 different batches on 12, 17, 24th Dec 2019.

Validation

[redacted] was reviewed and in line with the requirements. VMP was prepared on the plant level, but also for the product. The procedure [redacted] 10/06/2019 [redacted] covered approach to process validation, frequency and assessment if the product was considered validated or re- validation was required. According to the procedure 3 validation batches were required which was considered not scientifically determined number of batches and it was discussed that the site didn't apply it without justification of number of batches required. Qualification batches could be re-assessed for release after validation completed and assessment it is in line with all validation requirements.

[redacted] 04/01/2022 [redacted] – this procedure covered validation assessment at the start of each API campaign and new API or intermediate introduction in the plant.

Reviewed example DI water service validation assessment report 2021, [redacted] 28/05/2021. The last validation of the system was done in 2007. There were no changes significant to the process and quality, equipment; all annual reports confirmed adequate quality, no major deviations or impact to quality so the system was considered to remain in validated state.

Process validation

The [redacted] product had been previously validated for clinical supply on behalf of [redacted] A further prospective process validation exercise had then been carried out prior to manufacture of commercial stocks, under change control [redacted] Only minor changes to the process and equipment had been made since the clinical PV work (a flexible glovebox for final API packaging, and sprayballs in the filter drier). The validation protocols and reports were inspected; these also included a separate homogeneity study. All batches and homogeneity samples complied with the specification and the CPPs, and no issues were noted.

The procedure for Continuous process verification (CPV) [redacted] dated 28/05/2020 was reviewed. It was applicable to all products and critical synthesis steps. Minimal number of data points for appropriate statistical analysis was determined as 25. Consideration of data for lower number was explained as well. However, the procedure was not used as the reports were prepared only for some products ([redacted] example in 2017) and not on a regular basis. A deficiency was raised.

Cleaning Validation

The Cleaning procedure [redacted] 01/06/2021 covered cleaning and cleaning verification approach in all plants. The deviation had to be raised for failure. Visual inspection, swabs and rinse analysis of the vessels were analysed to confirm cleanliness each time. If more than 28 days(shortened from 3 months to 28 days since the last inspection) elapsed after cleaning vessel then assessment had to be made before start up as to whether further cleaning was required and documented in the turnaround document or cleaning protocol. HBEL reports PDE, ADE values had been calculated by toxicologist, if data available for material. If more than one acceptance criteria can be calculated the worst case scenario was used unless otherwise justified (lowest MACO).

The Quality risk assessment for establishing the period between cleaning of the [redacted] production train all stages, [redacted] 2016 was still considered applicable in terms of assessment of campaign manufacturing and prevention of build up, carry over in the dedicated production train.

C8 Production

Materials were transferred from warehouse to production plants based on the form for stock request. Transfer was done only after disposition and being on available stock in SAP system.

Manufacturing activities were performed in line with manufacturing batch records.

The procedure [redacted] dated 20/05/2019 was reviewed. Change control was the system used for documenting reprocessing. Impurity profile of reprocessed or reworked batch had to be compared against normal product. An assessment of appropriateness of the analytical method for potential new impurities was included. The requirement for stability monitoring was evaluated on each occasion. Also, the customer was notified when required.

To batch [redacted] reprocessing indicator was assigned 06/05/2021 [redacted] the batch record for heel scrape was reviewed. No issue identified.

Reprocessing batch [redacted] in [redacted] batch record and analytical worksheets/QC records were reviewed.

C9 Quality Control

The main QC [redacted] laboratory performed testing of raw materials, packaging materials, intermediates, APIs and stability samples for the whole site. The lab contained the typical range of equipment; there were several [redacted] HPLCs and GCs, UV, FTIR, KF, [redacted] and wet chemistry apparatus. Balances were subject to a daily check weight, a weekly three-point calibration and a 6-monthly service by [redacted] Raw materials were released by QC staff and all other materials by QA.

The oven No [redacted] was removed from the main QC laboratory in [redacted] plant without change control to evaluate this change or other controlled actions including keeping/ archiving documentation related to that oven. In addition, it was not clear why the calibration/ regular checks for the same oven were not maintained within the folder in QC since year 2017.

The new service provider [redacted] was used for re-qualification of [redacted] in Oct 2021. The documentation provided was reviewed by the QC with various issued identified in the form [redacted] but this was not timely recorded and investigated. The laboratory continued to use the instrument after re-qualification, but there was no record how this decision was taken or justified. There was no deviation raised due to not completed re-qualification activity and official acceptance by the QC. It was explained that the service provider was invited to a meeting to discuss documentation issues.

Laboratory in [redacted] was under the same system although there were also analysed non-GMP samples but followed the same procedures. Samples were booked in log book and results reported in [redacted] or samples on AR paper order and reporting (IPC, additional sampling for investigations etc). The same [redacted] was used in both laboratories. Columns usage was managed for HPLC in [redacted] Standards preparation was found satisfactory. Analytical report for [redacted] Jan 2022 was reviewed.

There were 5 stability cabinets covering the range of ICH conditions (two 25/60, 30/75, 30/65, 40/75); these were located in a locked room with secure keypad access for which the code was known to limited staff (due to the presence of controlled drug samples). Stability protocols were generated by QA, and the scheduling, sampling and testing was performed by QC. Typically, two bulk samples were placed on storage for each material; one was sampled at each time point, and the other kept as a spare. The list of samples stored within cabinet with reference to stability programme was displayed on the cabinet. The presence of [redacted] sample batch [redacted] was verified. No issue identified. The stability results were reported in [redacted] and there was 30 days deadline to complete analysis. The cabinets were continually monitored for

temperature and humidity via hardwired probes. Procedure on maintenance of stability chambers [redacted] required daily checks of water level, but in the record of checks done some gaps over the holidays were observed. There was no instruction how to ensure continuity of data review and avoid impact of less staff present e.g. during holidays.

Mapping of stability chamber reviewed 25 ºC /60 %RH, dated 22/04/2020. The bottom according to producer recommendation was not used. Probe positions were explained, no issue with conditions, so no need for relocation of the probe for continuous monitoring.

The number of OOS/OOT investigations were inspected including:

[redacted] – any other impurity individual not more than 0.5%, confirmed OOS, known manufacturing issue, so investigation directed in that area.

[redacted] – HPLC assay, batch [redacted] 48 months stability at 25ºC/60% RH, (98.0-102.0%) result above limits. Investigation of impact of temperature in laboratory resulted with method update for preparation of reagents and solutions sample at the same time to avoid impact of external parameters. However, there was no record of history review to support determined root cause related to specific method and no impact to other products/methods due to different temperature conditions in the laboratory.

VMP for QC related to qualification but also service and calibration from external services, explained expectation to review/ verify results for instruments on monthly bases were in the logbook, daily reviews, weekly for example KF were in notebooks/ worksheets, annual checklist for example HPLC in reports etc.

C10 Outsourced Activities

The outsourced laboratory analysis were used for the tests not available in house such as [redacted] and these were in the supplier assessment and audit programme. Also, the micronisation was outsourced to [redacted] but this was not change in the process since the last inspection. Both types of contractors were audited with 3 years frequency.

C11 Complaints and Product Recall

Complaints

The procedure was not reviewed during this inspection. Inspected records included:

[redacted] retest date on the label was 2 years, while certificate indicated 3 years which was correct. Leap year software issue was possible root cause, but no further investigation what could happened. One more batch labels for intermediate were printed on the same day and the same issue occurred, but there was no record of this checks done within the investigation (rather the information was collated on inspector's request). Human error contributed as it was missed to check dates on [redacted] and [redacted] o compare. Long term CAPA was related to changes into [redacted] system, while short term was manual checks.

[redacted] Medium Grade – colour of solution.

[redacted] – Customer has reported [redacted] had OOS to be OOS for Impurity B

Recall

There was no recall since the last inspection.

Returns

The list of returns with the reason was provided for the period since 2018 to present. Examples reviewed, see complaint [redacted] and some were caused by transport disruption due to Covid 19 situation.

C12 Self Inspection

Self inspection schedule for year 2022 and plan and realisation for 2021 were reviewed and found adequate. The topics were spread across 5 years cycle. References to requirements against ISO and GMP were considered, but there was no consideration of GDP for active substances.

Records of internal audits were made in [redacted] including audit finding and CAPA from those.

C13 Distribution and shipment (including WDA activities if relevant)

Not inspected during this inspection.

The majority of APIs were manufactured under contract for specific customers. [redacted] was used for transport, none product required special conditions.

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 List of Deficiencies

D1 Critical

None

D2 Major

None

D3 Others

3.1 The GMP Quality System was deficient in the following:

3.1.1 Investigations of deviations, complaints and OOS results didn't extend to other batches that were potentially impacted with the specific failure, deviation or defect, as evidenced by:

3.1.2 In the complaint [redacted] – Incorrect retest date on labels, there was no record of impacted labels of intermediate batch printed on the same day

3.1.3 OOS investigation [redacted] HPLC assay, [redacted] OOS at stability testing 48months, 25C/ 60% RH, didn't record the history review to support determined root cause related to specific method and no impact to other products/methods due to different temperature conditions in the laboratory

3.1.4	In the deviation [redacted] Batches failing EP appearance of solution, there was no recorded impact to other equipment (with same type of baffle)
3.1.5	The procedure [redacted] for continuous process verification hasn't been followed and there were no reports prepared for all products on determined frequency
3.1.6	Internal audits didn't cover requirements of GDP for active substance
3.1.7	Issues with the qualification of the [redacted] instrument done in Oct 2021 by the external service provider [redacted] were noticed but the same were not timely recorded and investigated and there was no clear decision recorded why the instrument could be used despite those issues.
EU GMP Part II	2.12, 2.16, 2.32.12, 2.50, 6.53, 8.15, 12.10, 12.60, 15.12, API GDP 7.5, API GDP 8.1

3.2	Documentation, procedures and records, were inadequate in a number of areas, as evidenced by:
3.2.1	Procedure on maintenance of stability chambers [redacted] SOP required daily checks, but in the record of checks done some gaps over the holidays were observed. There was no instruction how to ensure continuity of data review and avoid impact of less staff present e.g. during holidays.
3.2.2	Procedure for process validation [redacted] determined that validation was done on three batches without option to determine required number of batches and justification for that approach based on the complexity for example (Note: It was stated by the site that sometimes different number of batches were in scope of process validation).
3.2.3	The oven [redacted] was removed from the main QC laboratory in [redacted] plant without change control to evaluate this change or other controlled actions including keeping/ archiving documentation related to that oven. In addition, it was not clear why the calibration/ regular checks for the same oven were not maintained within the folder in QC since year 2017.
3.2.4	The quantity in drum of [redacted] Fine Seed was changed on the label from 5kg into 2kg without signature, date and reason provided
EU GMP Part II	2.12, 2.15, 2.16, 2.32.12, 6.14, 12.50, 13.12, 13.14

3.3	Cleaning processes and documentation were inadequate, as evidenced by:
3.3.1	In [redacted] SOP cleaning procedure for [redacted] plant there was no instruction how to proceed in case swab in step 67 failed.
3.3.2	In [redacted] cleaned parts in preparation for commissioning were located on trolley labelled as clean, but several issues were noticed:
3.3.2.1	Part was wrapped in plastic bag, tided and labelled as clean, but there was residue of liquid in the bag
3.3.2.2	There was some powder dirt on bags surface
3.3.2.3	One of the bags had small damages and holes (Note: The site stated that according to the procedures parts had to be reviewed prior to commencing.)
EU GMP Part II	2.12, 5.21, 5.22

3.4 EU GMP Part II	There was no regular training on GDP for active substances 3.12, API GDP 3.2, API GDP 3.3, API GDP 3.4

D4 Comments

4.1 During the inspection, it was communicated that [redacted] The site was reminded about availability of Interim Compliance Report to report changes even if there is no impact to API registration.

4.2 The responsible management was informed about number of CAPAs overdue due to staff left the site. While the recruitments was in-progress, those actions were not assigned to remaining staff as it required more systematic review of resources and job position responsibilities. The KPIs are regularly reported. In case there is significant backlog observed and no improvement trend recorded, it is required to report this to the MHRA.

Section E Site Oversight Mechanism

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

Section F Summary and Evaluation

F1 Closing Meeting

A closing meeting was held remotely on 24th February 2022 where the deficiencies were accepted and a positive commitment to provide a corrective action response was given.

F2 Assessment of response(s) to inspection report

An initial response was received on 17th March 2022 and some clarification was required. An acceptable response was submitted on 28th March 2022 following the request for further information.

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: 16/06/2022

Accompanying Inspector: **N/A**

Date: N/A

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	0	Last inspection:	0
Other deficiencies this inspection:	4	Last Inspection:	6

(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)

[redacted]

(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 noted in section (f) above

[redacted]

(h). Conclusions

[redacted]

(i). Expert/ Operations Manager / Compliance Management Team (CMT) Comments (Risk rating level 0, I, II):

[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