Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MIA 10592, API 10592

Licence Holder/Applicant: SMITHKLINE BEECHAM LIMITED

Details of Product(s)/ Clinical trials/Studies:

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	Y
Packaging - Secondary	Y
Importing	N
Laboratory Testing	Y
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: *Blending of API with excipients and other APIs*	N

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

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Site Contact: [redacted]

Date(s) of Inspection: 14th to 18th December 2020 (14th, 15th, 17th and 18th December remote, and 16th December on-site). The close-out meeting was held on the 23rd December.

Lead Inspector: [redacted]

Accompanying Inspector(s): N/A

Case Folder References: Insp GMP 10592/1524-0020

Section B General Introduction

B1 Background information

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The Irvine site has been open for approximately 47 years. When originally opened in 1973, the site produced [redacted] by [redacted]. In 1981, a multipurpose actives facility was opened. The introduction of the [redacted] manufacturing process occurred in 1987, with the process also being based on [redacted] The intermediate [redacted] facility was opened in 1998. [redacted] was sent to the GSK [redacted] site where it is processed to [redacted] [redacted] manufacture had ceased at the site in September 2020 (after having been reduced by 50% in December 2017) and there were a number of positions being lost. The drive for blending the [redacted] with either [redacted] was associated with the [redacted] salt being unstable in its pure form (a significant safety incident had occurred in 2013 associated with this instability). The [redacted] [redacted] mix was considered to be an intermediate drug product. The majority of the site's output was to supply other GSK manufacturing facilities, however, some [redacted] mixes were supplied to third party customers.

This inspection was carried out as a hybrid inspection with four days remote and one day on-site.

Previous Inspection Date(s): 15th to 18th September 2014
Previous Inspectors: [redacted]

B2 Inspected Areas

PQR, deviations, change controls, CAPA, OOS, Complaints, Batch Release, OOT, batch record review, management review, supplier approval, supplier complaints, maintenance, calibration, sampling, outsource activities, Document control, QC Laboratories, Production Facilities, Stability, Environmental Monitoring, Sampling, TSE, Self-Inspection, Warehouses, Validation Master Plan, Equipment Qualification, Training, Cleaning.

Limitations / exclusions to inspected areas

The inspection was conducted as a hybrid, with four days being carried out remotely and one day being on-site.

Recall, Solvent Recovery, distribution.

B3 Key Personnel met/contacted during the inspection

[redacted]

B4 Documents submitted prior to the inspection

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Document	Version /Date of document	Reflected activities on site?
Site Master File	[redacted] 24 Aug 2020	Y
Compliance Report	04 Dec 2020	Y
Comments: None		

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:

Implementation of a [redacted]

Implementation of Electronic Batch Records.

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

The site were undergoing a headcount reduction at the time of the inspection due to the cessation of the manufacture of [redacted] in September 2020.

C2 Action taken since the last inspection

The proposed responses to the deficiencies had been completed in the required timelines.

C3 Starting Materials

General

Supplier Audit Reports

The audit report for [redacted] was reviewed they supplied the [redacted] for the blend (excipient). The audit was carried out on 3rd December 2019. A re-audit frequency of [redacted] was recommended. The audit was carried out by one auditor. The previous audit was February 2016 and was an on-site audit. The site manufactured a range of products. Batch size was approximately [redacted] A sample was taken every 2 hours and a composite sample was supplied. The sample was not taken of the batch upon receipt (due to being hygroscopic). The sample was taken at the site (composite sample) and was shipped separately to the bulk A risk assessment had been generated in August 2017, however this was not a justification for the sample not being shipped with the bulk (see deficiencies). Container samples were put in plastic containers. The travelling sampling management agreement was signed 15 Sep 2014.

The audit report for the [redacted] was reviewed. The audit was of [redacted] on 19th April 2018. The previous audit was 15th May 2013. The next audit date was set at [redacted] The audit report did not specifically mention the sampling process for the travelling samples. A travel sample management questionnaire was available.

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The audit report for [redacted] dated 21 Jan 2020 to 11 Mar 2020 was reviewed. The audit was a desktop assessment to cover the supply of tert butylamine. The audit was carried out every [redacted]

The audit report (Record Number [redacted] for the supply of [redacted] of [redacted] was reviewed. The audit was carried out on the 15th Sept 2015 to 16th Sept 2015 by one auditor. The site manufactured a number of materials. The audit was focussed on other materials. The next audit date was recommended as [redacted] but had been postponed.

Vendor Complaints

The complaint SOP was [redacted] dated 27 Aug 2019. For a minor complaint, the supplier has 25 days to respond and then the site has an extra 10 day (35 in total). For Major supplier had to respond initially within 5 days and finally by 10 days and the site had a further 4 days to complete. For Critical complaints the supplier had 1 day for initial response, 2 days for final response and 1 additional day for site to respond.

There had been 26 complaints raised against vendors since the last inspection.

Sampling

The site had identified each material as either critical or non-critical and then on top of that had a separate system to identify the materials based on risk. The risk could either be low, medium or high. The sampling plan was then adopted based on risk. [redacted] applied to incoming material which required sampling. The exemptions to the risk assessment process were identified in Quality Document [redacted] Exemptions include materials that are received in a [redacted] and also included primary packaging materials and it was stated that all other materials had been risk assessed. Primary packaging materials were not taken through this process. Eleven materials were identified as being included in the risk assessment (once [redacted] had been excluded. The majority of suppliers were identified as being single sourced. A summary of material criticality, justification for this and the relative risk rating was reviewed.

[redacted] was reviewed. This was the risk assessment process that assessed the risk associated with a product and its supply chain. The SOP reassessment of materials was defined that it should be '*conducted periodically*'. The review was conducted every [redacted] It was described that this was required to be carried out in the event of a major/critical complaint, but none had been raised since the system was put in place. This was also required if there had been a significant change. The SOP risk assessment was considered to not be sufficiently rigorous to prioritise the sampling process and did not reflect the situation on site. The review of supplier performance covered a period of [redacted] There was no consideration of the complexity of the supply chain in the assessment. The template used to do risk assessed [redacted] effective October 2019 was reviewed. The numerical values to quantify the risks e.g. complaints was considered to be insufficiently discriminating for new suppliers. It was acknowledged that this did not reflect the current situation. The risk assessment for the [redacted]

Compliance with TSE Guidelines

Compliance with TSE guidelines was reviewed as part of supplier approval activities.

API Compliance

Not applicable, as this inspection covered the manufacture of APIs.

C4 Pharmaceutical Quality System

Product Quality Review

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The PQR process was governed by [redacted] dated 16th December 2019. The procedure identified that six PQRs would be prepared each year (although one was for a starting material).

- [redacted] (starting material compiled to enable annual review)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

PQRs were required to be approved within 3 months of the end of the review period. Any actions identified during the PQR were required to be completed within 6 months of formal issue of the report. Any extension to this date would require approval by the Site Quality Director. There was a requirement to generate a [redacted] and evaluate the results in the current reporting period against previous reporting periods. The process capability was evaluated using [redacted] with a value of [redacted] being identified as acceptable. There was a requirement to identify if any trends were observed in the analytical data.PQRs were required to be completed each year and five PQRs had been completed by the target date for the past three years. A number of PQRS were reviewed, including [redacted]

Deviations

The deviation SOP was [redacted] dated 15th July 2020. A flowchart identified that deviations were required to be raised within 1 day. The impact assessment was required within 1 day, the investigation within 20 days and reviewed and closed by 25 days. [redacted] stated that the report was required to be completed in 30 days. It was identified that there was an error in the SOP and the timeline had moved from 25 days to 30 days. Interim reports could be completed every 30 days until the investigation was completed. A review was required to determine if any similar deviations had occurred in the last 12 months for Minor deviations and 3 years for Major and Critical deviations. CAPA were required for all Major and Critical deviations. A justification was required if a CAPA was not identified for Minor deviations. Where 'Human Error' was identified as a significant contributor to the root cause, further review was required to assess the most influential area. Where the CAPA has not been completed as per the target date, an overdue CAPA form was required to be completed.

Open deviations were tracked at a daily tiered accountability meeting. Deviations were required to be trended every 6 months to identify adverse trends. A review was required to be carried out monthly and this was carried out in the site quality council. A review of the deviation system was required to be included in the internal audit programme. A deviation was not required to be raised for an equipment failure that had no product quality impact. These issues were tracked and trended by engineering. [redacted] (unexpected material is found) did not require a deviation if the contaminant was identified within the baseline document – in that case, the issue was required to be recorded on the associated GMP document and then closed. The trending of these events was reviewed annually and there was a trigger value for each type of material observed. The list of Deviations raised since the last inspection was provided. There had been 515 deviations since the last inspection. 9 were classed as Critical, 266 as Major, and 240 as Minor. The root causes were grouped into 44 different categories. The most prevalent categories were 'Individual Influenced by Job' 86 (16.7%), 'Not Assigned' was 77 (15%), 'Machine, Equipment Failure' 72 (14%), and 'System or organisational issue' 51 (10%). 135 of the 515 deviations (26%) referenced 'influenced' as the root cause e.g. 'Individual influenced by job', 'Individual influenced by Organisation', or 'Job design influenced by Individual'. The following deviations were reviewed;

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[redacted]

CAPA

SOP 'Investigation, Root Cause Analysis and CAPA' [redacted] effective 7th September 2020 was reviewed. There was a requirement to confirm the effectiveness of the CAPA. The CAPA effectiveness was determined no sooner than 3 months after implementation. Irvine uses a Root Cause Analysis (RCA) tracker which records the new [redacted] and opens the toolkit. Not validated as only used as a tracker.

The list of CAPA raised since the last inspection was provided and a number of CAPA were requested and reviewed: [redacted].

Change Control

The list of change controls since the last inspection was requested. The following were reviewed [redacted]

Validation Master Plan

The validation master plan addendums were reviewed. The site carried out Periodic Validation Review every [redacted]

Management Review

The 'Management Review by [redacted] for [redacted] SOP [redacted] dated Sep 2019 was reviewed. [redacted] related to the [redacted] The meeting was held monthly and had specific items that needed to be covered on a monthly, quarterly and annual basis. There was a requirement to carry out an annual effectiveness review of the [redacted]

Batch Release SOP

The batch release SOP was [redacted] dated 28 Jan 20. The list of batches released since the last inspection was provided. The number of batches released each year was approximately the same over the previous 3 years. All batches were released in [redacted] A usage decision could be made to restrict supply to certain markets e.g. Worthing, however this was not a common process.

Licences/Registrations

The MIA and API registrations were reviewed and no changes identified.

C5 Personnel

Staff Numbers

The SMF indicated that there were 307 employees at the site, with the following distribution:

[redacted]

At the time of the inspection, the site was going through a rationalisation activity after identifying that they would cease the manufacture of [redacted] which would result in the reduction in employee numbers of 75. This was ongoing at the time of the inspection.

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There had been a reduction of approximately 50 employees in late 2017 relating to a down-turn in [redacted] manufacture at that time.

Training

The training SOP was [redacted] dated September 2020. An electronic system identified as [redacted] was used. Learning plans and training curricula were identified and approved. All training was completed and recorded within [redacted]. There were three levels of training on site. Level 1 was site specific, level 2 was mandatory job specific training and level 3 was role specific training. Information was required to be provided to the quality council. Approximately 0.5 items per person were allowed before an issue was flagged. An annual review of a persons training record was carried out. Pass marks for electronic exams were 80% and if a person failed three times they were locked out. An [redacted] co-ordinator can then reset the account once a person has been spoken to. The status for the [redacted] team and the QA team were viewed on '[redacted]'. The site dashboard showed that the site were over the 0.5 overdue items per head and were sitting a level of 0.72 level. The value was significantly impacted by one individual that had left the company but had not been able to be removed from the system. When this person was excluded the overdue level was significantly reduced. People could be exempted from the site dashboard if they were e.g. on maternity leave. There was a process to ensure that they ere included when they return to work and this was monitored periodically by [redacted]

C6 Premises and Equipment

Warehouses

The Main Store Warehouse and the [redacted] were not provided with heating or cooling and had limits of 2 to 25°C identified. [redacted] dated May 2020 identified the storage and alarm conditions and defined the required storage conditions for each material handled. The [redacted] was identified as requiring storage at room temperature (approx. 25°C). There was also a large cold storeroom.

Clavulanate Fermentation Building

The [redacted] was prepared in the Process Support Lab under clean room conditions. A list of isolates normally encountered was provided. The SOP on contamination event handling was reviewed. The spores were shipped from the Worthing site at -70°C.

The batch staging area was inspected and it was noted that there was no canopy over the manual charging areas. [redacted] was observed not to be clean on the charge port [redacted] appeared to have dark flakes at the bottom of the extraction system which was located directly above the port that was opened for charging. The extraction was not always on and there was no routine cleaning regime. [redacted] was observed to have a significant amount of built up material internally (at the reverse sides of the baffles etc in the vessel) that had discoloured (despite having been cleaned). There was no requirement to use a torch when confirming cleanliness.

Clavulanate Extraction Plant

The batch was transferred by fixed line to the [redacted] building at 5°C. The process was highly automated and was well controlled. The API could be blended with excipients/APIs for stability and for ease of onward supply.

Stability

There were four stability chambers, of which three were in operation. One was set at 5°C and the other three were [redacted] (only two of these were operational). [redacted] were observed being stored in the central part of the stability cabinet – see Qualification section.

Environmental Monitoring

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The Microbiological Environmental Monitoring of [redacted] Review 2019 was reviewed. Settle Plates and active air samples were taken. Settle plates were exposed each month. The [redacted] monitoring was carried out twice each year in each of the [redacted] kegging areas. The alert and action limits were set at [redacted] and [redacted] respectively for the settle plates. Action was only taken on alert limits when two consecutive breaches were identified. The alert limits for the settle plates were not reflective of the results typically observed – which were usually around the [redacted] value. Additionally, action was only taken when the samples exceeded the alert value two months in a row. The Active air acceptance criteria was [redacted]

Maintenance

[redacted] May 2020 with a [redacted] review period. There was a monthly trend on performance of maintenance and calibration. The last report was generated in early December 2020 and this showed that the site was in a state of control.

Calibration

The '[redacted] [redacted] dated 18 Sept 2019 with a review date of September 2024 was reviewed. [redacted] 'Production Resource Tool (PRT) Master list was held on [redacted] Any changes to the instruments/parameters were required to be reflected in [redacted] Calibration work orders were created by [redacted] Where calibration was not done in time, a PM Frequency deviation report was required to be raised (as per [redacted] Where calibrations were observed to fail, a calibration deviation report was raised automatically in [redacted]. Defined windows for calibration were allowed, depending upon the frequency. Calibration results certificates were held in the [redacted] system. Admin access was with the System Owner in [redacted], but this was a different department. The calibration results were required to be signed electronically in the system. There was a period of 7 working days to action the pass/fail result. The majority of calibrations were done by GSK personnel. The remainder may be done on-site or sent away. A list of contract companies used for calibration was reviewed. A list of [redacted] was reviewed for fermentation. [redacted] was approved December 2019. This also referenced the maintenance plan for each item of equipment. The calibration for [redacted] was reviewed. The last calibration was carried out in August 2020. The calibration certificate was reviewed and no issues identified. [redacted] was calibrated every 52 weeks. The probe had been removed for calibration on 18/12/2020. Flow meters were removed from the location, replaced with a calibrated version and then sent to a contractor to the carry out the activity. There was a 56 day tolerance to get the calibration done for off-site items of equipment and the equipment was removed early to ensure the due date was achieved. [redacted] temperature transmitter calibration was reviewed. The results were input real time as the testing was carried out. The calibration activity for the temperature probe was done in the engineering workshop (other items were calibrated in situ). Results were identified as-found and as-left. The probe was calibrated at 0, 15, 38 and 60°C. The last calibration was [redacted] and was on a [redacted] routine. Where calibrations were done externally, the companies were audited to confirm compliance. The audit of [redacted] was done in line with [redacted] Appendix 2 of the SOP identified the requirements for a desktop audit. [redacted]

Equipment Qualification

The re-qualification of the stability cabinet [redacted] was reviewed. The protocol and report were available, and they identified that the mapping exercise had been carried out over 17 points and one of those had been mid-height in the centre of the unit. The worst case locations were identified.

Water

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[redacted] dated 2020 with a review date of [redacted] was reviewed. Microbiological testing of water points across the site were sampled and tested monthly. The process for handling action and alert level breaches was identified in the procedure. The water used on site in production was potable water. The data was trended on spreadsheet monthly and an annual report was generated. The 2019 report was reviewed and it was identified that the alert limits were significantly below the observed values and additionally there was a requirement to have two consecutive issues prior to action being taken.

C7 Documentation

Document Control

A list of SOPs was presented which included a number of non-GMP categories (including safety). Review dates were identified as being assigned up to [redacted] A number of SOPs that appeared to have a GMP content were assigned extended review dates e.g. [redacted] and [redacted] which had [redacted]

Batch Record Review

The batch record and release of batch [redacted] (released on 19 Oct 20) was reviewed. The batch release checklist was reviewed [redacted]. The [redacted] extract was reviewed. Part of the input had been reprocessed and the order of approval of the associated paperwork was discussed. It was identified that the review process hadn't been followed. This was identified as an error and a deviation was raised during the inspection. The reprocessing was carried out on a paper based system and the main processing was carried out on the [redacted] which had been recently introduced.

Data Integrity

The data integrity checks in the API lab QC equipment logbooks were not being filled in routinely. The daily balance checks carried out were not recorded/reviewed (despite being carried out prior to every weighing).

C8 Production

The processes were based on classical fermentation technology. For more detail, see the site master file.

C9 Quality Control

Laboratories

There were two main laboratories on site; Raw Materials lab and the API lab. The RM lab was day based. Samples from tankers were tested before offload. The [redacted] was not in use in the [redacted] and results were recorded on sheets. [redacted] was reviewed. It identified that predominantly only one sample was taken for each delivery. Full testing was carried out annually. [redacted] was reviewed. A number of deficiencies were identified: see section D3. There was no real time trending of data for raw material analyses. The API lab was manned for 24 hours 365 days a year. There were 5 shifts with 3 people per shift. The equipment was connected to the [redacted] The materials tested were [redacted] and solvent recovery. The reference standards were stored in a fridge, other than one which was stored in a freezer.

OOS/OOT

The OOS SOP was [redacted] issued 30 October 2019. The investigation followed a multi-stage process aligned to the MHRA guidance. The investigation was required

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to be completed 'within 14 – 25 days'. Where this was not achieved, a justification was required to be completed. Additional reports were required to be completed for each 25 days that the investigation was open. There was a requirement to review the [redacted] and generate a report every 3 months. The tracker was required to consider the number of aborted runs and a limit was assigned. The SOP defined that the number of retests required to justify overwriting the analytical result was at least 5.he list of OOS since the last inspection was provided. There had been 578 OOS recorded. Of the OOS identified, 354 (61%) concluded with the result being overturned and the batch being accepted. 38 of the overturned results had no identified root cause established (~6.5% of all OOS). 179 of the 578 OOS recorded 'Human Error' as the root cause classification one. A number of OOS/OOT were reviewed. OOT [redacted] was reviewed and it was identified that the conclusion lacked detail and no CAPA had been raised relating to the times for analysis, although this was considered a potential cause. It was described verbally that there may have been a problem with the instrument and that this could not be verified, but this was not documented. The delay to closing out the investigation was not documented (there was no detailed investigation as the issue had occurred previously). The original results were supplanted after five replicates were carried out, however, the results quoted was solely an extra (sixth) set of results and this was not proceduralised. This was identified as the routine way of working. OOT [redacted] related to optical rotation for neat [redacted]. OOT [redacted] related to a time point zero stability result moisture test. The investigation was reviewed and the stage [redacted] investigation stated that replicate 1 was OOS and replicate 2 was OOT and incorrectly stated that the average was OOT. It should be noted that the specification was incorrectly stated in the investigation and therefore the final result was OOT, not OOS. No root cause was identified, however no further evaluation was carried out of the result as the [redacted] to be used was discarded. The justification for the [redacted] being discarded from the stability trial was not valid, as there had been no abnormal processing, handling, or analysis on the [redacted] but rather, it had not been segregated prior to shipping to the contract warehouse location and could have been returned to the site. Not all results generated were reported on the [redacted] only the final value obtained (it was acknowledged that the other results were available for the Usage Decision). The site carried out retesting of OOT results to supplant the original result. This was not carried out as part of hypotheses testing.

C10 Outsourced Activities

Technical Agreement

[redacted] were audit on 19th March to 12th May 2020. There were no findings identified and the re-audit date was set for [redacted] The supplier questionnaire was reviewed. The quality agreement was dated May 2015 and an addendum in November 2020

[redacted] 'Outsourcing of Engineering and Facility Services' was reviewed.

Manufacturing/QC Testing

The site did not outsource any manufacturing or testing activities.

C11 Complaints and Product Recall

Complaints

The complaint SOP was [redacted] dated 27 Aug 2019. Complaints could be classed as Critical, Major or Minor. The SOP covered complaints on incoming goods and on materials manufactured at the site. Complaints could be classed as substantiated or unsubstantiated. There had been approximately 39 complaints against the site since the last inspection. Of these, 16 were classed as Minor and 23 were classed as Major. 9 of the 39 errors (23%) had a root cause of 'Human Error at External Warehouse'.Complaints [redacted] were reviewed which related to assay results being questioned by the customer.

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C12 Self-Inspection

The self-inspection process was managed by [redacted] dated March 2020. A schedule for audit was prepared annually. Audit reports were required to be approved and circulated within 45 days of the audit close-out. Findings could be classed as Critical, Major, Minor, note or Good Practice.

C13 Distribution and shipment (including WDA activities if relevant)

Not reviewed.

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

Not applicable.

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

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1 CRITICAL

None

2 MAJOR

2.1 **The process for investigating Out of Specification (OOS) and Out of Trend (OOT) results was deficient as evidenced by:**

2.1.1 [redacted] was not being followed, as evidenced by an un-proceduralised sixth retest routinely being carried out, with the result of that sixth retest being identified as the reportable result.

2.1.2 Investigations into recurring issues did not always seek to determine a root cause through hypothesis testing prior to retesting, for example OOT [redacted]

2.1.3 Retesting was being carried out on OOT results despite no analytical errors having been identified in the initial laboratory investigation.

2.1.4 The Certificate of Analysis generated did not report all the results obtained (it was however noted that the usage decision was based on all the results).

2.1.5 The investigation of OOT [redacted] was deficient as evidenced by:

2.1.5.1 The investigation stated that an OOS result had been averaged with an OOT result to give an OOT result. (It was subsequently noted that the specification was incorrect in the report and both results were actually OOT).

2.1.5.2 The justification for discarding the keg from the stability trial was not valid: it was stated it had been sent to the contract warehousing company and was therefore not suitable for use, however, it had remained within the approved supply chain at all times.

EU GMP Part II 6.53, 11.15, 11.42

3 OTHERS

3.1 **The vendor approval process was deficient as evidenced by;**

3.1.1 The risk assessment outlined in 'Incoming Materials Sampling Assessment Plan Risk Assessment Process' [redacted] was deficient as evidenced by this document;

3.1.1.1 Allowing reduced sampling where there was '*limited evidence towards homogeneity/stability of supplied material*'.

3.1.1.2 Allowing reduced sampling to occur (a single point sample from 1 container) after a limited number of deliveries (as little as 1) for bulk [redacted]

3.1.1.3 Not directly linking the number of complaints deemed acceptable to the number of deliveries (up to 3 Major Quality related complaints could be acceptable for a low number of deliveries).

3.1.1.4 Allowing reduced testing despite an undefined number of 'Major' audit actions being open that '*had not been adequately mitigated*'.

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3.1.1.5 Allowing multiple risks in the same category (e.g. Medium Likelihood risk factors) to occur simultaneously with no additional risk weighting (including all the points listed above).

3.1.1.6 Did not define the period that a review of the risk assessment should occur in.

3.1.1.7 Did not define the analytical testing confirmation to be carried out for materials classed as 'low risk'.

3.1.2 There was no ongoing trending of the analytical results obtained for raw materials tested against the values recorded on the supplier certificate of analysis.

3.1.3 A reliance on a single sample to identify ongoing quality related issues could not be justified where; samples were may not be representative, there was no retained sample (for investigations), and the audits of the suppliers were infrequent e.g. [redacted]

3.1.4 Audit reports of suppliers did not always confirm if multiple products were manufactured on site (e.g. [redacted] and provide appropriate assurance that the systems in place would prevent errors or mix-ups e.g. incorrect materials, grades, or physical forms being supplied.

3.1.5 The 'travelling samples' of [redacted] provided by the supplier could not be confirmed as being representative, as they were not shipped with the main batch.

EU GMP Part II 2.21, 7.31, 7.33

3.2 **The risk of contamination was not being minimised, as evidenced by;**

3.2.1 The cleaning of [redacted] was observed to be deficient, as there was material present in a number of areas within the 'clean' [redacted] hat appeared to have degraded/discoloured. It was considered that the observed areas would not have been cleaned via the installed spray ball.

3.2.2 [redacted] local extraction points directly adjacent to the charge-port were observed to have rust or degraded materials on them. These extraction points were not subject to routine cleaning and were switched off between use, allowing material to fall back down under gravity.

3.2.3 The alert limits for environmental monitoring and water testing results were not set based on the values observed.

3.2.4 There was no covering above the open manways used for charging the bulk raw materials, to prevent ingress of foreign materials.

EU GMP Part II 4.10, 5.21, 5.23, 8.50, 8.51

3.3 **Good Documentation Practices were not always being adhered to, as evidenced by:**

3.3.1 The periodic Data Integrity checks, on multiple pages of a number of QC lab logbooks reviewed, were not routinely being completed.

3.3.2 The daily calibration checks of the API QC laboratory balances were not being recorded, or checked in the audit trail, as having been completed

EU GMP C4.8 Part II 6.61

3.4 **Not all procedures within the Quality Management System were being reviewed and updated regularly, as evidenced by [redacted] and [redacted], which had been assigned a [redacted]**

EU GMP C4.5 , EU GMP Part II 2.31, 6.10

4 COMMENTS

None

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			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The attendees identified in section B3 were present at the close out meeting. The deficiencies were presented verbally and accepted by those present.

F2 Assessment of response(s) to inspection report

The Post Inspection letters was sent on the 30th December 2020, the initial responses and the RFI were dated the 29th January 2021 and the responses to the RFI were received and accepted on the 15th February 2021.

F3 Documents or Samples taken

None.

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

Given the information provided, the facilities observed and the commitments to findings made, the site are considered to operate 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.

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Name of Inspector (s):

Lead Inspector: [redacted] **Date:** 16th February 2021

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:	1	Last inspection:	0
Other deficiencies this inspection:	4	Last Inspection:	8

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

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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)

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(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 noted in section (f) above

[redacted]

(h). Conclusions

[redacted]

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

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[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