Medicines & Healthcare products
Regulatory Agency

INSPECTION REPORT

GLAXOSMITHKLINE RESEARCH & DEVELOPMENT
PARK ROAD
WARE
SG12 0DP
UNITED KINGDOM

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MIA(IMP) 5866, MS 5866

Licence Holder/Applicant: GLAXOSMITHKLINE RESEARCH & DEVELOPMENT

Details of Product(s)/ Clinical trials/Studies: The Ware R&D site manufactures, tests and QA releases intermediate Investigational Medicinal Product (IMP). These intermediate IMPs are sent to other GSK sites for onward processing.

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

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

Site Contact: [redacted]

Date(s) of Inspection: 31 October until 02 November 2023

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

Case Folder References: Insp GMP/IMP 5866/27277-0035

Section B General Introduction

B1 Background information

The Ware R&D site manufactures, tests and QA releases intermediate Investigational Medicinal Product (IMP). These intermediate IMPs are sent to other GSK sites for onward processing. There are staff based at Ware R&D site which support finished IMPs activities (packaging, labelling, distribution) that occur at other sites [redacted]

No finished IMPs are packed, labelled, stored or distributed to clinical trial markets at the R&D Ware site. Manufacture and testing of 'Specials' is also authorised. Refer to the Site Master File for further detail.

Previous Inspection Date(s): 25 - 26th May 2016

Previous Inspectors: [redacted]

B2 Inspected Areas

Risk management and risk register, Management review, Change management, Warehouse, sampling of starting materials (including packaging), goods in and out processes.

Cross contamination technical and organisational controls, toxicology assessments, NPI, risk assessments, cleaning validation, cleaning procedures.

Deviation Management & CAPAs, Customer Complaints, Recalls & Mock Recall

OOS / OOE review, Laboratories [redacted] and stability chambers [redacted] Stability protocols, timeliness, reconciliations, results. Analytical methods, validation, release of results.

Water (recent upgrade) and EM.

Manufacturing Plant [redacted], dispensing through to finished product. Equipment and facility maintenance, HVAC, calibration status.

Validation Master Plan, Equipment re-qualification and validation status / review processes.

Training

Batch records, review and certification.

Regulatory controls, PSF management and updates, change management, blinding controls/checks (if applicable).

Limitations / exclusions to inspected areas

Supplier Management, QTAs, controls on starting materials.

Self Inspection

Pest control

Distribution controls

B3 Key Personnel met/contacted during the inspection

Refer to Annex 2

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	[redacted]	Yes
Compliance Report	23 October 2023	Yes
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:

None

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

None

C2 Action taken since the last inspection

The actions arising from the previous inspection had been addressed satisfactorily.

C3 Starting Materials

General

Not reviewed in detail at this inspection.

Compliance with TSE Guidelines

The plastic bags used to contain dispensed materials were challenged and confirmed to have been assessed and an appropriate TSE statement was available. It could not be evidenced what specific controls were in place for imported material around TSE management, particularly those associated with unlicenced medicine import.

API Compliance

This was not inspected in detail. Requests were made on inspection around management of API manufacturers, technical agreements, and audit. However not all information was not available without delay and therefore was not reviewed.

C4 Pharmaceutical Quality System

The company at the time of the inspection was undergoing a [redacted] transition to align the R&D and Commercial functions into one closer working unit. Some procedures had begun to align.

Deviations & CAPA

The deviation handling, R&D Global GMP Areas procedure [redacted] version [redacted] was reviewed during the inspection.

[redacted] – During review of data in a PDF measurement report for dissolution testing it was noted that they could be re-converted back into Word format and altered. No comments were raised.

[redacted] – This deviation related to two equipment impact evaluations being found to be outside of compliance with validation procedures. One issue related to an IE being raised and not completed within the required timescales and another related to an out of Tolerance being identified and a two-and-a-half-month gap taking place before this was raised and completed in [redacted] It was noted that actions related to a prior incident had therefore not been effective. The pipette which was out of tolerance had been out of use since 2017 and was being decommissioned.

[redacted] – This deviation was related to quality testing performed for [redacted] using media with incorrect quantities of inactivators. MLT and in process testing was carried out using [redacted] and [redacted] versus [redacted] and [redacted] and was not noted by the approver that this was incorrect. No growth had been identified on TAMC/TYMC plates and low level staph had been identified in the broth, this was noted as typical for inhalation products. Despite lower levels of inactivator being used the results were still considered valid; this was concluded on the basis of prior work to establish whether lower levels of inhibitor would remain effective and also as due to staph growing other microbial life would also be supported. Repeat testing was performed before release. Historically one concentration of inactivator was used however a second lower concentration was also used for other purposes. The root cause was determined to be insufficient labelling. No further human error investigation was possible as the analyst had left the organisation.

[redacted] – This deviation related to brown and black particles found in [redacted] The issue occurred on 08 March 2022 and was detected on 09 March 2022 and was identified during removal of the chopper following granulation using the [redacted] the most probable root cause for the brown particles was identified to be material build up behind the chopper blade during granulation between sub lots and for the black particles fragments of vacuum nozzle used during the cleaning processes. Red particles were later found during compression of the granule into tablets; the root cause of this was considered to be due to shedding from scoops used during the process. Following this investigation CAPAs to clean the equipment between [redacted] was implemented along with introduction of single use vacuum nozzles and a documented post-use check to identify any shedding. [redacted] was reviewed related to the vacuum nozzle usage. Separately during the investigation there was a determination that if brown particles were identified these would not be raised as deviations but instead as events. There was no requirement to re-test and left as a discretionary action. This was not considered adequate.

[redacted] – The environmental monitoring system related to a user going in to make a modification or a change, e.g. a beacon and alarm restart. This issue occurred on 13 December 2021 and was identified on 09 March 2022. It was described that a coding error had been made in 2002 when the system was originally designed, and while this had been identified as a root

cause, the reason for this coding issue to begin expressing itself in this way had not been considered, for example changes to underlying operating systems that may change the way in which the software works. As such the root cause analysis was not sufficiently extensive to ensure potential risks in future underlying system upgrades were properly considered.

[redacted] – this deviation was ongoing investigation at the time of the inspection and related to powder contamination found in a clean [redacted] 60 L bowl. The issue had occurred on 14 August 2023 and was originally due on 13 September 2023. An extension to the deviation was required to complete the investigation and a revised due date of 13 November 2023. An investigation meeting, 5-whys and fishbone investigation exercise had been conducted. The 10L and 65L bowls were inspected and the same issue was identified. All product associated with this equipment had been put on hold where it had not yet been distributed. Some trial materials had been provided to trials and the company determined that there had been a potential risk of contamination to batches produced in the respective equipment; while patient safety had been considered the impact on trial performance had not been considered at the time of the inspection.

[redacted] – This related to an action arising from [redacted] update of training documentation for particle size analysis. The objective was to agree a simpler approach for the content of the documentation, and re-issue updated documents. The due date of the action was 12 October 2023 and was open at the time of the inspection; the CAPA had been raised on 31 January 2023. The overall due date for the associated continuous improvement project [redacted] was 29 February 2024.

Change Management

The change control in [redacted] was reviewed during the inspection. The scope of the procedure was for planned and emergency changes, as well as GXP and EHS changes. The procedure sat as part of a suite of other SOPs that controlled other aspects such as introduction of new products, changes to global supply chains, introduction of new products intended for commercial supply as well as other unplanned changes. Changes required pre-approval and the level of approval required (Level 1, 2 and 3) depended on the complexity of the change. Post implementation reviews were conducted through a review of pre-known potential risks as well as those that were originally unforeseen; factors for this had to be pre-defined.

[redacted] – This change control related to the introduction of the [redacted] QMS for R&D. This change was raised on 11 November 2021 and had been completed at the time of the inspection. This included the introduction of change control, deviations, lab investigations, incidents logs, significant quality issues as well as other standard pharmaceutical quality system aspects. The pre-existing [redacted] system had data archived for the required retention period. The post-implementation review required by version [redacted] of the SOP that was live at the time of the system required a review of the cumulative effectives of the change summary, review of the impact and risk assessments to assess if significant risks are in control or mitigated to an acceptable level, any new quality risks or impacts introduced from the deviations ave been controlled and mitigated.

[redacted] – This change related to the creation of an [redacted] area within the existing [redacted] facility at R&D Ware. The change had been determined as a Level 2 change however there was no justification documented as to why this level of change had been selected. This change control had been raised in 2019 and since that time the system had been updated to require further detail. The change was still open at the time of the inspection however a post implementation of risks and new risks had not been predefined for completion despite this being

part of the procedure. As part of the pre-inspection activities the site had reviewed the associated cross contamination risk assessment and identified that required actions had not been completed and raised a deviation.

[redacted]– This change control related to an update to how equipment was sampled for cleaning verification. The impact assessment for this change was reviewed. No comments were raised.

Management Review

The [redacted] was reviewed during the inspection. The data set from July 2022-June 2023 highlighted a 'red trend' from January 2023 for % Extended CAPA Approved which fell below the KPI of less than 10%. The action tracker was reviewed during the inspection.

The technical change management procedure [redacted] governed corporate facing computerised systems under normal, emergency, and standard conditions. An email had been sent to add a room onto [redacted] According to the SOP this was classified as a normal change and required preapproval from a change manager, technical/peer reviewer, a QCA, and a CAB/eCAB, and following implementation a further QCA. No paperwork had been generated and as such the change had been made outside of the formal change management process.

C5 Personnel

A transferring QP's training and onboarding to be named on the MIA(IMP) was reviewed during the inspection. A new starter induction and training plan for clinical supply chain quality assurance was reviewed. A competency assessment was then performed following initial review of batches prior to full signoff. [redacted] which was a corporate training record system was used to guide new staff through the internal curriculum based on their site and role. QPs were responsible for releasing unlicenced medicines under the Manufacturer Specials authorisation however training in this area was not required as part of onboarding at this site.

C6 Premises and Equipment

The procedure for disassembly of the [redacted] was reviewed during the inspection, [redacted] Focus was placed on the disassembly and cleaning of silicon tubing used as air lines within the machine space, as well as control of ioniser tubing that could not be removed for cleaning using the 'immersible method' in the wash bay. It was noted that the procedure for cleaning the ioniser tubing stated to clean the part in situ with a cloth moistened with purified water followed by a detergent wipe followed by water and drying. It was not clear how all variables such as cloth wetness and wiping times were controlled as these were not stated.

The cleaning validation of the manual cleaning method for removable product contact parts in the wash bay sink was reviewed, [redacted] version [redacted] along with the corresponding report [redacted] The method involved grossly contaminating representative equipment with insoluble 'worst case' starting materials and leaving them to dry for 14 days, prior to performing the [redacted] cleaning method and performing analytical testing for product and detergent residues following a reduced rinsing process (e.g. PW final rinse and IPA wipe). This process was repeated annually. The validation was reviewed along with the cleaning method [redacted] which applied to manufacturing equipment, ancillaries, change parts, small parts and utensils. The water temperature cleaning was dispensed at 65 degrees

and the validation covered cleaning at 45 degrees, however the method described that a 'significant' drop of water temperature would be an issue but what this was had not been defined. For cleaning validation only parts that were direct product contact were considered, there was no assessment of risk for equipment that could not be fully immersed in water due to design (e.g. ioniser tubing) that may be indirect product contact during manipulation during manufacture. Where direct product contact parts could not be immersed these would be clean verified using analytical methods. Following cleaning a visual inspection was performed and documented in [redacted] In the event of failures this was recorded in that system. The last two reports that reviewed these occasions, [redacted] A failure of cleaning during the visual inspection check of the [redacted] Tablet Press that occurred on 25 July 2023 prior to re-build, at the time the equipment had been initially verified as clean. Within the record while the die holder was re-cleaned there was no evidence of any investigation or assessment with reference to the cleaning process and its effectiveness or root cause analysis which was not in compliance with the sites procedures.

The review of cleaning verification and validation activities Ware R&D Building [redacted], 2022 was reviewed, [redacted]. An example of a cleaning alert limit breach was reviewed whereby in the [redacted] Tablet Press bellow for the adapter plate reached the alert limit of [redacted] with a value of [redacted] The report noted that the equipment was recleaned and no additional cleaning validation was performed. The relevant procedure required an investigation to take place and this was uploaded into the Lab Experiment record however it has not been included in the overall review report. The discussion of the incident was contained in an email however the level of formality of the investigation was not appropriate.

Isolator in the [redacted] area was identified as having white residues on the surfaces of the extract and an O ring used to hold gloves in place had discoloured residues that could not be identified, as a result a deviation was raised. The site could also not justify the selection of white gloves rather than other colours that might better highlight residues.

The combined validation documentation approach for the [redacted] and [redacted] was reviewed during the inspection. No comments were raised.

The preventive maintenance protocol for the [redacted] was reviewed. No comments were raised.

The schematic diagram for the [redacted] was reviewed in terms of the air flows and potential for air flow reversals. No comments were raised.

Warehouse

This was in building [redacted] and there were three warehouse rooms at 15-25oC and 35-65% RH. There was also a cold store at 2-8oC. These areas were all continuously monitored via a Building Management System. Approximately 1-2 deliveries were receipted in a week. Areas were all clearly defined and there were segregated areas where required, e.g for quarantine and rejected stock.

Goods in checks were reviewed for [redacted] samples receipted on 19/10/2023. Data logger data was downloaded and reviewed. There was also a review of security seals and a cross check of the seal serial number where provided. It was discussed that it should be considered if seals without serial identification had adequate security controls in place. Stock movement was controlled a [redacted] Inventory tracker.

Waste management was outsourced to [redacted] There was no formal control around confirmation of destruction of pharmaceutical material.

Temperature Mapping

The mapping for ambient room [redacted] completed in Jul 2021 was reviewed. It was conducted for 72 hours. There was sufficient detail around how the mapping activity was conducted, data capture and equipment calibration. However, there was no formal assessment of the data generated and no evidence of a data trend review. This was also the case with the periodic validation review, which occurred three yearly and deemed that mapping would as a minimum reoccur every nine years or as an output of the three yearly review. The [redacted] review conducted in Feb 2021 was reviewed.

The associated procedure [redacted] detailed the minimum mapping criteria for different temperature conditions and when re mapping assessments would occur. The procedure did not clearly detail the scope of the three yearly review, particularly around delayed excursions assessment, engineering works, and other trends.

Temperature and humidity monitoring was continuous, but excursions would only lead to deviation investigation if the "temperature conditions exceeded the action limit." This differed for different ranges, e.g. the 2-8°C cold room [redacted] allowed a delay in timers of 45 minutes. It was unclear why this delay was allowed. The allowed delay different between the procedure and specification, the latter allowed up to one hour and allowed for an excursion of up to 15°C. The associated documents were [redacted] and [redacted] Due to this approach in logging excursions it was unclear if the mapping three yearly validation review would consider the delayed excursions as part of the review and the impact of that. The EMS server log books [redacted] and [redacted] for building [redacted] were reviewed for the period of May 2023 to current. It could be seen that there were multiple excursions that related to issues with the [redacted] performance and others due to excursions in high excursions with temperature and/or humidity. It was frequently deemed that there was no impact. However, there was no evidence as to why this was the case and why deviation investigation was not required.

C7 Documentation

Applications to vary the site's authorisations were reviewed.

MIA(IMP)

The variation to version [redacted] of the authorisation was reviewed during the inspection. This consisted of personnel changes, a change of site address (though the same buildings were being utilised) and removal of disused authorisations for manufacture of liquid IMPs for internal use and biotechnology products. Five analytical laboratories were also being removed.

MS

The variation to version [redacted] of the authorisation was reviewed. Similar changes were being made as per the MIA(IMP).

Batch review

This was managed by [redacted] Bach certification for commercial Lot [redacted] was reviewed. There was a detailed QA and QP checklist, which included review of the IMPD for market specific requirements.

There was limited detail around management of unlicenced import. It could not be evidenced robust procedures and processes were in place that detailed controls around import, including

TSE management, assessment of special clinical need, a clear control around who the trained batch releasers were and how they maintained their knowledge of unlicenced medicine. The associated procedures [redacted] and [redacted] were reviewed.

Batch release of unlicenced medicinal products was conducted by Qualified Persons. No releasing officers were utilised.

C8 Production

Manufacture

Summary report of the hold time study for [redacted] and [redacted] coating suspensions [redacted] was reviewed, this report had been completed on 22 April 2022 and involved the increase of hold time from 24 hours to 72 hours. Three suspensions were created using a 12% powder to 88% water mixture. Minimal growth was identified, and the hold time was extended accordingly, however recommendations to repeat the study using a higher sensitivity method had not been captured or actioned.

Purified Water

The changes to loop [redacted] made in 2021 were reviewed. This was the only loop that supplied the site. It has two associated loops: demineralised and spray ball. It was unclear how all the changes were assessed, e.g. removal of non return valve [redacted] and modification to pipework between point [redacted] and [redacted] The [redacted] which covered IQ and OQ was reviewed as well as the [redacted] The CVP passed and the PQ was conducted at risk for six months. The conclusion of this was that the system could go back to routine monitoring. Routine monitoring involved investigating microbiological failures above the action limit of [redacted] and three continuous alert failures above [redacted] All organisms were identified if any counts were identified.

The routine monitoring process included an annual plan which was generated at the start of each year. This was determined based on report [redacted]

The annual water report for 2022 [redacted] quarter 4 2022 report [redacted] quarter 1 2023 report [redacted] quarter 2 2023 report [redacted] were reviewed. They adequately detailed information to allow for trend identification. The Q3 2023 report was also reviewed, however this was still in draft at the time of inspection.

The following excursions were reviewed:

[redacted] this related to a laboratory user point alert level failure.

[redacted] this related to a wet in place skid alert level failure.

It was discussed that investigations were limited in scope. For example, the WIP skid investigation did not consider the other recent action and alert level failures for this user point or the other WIP skid, both of which was used for cleaning of coating machines.

C9 Quality Control

Chemistry

There were separate QC chemistry laboratories on the 1st and 2rd floor of building [redacted] (for commercial and R&D testing). Systems were shared and the intent was that all laboratories worked to GMP standard

Incoming samples were recorded in [redacted] which also outlined the quantities delivered/used/disposed, and which analysts had used the samples.

Analytical balances were subject to a weekly and monthly calibrations, which tested accuracy and repeatability respectively. See section D for deficiency details.

There were various rooms within the QC department. Reagents, buffers and mobile phases were clearly labelled and assigned an appropriate shelf life.

Dissolution baths were equipped for both basket and paddle methods. Each bath received a 6-monthly calibration check, involving physical measurements (dimensions, level, wobble, rotation speed, etc) and chemical testing.

Reference standards were either third party reference substances such as [redacted] or in-house working standards qualified against the primary material. Preparation of [redacted] was reviewed.

OOS was managed by [redacted] The following OOS were reviewed:

[redacted] Out of Specification impurity for [redacted] It was investigated to lab investigation part [redacted] and a root cause identified.

[redacted] Out of Specification for content. This investigation did not evidence if this was a truly isolated incident and if further action was required to stop the risk of reoccurrence in selecting the incorrect pipette.

[redacted] Nitrosamine failure. This was adequately investigated.

The procedure clearly detailed how out of specification investigations would be investigated and how assessments were made for atypical results.

An annual review of OOS and ASF was conducted. The review for 2022 was inspected. It included attributable errors by category, a comparison of the causes with root causes of previous years, deviation compliance and investigation close out times.

HPLC testing for impurity was reviewed for batch [redacted]. This was conducted in [redacted] The data was suitably managed. It was however discussed that there was no control or check in place for generation of orphan data.

Procedure [redacted] detailed how manual integration would be calculated, including for scenarios such as valley point, forced peak end point, derivation in presence of a gradient, peaks eluting close to the solvent front, fused peaks and tangent skimming.

Stability

The stability chambers were continuously monitored by the site EMS. There were chambers for standard ICH conditions and chambers were often in duplicate to allow sufficient storage.

The following protocol [redacted] was reviewed and it clearly defined how testing would be managed. Inventory aligned with protocol requirements for the 20oc- and 75%RH conditions.

Microbiology Laboratory

The majority of tests were of microbial limit, purified water and environmental monitoring samples. There were separate entry routes and rooms to segregate sample testing from positive inoculations.

Media was purchased pre-prepared, and subject to growth promotion testing. There were four incubators at different conditions and temperatures were constantly monitored using the same Business Management System as the warehouse.

Data was predominantly captured in a [redacted] system. There were no specific procedures in place detailing requirements for regular, holistic audit trail review for specific data systems e.g. data capture within [redacted] An audit trial review of MLT and environmental monitoring test data was conducted but there was no consideration of high-risk data such as orphan data.

Microbial Limit Testing

This was managed by [redacted].

The procedure detailed relevant criteria for what level of testing would be required at each phase. Phase III would require a three run validation. The MLT validation was reviewed for [redacted] a [redacted] oral solid dose. This included a review of the: associated reports [redacted] and [redacted] Protocol [redacted] Report [redacted] Two runs were completed by [redacted] and one by the site. It was discussed that the management of the validation activity by [redacted] was reviewed within the final report which included a summary of the data from both sites. However, it could not be evidenced that this included a detailed review of any associated activities raised within the QMS, such as deviations, changes, raw data. The deviation [redacted] raised by [redacted] had not been reviewed by site to ensure the reason for retesting, approach and root cause were agreed.

The organisms used for testing were purchased and had certification in place, as exampled by E. Coli batch [redacted]

Growth Promotion Testing

There was a detailed procedure, [redacted] The procedure was suitably detailed. It included information regarding media control and testing failures. The dataset associated with [redacted] was reviewed.

C10 Outsourced Activities

This area was not inspected in detail. Initial requests were made around management of technical agreements and a list of outsourced QC activities. However not all information was not available without delay and therefore was not reviewed.

Agreements with the trial sponsor [redacted] were reviewed. The agreements were detailed in numerous areas, including record retention, storage, shipping, release, regulatory filing, and recall. There were no clear criteria for how subcontracted activities would be managed, e.g. if the Sponsor made changes to arrangements that impacted manufacture at the local site, such as the API.

See section D for deficiency details.

C11 Complaints and Product Recall

Complaints

This was managed by SOP [redacted] This was not reviewed in detail as the organization had not had complaints during the last three years. The procedure was suitably detailed.

Recall

This was managed by [redacted] The site had not had a recall in the last three years so the current mock recall was reviewed. This was last conducted in Nov 2022. It was

sufficiently detailed and included both internal and external suppliers in the chosen simulated scenario. The organisation was able to identify all customers and notify them within 24 hours. Some improvements were identified that were captured as part of CAPA. It was discussed that the recall simulation did not challenge the complexity of supply chains the organisation operated or the ability to unblind or consider any impact to open or ongoing studies. There was some consideration for review of comparators and their recall status.

C12 Self Inspection

Not reviewed during this inspection.

C13 Distribution and shipment (including WDA activities if relevant)

Not reviewed in detail during this inspection.

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

D1 Critical

None

D2 Major

None

D3 Others

3.1 **Controls to minimise the risk of cross contamination were deficient, in that:**

3.1.1 In respect of the isolator in the [redacted] area that was in a 'clean' condition:

3.1.1.1 Unknown white residues were identified inside the isolator on the extract system.

3.1.1.2 Unknown residues were identified on the glove port O ring.

3.1.1.3 The reason for discolouration of the product out-feed hatch had not been identified or investigated.

3.1.2 The risk of using white isolator gloves that might present increased challenges to effective post cleaning visual cleanliness checks had not been assessed.

3.1.3 There was no justification for the site to not perform periodic analytical swab analysis of manually cleaned product contact parts during routine manufacture to verify the effectiveness of routine manual cleaning processes.

3.1.4 Cleaning process variables were not adequately controlled, for example the minimum validated water temperature for use during cleaning (etc) were not defined in the procedure, nor was there sufficient detail of how to control the cleaning of equipment that required turning during the 5-minute soaking stage.

3.1.5 There was insufficient assurance that cleaning methods were effective in removing potential contaminants from indirect product contact parts that could not be easily removed for cleaning or subjected to the level of wet cleaning validated, for example the silicon tubing associated with the ionizer within the encapsulation equipment that could be used for [redacted] products.

3.1.6 There was no instruction to discard single use brushes used for cleaning product contact parts in the site's procedures.

3.1.7 There was insufficient justification to support the site's approach of using brand-new polymeric seals as part of manual cleaning verification studies in place of using those already utilized on equipment that would take account of wear and tear and the additional burden on cleaning this may present.

3.1.8 There was inadequate definition within the site's procedures to ensure that where repeated manual cleaning of equipment to achieve a satisfactory level of cleanliness would be recorded and investigated.

Reference: EU GMP C5.10, C5.18, C5.21, A15.10.2, A15.10.5, A15.10.15

3.2 **Processes and controls supporting investigations were deficient, in that:**

3.2.1 An appropriate level of root cause analysis was not always performed, for example there was no requirement to raise a deviation in the event of further brown particles being identified during manufacture of product [redacted] or adequate control to ensure samples of such particles taken during manufacture would be analysed.

3.2.2 The cleaning failure on the [redacted] that occurred on 25 July 2023 had not been investigated in accordance with the site's procedures, and instead was recleaned and returned to use.

3.2.3 There was insufficient investigation of microbiology alert and action level failures as exampled by investigation [redacted] of a skid water point. The investigation did not consider the other action and alert level failures for this user point or the other wet in place skid, both of which were used for cleaning of coating machines. Therefore, it also did not adequately consider corrective actions as a result.

3.2.4 The root cause of the residue alert limit breach on the Tablet Press adapter plate described in [redacted] had not been adequately investigated in accordance with the site's procedures.

3.2.5 The root cause analysis of [redacted] was limited as it did not consider the factors that led to the system code issue manifesting itself as a data integrity issue several years after the system had been introduced, for example operating system upgrades, to prevent future impact on other systems.

Reference: EU GMP C1.4(xiv), C1.8(v), C1.8(vii)

3.3 **The management of change was deficient, in that:**

3.3.1 The company's defined change process to amend the [redacted] system to add two additional dispensing areas had not been followed.

3.3.2 The intention to perform the coating solution hold time study at a higher microbiological method sensitivity as recommended in change [redacted] had not been captured in the pharmaceutical quality system to ensure that this would be performed and had not been completed at the time of the inspection.

3.3.3 Post implementation review requirements defined in the site's procedures were not always completed as there was no review of risk assessments for the change or an assessment of whether significant risks were in control or if new risk impacts had been identified and controlled in change control [redacted] or [redacted]

3.3.4 It could not be evidenced robust arrangements were in place for the prospective evaluation of changes and their approval prior to implementation, for example the change to the purified water loop. It was unclear how all the changes were assessed as required and therefore appropriately implemented, e.g., removal of non-return valve [redacted] and modification to pipework between point [redacted] and [redacted]

Reference: EU GMP C1.4(xii), C1.8(v)

3.4 **Documentation and data integrity controls**

3.4.1 There were no specific procedures in place detailing requirements for regular, holistic audit trail review for specific data systems e.g. data capture within [redacted] or [redacted] An audit trial review was performed, but this was limited to an experiment or project specific data audit. It did not consider high risk data such as orphan data and generation of "test" injections.

3.4.2 Labels used within production areas were not always adequately controlled, for example there was no defined standard to specify which information had to be applied to hand written labels adhered to drums containing dispensed materials for production.

3.4.3 No [redacted] label had been applied to [redacted] contrary to the requirements of the procedure.

3.4.4 The hybrid (electronic and paper) management of weekly and monthly balance calibrations in the QC laboratory was ambiguous. The current controls did not evidence an analyst would not be at risk of incorrectly using a balance beyond the worst case tolerance date for retest of +3 days.

3.4.5 The contracts between [redacted] and GSK/GSK R&D (issued in Jan 2022 and Jan 2021) did not clearly detail which operation they related to, i.e. which specific GSK organisations were inscope and who the contract giver or acceptor was.

Reference: EU GMP C4.1, C4.3, C5.13, C7.1, A11.9

3.5 **Production and warehouse management procedures were deficient, in that:**

3.5.1 <u>Production</u>

3.5.1.1 There was no justification for using starting material manufacturer expiry dates for dispensed materials and no dispensed material hold time studies had been performed.

3.5.1.2 There was no justification for storing cleaning agent [redacted] between 15°C to 25°C degrees outside of the manufacturers recommended conditions of 10°C to 20°C degrees or knowledge of whether storage outside of these conditions could impact on its performance.

3.5.2 <u>Warehouse:</u>

3.5.2.1 There were no procedures or records for destruction of obsolete goods.

3.5.2.2 It could not be evidenced there was sufficient data review during the three yearly mapping review or of other control systems, such as deviations, event reports or risk management to establish that mapping was repeated appropriately. This was evidenced by the 2021 validation report for room [redacted]

3.5.2.3 Documentation [redacted] and [redacted] around temperature monitoring for excursions:

3.5.2.3.1 Was not clearly detailed and contradictory in requirements for alarm reporting.

3.5.2.3.2 Could not evidence what the impact to product would be if it was not stored under labelled conditions and why delays in alarm reporting were acceptable.

3.5.2.3.3 Did not consider the risk in recording excursions from labelled conditions as “events” rather than “deviations.

Reference: EU GMP C1.13(ii), C4.3, C5.7,
EU GDP 3.2.1, 5.6
Guideline on manufacture of the finished dosage form
(EMA/CHMP/QWP/245074/2015)

3.6 **Procedures supporting the supply of Unlicensed Medicines were deficient, in that:**

3.6.1 There was insufficient detail within the pharmaceutical quality system concerning the management of unlicensed medicines, including local requirements release, import and unmet clinical need.

3.6.2 Onboarding processes for Qualified Persons responsible for the release of batches under the Manufacturer Specials authorisation did not include specific training on unlicenced medicinal products.

Reference: EU GMP C2.11
The supply of unlicensed medicinal products 'specials', MHRA guidance note 14. (https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials)

3.7 Batch review and certification was deficient in that it could not be assured atypical and out-of-trend investigations would be completed to a sufficient level to support certification as it could not be evidenced such data was reviewed for trends. Therefore, it was unclear if the need for further or escalated investigation would be required that it would be identified, e.g., via deviation management.

Reference: EU GMP A16.1.7.16

3.8 MLT validation for [redacted] (conducted at both [redacted] and R&D sites) did not robustly assess reproducibility and that acceptance criteria was based upon the current validation study methodology at both sites. This was evidenced by the limitation in data review associated with Report [redacted]

Reference: EU GMP C6.39(v)

D4 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	✓	[redacted]	[redacted]
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

During the closing meeting the deficiencies were verbally described by the inspectors and accepted by the sites representatives who committed to responding to the post inspection letter with actions within the prescribed timelines.

F2 Assessment of response(s) to inspection report

The site submitted their response to the post inspection letter on 07/12/2023 and following review by the inspectors was accepted and the casefolder closed.

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: 08/01/2024**

Accompanying Inspector: [redacted] **Date: 22/01/2024**

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:	8	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)

[redacted]

(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

[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

Annex 2 – Persons met during the inspection

Name	Job Title	Opening Presentation Attendance	Closing Presentation Attendance
[redacted]	[redacted]	Y	Y
		Y	N
		Y	Y
		Y	Y
		Y	Y
		Y	Y
		Y	Y
		Y	Y
		Y	Y
		Y	Y
		Y	N
		Y	Y
		N	Y