Medicines & Healthcare products Regulatory Agency

MHRA

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OFFICIAL – SENSITIVE COMMERCIAL

[redacted]

Dear [redacted]
GLAXOSMITHKLINE RESEARCH & DEVELOPMENT
PARK ROAD
WARE
SG12 0DP
UNITED KINGDOM

09 November 2023

Case No: Insp GMP/IMP 5866/27277-0035

Subject:
THE HUMAN MEDICINES REGULATIONS 2012 (as amended) (SI 2012/1916)
THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 (SI 2004/1031)
AUTHORISATION NO. MIA(IMP) 5866, MS 5866

Dear [redacted]

May I thank you and your colleagues for the courtesy and co-operation shown during the inspection of your premises at Ware on 31 October until 02 November 2023.

During the inspection a number of failures to comply with the Guide to Good Manufacturing and Distribution Practice were observed and these are listed in the Appendix to this letter.

Please reply within 28 days, giving your proposals for dealing with these matters, together with a timetable for their implementation. Please send your response electronically by e-mail to me at the address below copying in my colleague [redacted] .

It would be appreciated if your response was in the following format:

1. Restate the deficiency number and the deficiency as written below.
2. State the proposed corrective action and the target date for completion of these action(s)
3. Include any comment that the company considers appropriate.
4. Please provide the response as a word document.

Further guidance on responding to inspection deficiencies can be found at the following web link
https://www.gov.uk/guidance/guidance-on-responding-to-a-gmpgdp-post-inspection-letter

Yours sincerely

[redacted]
GMDP Inspector
Email: [redacted]

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

File Ref: Insp GMP/IMP 5866/27277-0035
Inspection Date: 31 October to 02 November 2023
Company: GlaxoSmithKline Research and Development

FAILURES TO COMPLY WITH THE GUIDE TO GOOD MANUFACTURING PRACTICE

1 CRITICAL

None

2 MAJOR

None

3 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 Tablet Press Dye ([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] [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 5G605.

3.5.2.3 Documentation [redacted] v.[redacted] and [redacted] v.[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 GSC 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] v.[redacted].

Reference: EU GMP C6.39(v)

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4 COMMENTS

None