Medicines & Healthcare products Regulatory Agency

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Date 31/05/2022

Case No: Insp GMP 17907/13988-0035

**SUBJECT: THE HUMAN MEDICINES REGULATIONS 2012 (as amended) (SI 2012/1916)**

**AUTHORISATION / REGISTRATION NO. MIA 17907, API 17907, WDA(H) 17907**

Dear [redacted]

I refer to the inspection carried out at your company's premises at the above address on 16th to 20th May 2022 by medicines inspectors [redacted] and [redacted]

The inspection findings indicate that there are serious deficiencies in your operations that will be escalated to senior Inspectorate staff for consideration. Following this review, any further actions will be communicated to you as separate correspondence. An explanation of compliance escalation can be found at the following web link: https://www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice#actions-after-the-inspection.

The Inspectorate may also consider whether to refer the inspection findings to the Inspection Action Group to determine whether there are grounds for the Licensing Authority to take action against your authorisation and / or to issue a statement of non-compliance with GMP or GDP.

The failures to comply with the principles and guidelines of Good Manufacturing Practice and / or Good Distribution Practice are listed in the Appendix to this letter.

Correspondence relating to this inspection, including any proposals you have for dealing with the deficiencies identified, should be sent electronically to me at the address below,

within 21 days. A copy of the response should also be sent electronically to the inspector [redacted] and [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
Telephone: [redacted]
Email: [redacted]

## FAILURES TO COMPLY WITH THE GUIDE TO GOOD MANUFACTURING / DISTRIBUTION PRACTICE

### 1. CRITICAL

None

### 2. MAJOR

2.1 **Elements of the pharmaceutical quality system were deficient in that:**

2.1.1 **Deviations were not fully investigated and assessed to determine appropriate corrective actions as evidenced by:**

2.1.1.1 Deviation [redacted] for the calibration failure of sieves used for QC particle size analysis did not fully assess the impact on API batches tested since the previous satisfactory calibration or on the finished product batches made from them.

2.1.2 **Complaints investigations and records were found deficient, examples given:**

2.1.2.1 The investigation [redacted] for discoloured brown tablets in blister, crumbling apart didn't consider the history review of previous quality defects report of very similar complaint [redacted] regarding slightly odd taste and some discoloured and brown tablets for any indication of recurring problems.

2.1.2.2 The investigation review/ approval process was not consistently followed in case there was an update to investigation e.g. complaint sample received, decision taken if an update of complaint response was required.

2.1.3 **Quality risk management was not applied in generation of internal audits schedule for example there was no impact of trending and evaluation of the outcome including if critical deficiencies were observed during some audit**

2.1.4 **Arrangements in place for the prospective evaluation of planned changes and their approval prior to implementation were deficient as evidenced by:**

2.1.4.1 There was no justification provided in the change control [redacted] for revision of MBR for [redacted] pressure limit of [redacted] with respect to corridor to be changed from -8 pascal to -2 pascal. In addition, the risk assessment didn't reflect the pressure cascade completely and cross contamination prevention measures in place.

2.1.4.2 The change control [redacted] for introduction of [redacted] and [redacted] packaging at Luton site was not referenced to the corporate related change control [redacted]

2.1.5 **There was no evidence that the batch record, production documentation and assessment of other potential deviations was completed for batch [redacted] rejected due to assay OOS e.g. the batch record was not signed for**

**review.**

EU GMP C1.4(xii), C1.4(xvii), C1.8(vii), C1.9(vi), C1.13(i), C8.12, C8.14, A16.1.7.6

2.2 **Qualification and Validation, including the control of equipment was deficient in that:**

2.2.1 **Not all equipment had been re-qualified to confirm it remained in a state of control as evidenced by, but not limited to:**

2.2.1.1 QC laboratory particle size analyser [redacted] had been brought into use following verification by the service engineer without performance qualification being completed in line with the site procedure.

2.2.2 **Not all equipment had been maintained and installed to prevent any risk of error as evidenced by but not limited to:**

2.2.2.1 QC laboratory dissolution systems could not be setup in accordance with the stipulated configuration as serial numbered vessels had been replaced without the configuration instruction being updated to reflect the changes, resulting in the expected vessels not being present, additionally paddle serial numbers were difficult to read.

2.2.3 **A quality risk management approach wasn't adequately used for qualification and validation activities and there was lack of documenting the way in which risk assessments were used to support qualification and validation activities as evidenced by:**

2.2.3.1 Packaging process validation did not establish the ranges for the worst case of a blistering machine considering the line speed and forming/sealing temperature.

2.2.3.2 The SOP for [redacted] didn't consider stability studies even in case where it allowed bulk product beyond 180 days.

2.2.3.3 Temperature mappings weren't done under representative conditions and following the risk assessment principles, as evidenced by but not limited to:

2.2.3.3.1 The temperature mapping Summer Aug 2019 Report for warehouse Unit [redacted] & [redacted] didn't contain data of external temperature at the time exercise was done

2.2.3.3.2 There was no discussion/ impact assessment of temporary seasonally installed chillers and their position, movement and off-side storage, when not in use.

2.2.3.3.3 Temperature mapping report for storage Unit [redacted] didn't provide confirmation, if temperature set point has been changed during mapping

2.2.3.4 In the warehouse Unit [redacted] in the area specified for storage at 15-25 C there was no alarm triggered to indicate excursion below 15C i.e. this was set at 2C with no evident justification.

2.2.3.5 There was no justification why PQ of e.g. FBD in Granulation [redacted] was appropriately performed during the manufacturing of the regular commercial batch and clear confirmation it was satisfactory and met all criteria.

EU GMP C3.34, C3.35, C3.38, A15.3.13, A15.4.1, A15.5.2(1-2), A15.7.2
EU GDP 3.2.1
EMA/CHMP/QWP/245074/2015, Guideline on manufacture of the finished dosage form

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| 2.3 | **Cross contamination controls were deficient:** |
| 2.3.1 | **Quality Risk Management was not being adequately used to assess and control cross contamination risks as evidenced by:** |
| 2.3.1.1 | HBEL reports available for active substances manufactured did not consider pediatric formulations and if additional controls were required |
| 2.3.1.2 | The quality risk assessment was performed for manufacturing of [redacted] product campaign in the shared facility outside of the potent area, but there was no evaluation post campaign of adequacy of all measures and their effectiveness |
| 2.3.1.3 | The cleaning validation of [redacted] was deficient as there was no rational how the swabbing location were chosen for example in packaging area, which contact surfaces were sampled |
| 2.3.1.4 | There was no assessment of the brushes in the blistering line for example as they were not included in the sampling plan, i.e. how the existing [redacted] line limit for brushes based on the 2016 year was still applicable |
| 2.3.2 | **Technical and organisational measures required to control risks for contamination/ cross-contamination were not adequately followed and premises were not adequately maintained as evidenced by:** |
| 2.3.2.1 | Doors between plant technical area and sachet packing area were left open. Note: The line was not in use. |
| 2.3.2.2 | During the inspection tour in the manufacturing plant, it was observed that some doors between processing areas and corridor were not closing properly. |
| 2.3.2.3 | In the wash bay room the floor was found wet during the inspection tour and there was no consideration how to prevent leave the room if wet floor left |
| 2.3.2.4 | Alarms limits for the "potent area" were not in line with the required differential pressure example given the entry to the potent area airlock [redacted] and corridor (-2 Pa required, alarms set to -1Pa). |
| EU GMP | Chapter 3 Principle, C3.2, C3.37, C5.10, C5.20, C5.21(all)<br>Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (EMA/ CHMP/ CVMP/ SWP/169430/2012) |

## 3. OTHER

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| 3.1 | **Documentation practices were deficient in that:** |
| 3.1.1 | **Not all procedures were adhered to as evidenced by:** |
| 3.1.1.1 | Procedure [redacted] for entry into the microbiology lab required all personnel, including visitors, to wash their hands before gowning and entering the laboratory testing area [redacted] This part of the procedure was not followed during the inspection. |
| 3.1.1.2 | Procedure [redacted] stated that a list of named persons to contact in the event of a stability chamber alarm was present in the stability area – this was not the case. |

3.1.2 **The content of some procedures was ambiguous as evidenced by:**

3.1.2.1 Procedure [redacted] did not adequately describe the process for handing stability chamber alarms out of normal business hours e.g. evenings and weekends. Additionally, the terminology used to describe the criticality of alarms was confused, with the terms "serious" and "significant" used without definition.

3.1.2.2 The procedure for gowning presented in the visitors change room didn't provide detail instruction for de-gowning while exiting the manufacturing area e.g. no correct order of actions or photos provided.

3.1.2.3 The technical agreement for Contract Warehousing (Storage and Distribution) between [redacted] and Bristol Laboratories Limited (CA) required to notify the [redacted] if temperature conditions were [redacted] but internal procedure and monitoring process required actions to be taken if temperature was above [redacted]

3.1.2.4 The procedure for alarm review in the "potent area" didn't provide clear instruction how and in which timeline data should be reviewed e.g. the report of the alarms for period 16-17/ May 2022 was reviewed on 19/05/2022. In addition, the report was not generated on the next working day as expected on 18th May to cover 17-18th May 2022 than on 19th May covering 17-19 May 2022.

3.1.2.5 There was no justification for the sampling plan used in the procedure for in process control of leak test in case of test failure e.g. why double size sample was representative if failure cause unknown or how the previously produced quantity was tested

3.1.3 **Not all records were completed in a manner which allowed full traceability as evidenced by but not limited to:**

3.1.3.1 Confirmation of addition of materials into the manufacturing process, documented in the batch manufacturing record for [redacted] batch [redacted] were not fully recorded as part of the approved batch manufacturing record. Confirmation of the quantity added was recorded on a sperate sheet generated by the SAP system and the record of addition was not dated.

3.1.3.2 Dates of completion of preventative maintenance and calibrations, recorded on the relevant schedules, were not traceable to the person who made the entry.

3.1.3.3 Additional entries were made into the change parts logbook [redacted] following relocation of change parts to another storage location without any explanation as to what had occurred. The entries were not traceable to the individual who made them.

3.1.4 **Data was not recorded in a manner which permitted trend evaluation as evidenced by:**

3.1.4.1 The 2021 annual review of microbiological test data associated with the manufacturing purified water system was not presented in a way which permitted trend evaluation, additionally no comparison of the data against action and alert limits was documented, neither was an assessment of the continued suitability of said limits.

3.1.5 **Documents were not prepared and distributed with care and there was lack of control for electronic documents such as templates, forms as evidenced by:**

3.1.5.1 The matrix for the cleaning validation was prepared, but not in line with

the procedure template [redacted] e.g. it was not updated to newer version in the SOP and there were additional columns and different measurement units (OEL column, levels flg/m3)

3.1.6 **Documents were not regularly reviewed and kept up-to-date as evidenced by the WDA(H) 17907 which didn't reflect accurately all activities carried out from various locations for example export.**

3.1.7 **The records were not providing evidence of actions taken to demonstrate compliance with instructions as evidenced by but not limited to:**

3.1.7.1 An onsite audit could be substituted by the desktop one in case of travelling restrictions, dangerous/ non-safe locations/ situations, but there was no rational recorded why this was applied to the API [redacted] manufacturer [redacted] in March 2022.

3.1.7.2 In the validation report for requalification of [redacted] in [redacted] area for paste preparation there was no final conclusion recorded if the equipment is fit for use as required by the template.

EU GMP Chapter 4 Principle, C1.9(i), C1.9(ii), C4.1, C4.2, C4.3, C4.8, C4.9, C6.9, C6.12

3.2 **Materials handling, labelling and storage under the appropriate conditions were deficient, for example:**

3.2.1 There was no process in place to ensure that there was no impact to the quality of empty capsules requiring controlled storage conditions of temperature and humidity during storage in the "temporary daily storage area" as there was no relative humidity monitoring (min and max values) in this area, neither there was monitoring of the time they were kept in that area/ outside of the controlled area.

3.2.2 The active substance [redacted] required storage at 2-8 ºC, but there was no control of material movements outside of the storage area at this condition e.g. during the temporary storage within manufacturing area in case of campaign manufacturing.

3.2.3 Materials/ bulk containers were not appropriately labelled at all times, as evidenced by the external label on the containers of the bulk tablets [redacted] batch number [redacted] moved from [redacted] to Luton site for packaging which did not stick properly.

3.2.4 Inadequate maintenance which could lead to inadequate storage conditions was observed in the storage, as evidenced by the damaged sunlight protection on the roof in Unit [redacted]

EU GMP C3.2, C3.3, C3.19, C5.2, C5.7, C5.12

## 4. COMMENT

4.1 There was a number of changes which included implementation/ installation of new manufacturing and control equipment, as well as new computerised systems since the last inspection. Also, several new molecules/ products were introduced, and production capacity was increased to 30-40 %. The site was reminded to use the Interim

Compliance Report to communicate any significant change when there is no licence variation required, including the above-mentioned examples.