



Medicines & Healthcare products  
Regulatory Agency



**MHRA**

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RESTRICTED – COMMERCIAL

[REDACTED]  
Aesica Queenborough Limited  
North Road  
Queenborough  
ME11 5EL  
United Kingdom

Date 24/05/2022

Case No: Insp GMP/IMP 32496/30433-0046

**SUBJECT: THE HUMAN MEDICINES REGULATIONS 2012 (as amended) (SI 2012/1916)  
THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 (SI 2004/1031)  
THE VETERINARY MEDICINES REGULATIONS 2013 (SI 2013/2033)**

**AUTHORISATION / REGISTRATION NO. MIA 32496, MIA(IMP) 32496, ManA 32496**

Dear [REDACTED]

Thank you for the courtesy and co-operation shown during the inspection of your premises at the above address on 17/05/2022.

During the inspection a number of failures to comply with the principles and guidelines of Good Manufacturing Practice and / or Good 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. The response should be sent electronically to me at the email address below.

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>

In view of the serious inspection findings, urgent improvement is required. MHRA may consider that a special inspection is necessary after a shorter interval than normal, to determine whether alterations or improvements have been satisfactorily carried out. Failure to demonstrate the required improvements during a subsequent inspection may result in consideration of regulatory action against the company.

Yours sincerely

  
GMP/IMP Inspector

E-mail: 

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

**1. CRITICAL**

None

**2. MAJOR**

- 2.1 Controls to minimize cross contamination were deficient as:
  - 2.1.1 The revalidation of manual cleaning of the mixer on the shared [REDACTED] line was deficient in that:
    - 2.1.1.1 The planned activity revalidation was scheduled outside of the three yearly time point.
    - 2.1.1.2 The planned swabbing activity was not performed, instead a document review was performed with no impact assessment or deviation.
    - 2.1.1.3 The original signed documentation could not be located during the inspection.
    - 2.1.1.4 There had been no overall risk assessment of the impact and extent of overdue cleaning revalidation activities.
  - 2.1.2 The validation of the [REDACTED] cleaning was incomplete as:
    - 2.1.2.1 There was no final QA approved summary for the updated analytical method validation for cleaning of [REDACTED]
    - 2.1.2.2 It was seen that repeated results required recalculation and no formal impact assessment or deviation was raised to document this.
  - 2.1.3 There had been no assessment if the washing machine used for filter bags was free of active residue at the end of the cleaning cycle.
  - 2.1.4 It was not required to trend or investigate manual cleaning failures.
  - 2.1.5 Visible residues were seen in the [REDACTED] Compression room in seals and the outlet port.
  - 2.1.6 Equipment and Room Status in Building [REDACTED] was not always clear as
    - 2.1.6.1 Equipment in corridor in Cell [REDACTED] was labelled as to be cleaned when it additionally required verification for removal of residues.
    - 2.1.6.2 The cleaned status of items in Cell [REDACTED] wash bay sink was not clear
    - 2.1.6.3 Rooms under development were not labelled with details of product and in Cell Room [REDACTED] there were visible white powder residues on trolley wheels
    - 2.1.6.4 Although it was described that equipment from each room in Cell [REDACTED] were cleaned and when verified returned to the room the spray guns were not with the cleaned equipment in the coater room.
  - 2.1.7 The SOP [REDACTED] did not describe whether cleaning cloths such as the Sponge scourer were required to be disposed of following cleaning.
  - 2.1.8 Periodic requalification of manual cleaning processes did not consider events which may have impacted cleaning for example the effect of cumulative change controls, deviations and customer complaints.

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- 2.1.9 There were no specific manual cleaning instructions regarding the reusable plastic scoops used in packaging
- EU GMP C1.4(viii), C1.12, C4.10, C5.12, C5.13, C5.18, C5.21 Organisational Measures, C5.22, C5.26, A15.1.8, A15.2.7, A15.2.9, A15.2.10, A15.3.1, A15.10.5, A15.11.6
- 2.2 QC Controls for release and stability management were deficient as:
- 2.2.1 Stability test points were not adhered to and no impact assessment had been made or deviation raised as exemplified by [REDACTED] batch [REDACTED] set down as part of the 2020 stability commitment.
- 2.2.2 A deviation had been raised in September 2021 to address a general failure to test stability timepoints at specified timelines however to date no impact assessment or formal action plan had been documented.
- 2.2.3 The SOP for stability allowed 90 days to set the samples down on stability before initial test point was required to be confirmed, this was in contravention to client required timelines of 30 days.
- 2.2.4 Stability Samples were not stored and labelled in a secure, consistent manner or in accordance with SOP in that:
- 2.2.4.1 [REDACTED] were not labelled with required storage conditions.
- 2.2.4.2 [REDACTED] was identified as [REDACTED] on the stability identification label.
- 2.2.4.3 Samples from each study were not adequately segregated as exemplified by loose tablet strips for different studies located in stacked document trays
- 2.2.4.4 Product packed in un-labelled white bottles were only annotated with code and batch number.
- 2.2.5 [REDACTED] reference standard was stored in the ambient reference store but required refrigeration.
- 2.2.6 Empower data integrity reviews had not been completed in line with procedural timelines as required by SOP [REDACTED] and in addition the check for deleted data was ambiguous as it was signed for but not clear what was being checked.
- 2.2.7 Root cause analysis did not always apply principles of risk management. For example, [REDACTED] did not consider the impact of conducting phase IA and IB investigations using a different column [REDACTED] to that used for the original test [REDACTED]. Therefore, it was also unclear if root cause was correctly identified.
- EU GMP Chapter 4 Principle, C1.4(viii), C1.4(xiv), C1.8(v), C1.9(v), C6.13, C6.22, C6.26, C6.29
- 2.3 Quality Management Systems were deficient in that:
- 2.3.1 Deviation management was incomplete as:
- 2.3.1.1 It was unclear how during batch review and certification it would be known if a "corrective action outline (CAO)" was associated with the batch under review and therefore that all GMP critical data associated with said batch would be visible to the QP. For example,

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	not all CAO for the [REDACTED] line camera failures were linked to a deviation, so it was unclear how they would be tracked through a batch record.
2.3.1.2	There was no evidence of the longer-term product impact or risk assessment to deviations, CAPA or "corrective action outline" when investigations and action timelines were extended. For example, Deviation [REDACTED] raised in Nov 2019, related to a packaging line camera failure, had further associated events and deviations raised throughout 2020 and 2021 without further action but reliance on the original "corrective action outline." This included no assessment of manual IPC checks, training, procedural updates and process verification/validation assessments due to the longevity of interim controls.
2.3.1.3	Root cause investigations were not robust. For example, [REDACTED] related to dissolution failures/low weight for [REDACTED] did not evidence how root cause was identified. It was unclear why issues with low weight did not impact product efficacy and how it was concluded root cause related to solvent coating solutions but not other factors such as API content or supplier quality.
2.3.1.4	The deviation procedure was ambiguous as it was not clearly defined how "preliminary criticality" was classified and related to the risk score generated. For example, "preliminary criticality" was selected as critical, major, or minor for the deviations reviewed but there was no definition for what these categories were and how they were selected.
2.3.1.5	The deviation procedure defined minor events as those with no product quality impact. The procedure was not followed as some of the following deviations to [REDACTED] were inaccurately raised as minor events.
2.3.1.6	The manner in which the risk score calculation was inputted within the [REDACTED] system was not documented or defined within the currently approved QMS.
2.3.2	CAPA management arising from [REDACTED] was weak as:
2.3.2.1	A procedural update was given a timeline of five months to complete and remained overdue at time of inspection.
2.3.2.2	A required staff briefing had not been done until six months later following the incident and the CAPA had been extended with no robust justification, in addition further batches had been processed prior to the briefing being made.
2.3.3	Change control sop was silent as to when effectiveness checks were required, and which criteria should be employed for their use.
EU GMP	C1.4(ix), C1.4(xii), C1.4(xiv), C4.1, C4.5

3. **OTHER**

3.1	Documentation controls were deficient as:
3.1.1	Documentation relating to [REDACTED] trial material had not been completed correctly for example the material balance sheet had not been completed.

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- 3.1.2 The logbook in the Quarantine area was not correctly populated for example there was no record of the batch number of capsules.
- 3.1.3 The level one Autonomous Maintenance Schedule within the production environment did not capture GMP significant activities in an indelible and unambiguous manner as it was unclear how alterations would permit reading of the original data and ensure that the integrity of the record would be maintained via a defined retention period due to the format and nature of the document.
- 3.1.4 Documents were not reviewed in a timely manner as exemplified by [REDACTED] where activities had been completed on 26 April 2022 but this had not been verified as acceptable.

EU GMP C4.3, C4.5, C4.7, C4.8, C4.9, C4.10

- 3.2 Materials management
- 3.2.1 Capsules shells were stored in the uncontrolled humidity quarantine area.
- 3.2.2 [REDACTED] capsules for packaging were stored in the "Hot room" however this was not humidity controlled or monitored despite the product requiring storage at less than 50% Humidity.
- 3.2.3 The SOP [REDACTED] was silent with the requirement to reconcile products sent for destruction or to obtain evidence of destruction from the waste company.
- 3.2.4 Records relating to the 12 May 2022 disposal did not have a SAP printout of materials sent for destruction as required to be taken by the [REDACTED]
- 3.2.5 TSE certificates for excipients were not required to be renewed or updated for 5 years which was considered excessive and no TSE statement for lubricant [REDACTED] was available only a certificate relating to Food Standards which was dated 2008.
- 3.2.6 There was no evidence of how transport risk assessment was managed. For example, it was not assured the transport of a controlled drug, [REDACTED] was under secure and labelled conditions.
- 3.2.7 Product storage vessels in the warehouse in Unit [REDACTED] were labelled as on hold for swabbing but this was not a formal document which could be attributed to a project or validation exercise and the process was unclear as to when they could be placed back into use.

EU GMP C4.5, C5.7, C5.12, C5.13, C5.66, A16.1.7.10  
EU GDP 9.2

- 3.3 Facilities and equipment management
- 3.3.1 Within the multiproduct facility it was unclear if action was taken around pest control management and if conclusions were always documented. For example, in Dispensing Booth [REDACTED], which was under a "clean" classification a spider and web were noted and within the Pharm warehouse area a Pigeon was observed. It was not evaluated if the premises allowed maximum protection against the entry of insects or other animals.

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3.3.2	Temperature mapping was deficient in that:
3.3.2.1	Risk assessment was limited in scope. For example: there was no assessment for why the summer mapping was not conducted in the peak of summer but in a shoulder season (Spring) and what the methodology for the three yearly mapping was.
3.3.2.2	It was unclear why the procedure [REDACTED] allowed excursions to be logged as events rather than a deviation
3.3.2.3	It was not documented why excursions were not recorded in line with procedure. Excursions were only formally assessed if they were above 24 hours and 30oC for the ambient storage and above 24 hours for the cold store
3.3.3	Facilities were not always suitably maintained as exemplified by the seals between the wall and floor in the [REDACTED] Compression room which were visibly damaged.
3.3.4	The procedure for LOD testing conducted in the unit [REDACTED] granulation suite did not detail the need to raise a formal investigation to assess the output of a failed LOD on the third occurrence.
EU GMP EU GDP	C1.4(xiv), C3.1, C3.2, C3.4, C4.1, C4.7, C4.29 3.2.1
3.4	Outsourced activities were deficient as:
3.4.1	There was no Quality Technical Agreement for one of the contract QPs.
3.4.2	The Quality Technical Agreement with [REDACTED] did not require that deviations, stability failures, complaints, recalls and other issues which may negate QP certification were communicated.
3.4.3	The technical agreement with [REDACTED] was inaccurate in that it did not define who was the contract giver and acceptor and the agreement was limited in scope. for example, it did not clearly define recall management responsibilities or include a complete product list in appendix 1.
EU GMP	Chapter 7 Principle, C7.2, C7.14, C7.15, A16.1.7.17
3.5	Recall Management was deficient in that:
3.5.1	The mock recall conducted on 19 January 2021 was reviewed. It was not clearly evidenced that a recall could be conducted promptly. For example, it was unclear within what timeframe the recall was completed, including whether the process was capable of handling the worst case "Class 1" type recall and out of business hours activity.
3.5.2	The mock recall did not robustly challenge the QMS in that IMP products were not part of the scope.
EU GMP	C8.24, C8.30
3.6	Management Review was incomplete in that:

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- 3.6.1 In the Apr 2022 Management Review it was noted that regulatory updates were not included as per procedure and that the review was limited in scope. For example, there were no metrics related to training or resource management.
- 3.6.2 It was not trended how many investigations were raised as "events" and what the trending root cause categories were.
- 3.6.3 The manner in which reoccurrence was trended was not conducive to ensure timely reaction to repeat issues. For example, it was not visible via the trend presented that there were a number of open repeat incidences with the [REDACTED] related to camera system failures.
- 3.6.4 KPI(s) were not reported to [REDACTED] to demonstrate target of 30 days was met on individual basis, for example the number of deviations or OOSs overdue were based on a percentage of total closure rate, rather than how many individual overdues there were. (This is a repeat deficiency).

EU GMP C1.6

4. COMMENT

None