Medicines & Healthcare products Regulatory Agency

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OFFICIAL – SENSITIVE COMMERCIAL

[redacted]

[redacted]
CP PHARMACEUTICALS LIMITED
ASH ROAD NORTH
WREXHAM
LL13 9UF
UNITED KINGDOM

Date 04/11/2022
Case No: Insp GMP/IMP 4543/15498-0055

Subject: **THE HUMAN MEDICINES REGULATIONS 2012 (as amended) (SI 2012/1916)**
THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004
AUTHORISATION / REGISTRATION NO. MIA 4543, MIA(IMP) 4543, WDA(H) 29831, API 4543

Dear [redacted]

I refer to the inspection carried out at your company's premises at the above address on 12-16 September 2022 by [redacted]

At this inspection, although we acknowledge the plans and intent of the management team to further improve GMP/GDP compliance at the site, the inspection findings indicate that insufficient progress has been made in some areas to resolve previous inspection findings and therefore support a return to a routine risk based inspection programme frequency. The site will therefore remain under the oversight of the Compliance Management Team (CMT).

CMT will closely monitor your remediation plans, all commitments from previous inspections, and your responses to this inspection to ensure that they result in the GMP improvements which we have not seen to date. Failure to demonstrate the required improvements increases the likelihood of regulatory action against your company.

Any further actions as a result of this inspection will be communicated to you as separate correspondence directly from CMT. 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 failures to comply with the principles and guidelines of Good Manufacturing 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 inspectors [redacted]

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

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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.

Any issues preventing resolution or implementation of actions which result in a delay to CAPA or the action plan, should be formally communicated to the inspectors.

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 or not 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

[redacted]
Lead Senior GMDP Inspector
Email: [redacted]

Medicines & Healthcare products Regulatory Agency

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FAILURES TO COMPLY WITH THE GUIDE TO GOOD MANUFACTURING PRACTICE

1. CRITICAL

None

2. MAJOR

2.1	**Deficiencies relating to the Pharmaceutical Quality System from previous inspections had not been robustly addressed. This was evidenced by but not limited to:**
2.1.1	The management of deviations was deficient in that;
2.1.1.1	Quality Risk Management principles were not utilized to ensure that investigations were progressed in a timely manner, commensurate to risk, with all deviations being assigned a 30-day target for closure.
2.1.1.2	Investigations were not being closed out in a timely manner to ensure adequate control as evidenced by of the 1126 deviations raised during the review period (August 2021 – Sep 2022), 283 had been closed out beyond the 30 days stipulated within the SOP with 38 events being closed out in excess of 100 days.
2.1.1.3	Whilst the SOP for investigations contained a requirement to utilise QRM principles, there was no detail as to what this meant in practice thus driving no differentiation in the process.
2.1.1.4	Deviation [redacted] had been cancelled without sufficient justification.
2.1.2	Appropriate actions were not always identified from investigations as evidenced by:
2.1.2.1	Deviation [redacted] raised in relation to an issue with a contract manufacturer but had not considered whether a for-cause audit was needed.
2.1.2.2	Deviation [redacted] had not considered whether an additional audit was needed for a contract manufacturer that was unable to identify why the Microbiology quality test was out of specification when tested on import but had previously passed testing at the contract manufacturer's site.
2.1.3	The management of product complaint investigations were deficient as evidenced by:
2.1.3.1	Complaint investigation [redacted] had been closed without evidence of any review or testing of the complaint samples that had been received from the customer.
2.1.3.2	It was described that if a complaint was considered as initially a major risk, it was termed "Justified" which was an ambiguous term. It had not been considered that complaints that represented actual quality defects could have different levels of risk to a patient.

2.1.3.3	The form for recording complaints did not prompt for an explanation for why an initial risk rating had been selected or how the assessment for potential product falsification was considered making it difficult to understand the decisions made at the start of a complaint investigation.
2.1.3.4	There was no category for unsubstantiated complaints on closure of an investigation with these being included in the category of substantiated minor complaints that prevented accurate trending of substantiated complaints.
2.1.4	Change control record [redacted] did not adequately document the assessment of the change to the stopper manufacturing process by [redacted] to use a site in [redacted]
2.1.5	The use of Quality Risk Management principles was deficient as evidenced by, but not limited to:
2.1.5.1	QRM principles had not been employed in determining the need for end of shift qualification of visual inspection operators.
2.1.5.2	AQLs used in the receipt and approval of printed materials had not been justified.
2.1.5.3	The risk of not detecting missing print errors had not been considered when using a single acetate for the inspection of printed materials such as PILs.
2.1.5.4	Risk to validity of calibration and contamination control had not been adequately considered when moving the sampling balance into the sampling booth.
2.1.5.5	Random periodic analysis of samples taken after importation were not appropriately based on risk. The same sampling programme was applied to all finished products regardless of the number of batches imported (these ranged from 100 batches a year to less than one batch a year).
EU GMP	C1.4(viii), C1.4(xii), C1.4(xiv), C1.8(iv), C1.13(i), C3.38, C4.3, C8.6, C8.9(iii), C8.9(iv), C8.14, C8.19, A8.5, A16.1.5.6(iii)
2.2	**Precautions and risk assessments intended to minimise potential contamination of sterile products were inadequate as evidenced by:**
2.2.1	A crack was observed in the seal and viewing panel of the depyrogenation tunnel cooling zone on Ampoule Line [redacted] between the Grade C area and where ampoules were exposed inside the tunnel.
2.2.2	There was inadequate justification available to support why an extended fill time of up to 72 hours was stipulated in media fill reports when data indicated a typical fill time significantly shorter.
2.2.3	Change Control [redacted] that was open at the time of inspection describing the continued use of freeze dryer [redacted] without an

	independent chart trace had not adequately considered the risk of removing it for assurance of the sterilization cycle of the freeze dryer.
2.2.4	The validation of the VHP production transfer hatch was inadequate in that the risk of using a surface area approach for qualifying loads in place of considering standard loading patterns had not considered risks such as changes to airflow and the effects of different materials on the VHP cycle.
2.2.5	There was no list of authorised lubricants available for use in the production environment. No TSE certs were available for those actually in use.
2.2.6	Clean room classification of manufacturing areas was limited to 'at rest' challenges only.
2.2.7	The findings of the audit by external consultants to identify actions required to minimise risks of contamination in relation to sterility assurance have not been repeated here, however it was discussed that the site is expected to progress the associated CAPAs from this.
EU GMP	Annex 1 Principle, C1.4(xii), C3.38, C5.18, A1.4, A1.7, A1.79, A15.1.7 Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)

3. OTHER

3.1	**Assessment of data integrity risk and associated data integrity controls were deficient as evidenced by, but not limited to:**
3.1.1	It was possible for QC Analysts to change the date and time settings of the UV Vis (it is noted that this had been identified by the site in [redacted]
3.1.2	Data system descriptions detailing the physical and logical arrangements, data flows and interfaces with other systems were not available for the HPLCs.
3.1.3	The management of mass data generated by the automated visual inspection systems had not been considered as part of the URS with a reliance on the supplier/installer's set-up.
3.1.4	There was no data integrity risk assessment for filter integrity testing in the manufacturing areas, for example to consider the risk of depending on only printed records.
3.1.5	Not all data was reviewed or stored. For example, where two loggers were included in different positions for an imported batch, only one of these was downloaded and reviewed, with the other unit deleted and not checked.
3.1.6	There was inadequate evidence to support the practice of calibrating an Oxygen Sensor at a single point in that it was unclear how this

related to accuracy at the working range of the process. In addition, the equipment was not subject to periodic validation review and the most recent validation was from 2002.

EU GMP C3.41, A11.1, A11.4.3, A11.12.4, A15.3.2, A15.4.1

3.2 **Procedures were ambiguous in that:**

3.2.1 SOP [redacted] did not describe how annual requalification of customers was recorded. For legacy customers there was no requirement to assess them against the new customer form to ensure that they were compliant with current procedures.

3.2.2 The procedure for [redacted] did not describe how line clearance was performed to avoid the risk of mix up when sampling was performed in Unit [redacted]

EU GMP C1.8(iv), C5.9
EU GDP 5.3

3.3 **Control of materials was inadequate in that:**

3.3.1 The Grade C autoclave lobby was not temperature monitored despite there being materials that required temperature controlled storage conditions ([redacted] packs and VHP indicators).

3.3.2 Tamper evidence seal codes on API packages were not verified against the data provided by the manufacturer.

EU GMP C3.3, C5.30

3.4 **Adherence to written procedures was deficient as evidenced by;**

3.4.1 SOP # [redacted] had not been adhered to as evidenced by Planned Maintenance Order [redacted] not having been QA authorised.

3.4.2 No NTM (notice to management) was raised following notification to site of the MHRA inspection as required by SOP [redacted]

EU GMP C1.8(v)

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4. COMMENT

4.1 It was acknowledged that the site has developed a Compliance Improvement Plan however this was in progress and not complete at the time of this inspection.

4.2 It was discussed that the site was intending to make some licence updates to reflect current functions and people.