Medicines & Healthcare products Regulatory Agency

MHRA

10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

OFFICIAL - SENSITIVE COMMERCIAL

[redacted]

CIPLA LIMITED (UNIT V)
UNIT V, PLOT NO L-139, S-103 & M-62
VERNA INDUSTRIAL ESTATE
VERNA
IN-403 722
INDIA

10 Jul 2023

Case No: Insp GMP 14694/1071938-0003
Subject: THE HUMAN MEDICINES REGULATIONS 2012 (as amended) (SI 2012/1916) INSPECTION OF OVERSEAS MANUFACTURING AND CONTROL SITES

Dear [redacted]

Thank you and your colleagues for the courtesy and co-operation shown to us during the inspection of your premises at the above location on 19 Jun 2023.

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. Please send your response electronically by e-mail to both of us at the addresses below.

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

1. Use the provided word version of this document to respond to each point.
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]
Senior GMDP Inspector
E-mail: [redacted]

[redacted]
GMDP Inspector
E-mail: [redacted]

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

File Ref: **Insp GMP 14694/1071938-0003**
Inspection Date: **19 to 23 Jun 2023**
Company: **Cipla Limited (Unit V)**

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

D1 CRITICAL

None

D2 MAJOR

2.1 Controls in place to ensure reliance on the sterilisation process by filtration, were deficient as evidenced by, but not limited to:

2.1.1 The integrity of the sterilised filter was not verified before use (PUPSIT).
This was deemed particularly relevant given the inherent properties of the bulk product and its potential to clog filters that could potentially mask an integrity issue at the beginning of the filtration that may not be identified by the post use integrity test.

2.1.2 The level of formality of the quality risk management process for the sterilisation of [redacted] was not commensurate with the level of risk. For example, the Contamination Control Strategy described sterilisation by redundant filtration and did not adequately consider risks of the process for [redacted] for example that there was a hold vessel in between the two filters or that there were two further vessels (hold & buffer) between the last sterilising filter and the filling point.

Reference EU GMP C1.4(ii), C1.13(ii), A1.111, A1.113, A15.2.1

D3 OTHER

3.1 Controls to ensure adequate environmental conditions for storage and transport were deficient, as evidenced by, but not limited to:

3.1.1 Storage conditions were not being adequately checked in that the registration batches were labelled as requiring storage between 20°C to 25°C, however the finished goods store was set to alarm at 16°C to 24°C that was outside these limits. It is acknowledged that the site described that this was an error on the shipper labels.

3.1.2 The general transport protocol used for [redacted] API, [redacted] v[redacted] (issued 30 Mar 2021) had an acceptance criteria of transit temperature not to exceed 30°C, however the manufacturer, [redacted] had described transport conditions of up to 25°C. It is acknowledged

that data reviewed was below 25°C.

3.1.3 Seasonal variations were not adequately considered in the general transport study [redacted] v[redacted] in that the study was performed during winter months and did not consider transport during summer months.

Reference EU GMP C1.8(iii), C1.8(ix), C3.19

3.2 Controls in place for documentation management and data assurance were deficient, as evidenced by, but not limited to:

3.2.1 The summary of the product validation report for [redacted] from June 2022 had not been updated to reference that an additional validation batch would be required. It is acknowledged that an amendment had been approved in May 2023 describing this, however this amendment was not referenced on the report.

3.2.2 The process validation protocol/report did not describe that this was a repeat of the validation of batches manufactured in 2015 following some changes to the process and upgrading of the facility. It is acknowledged that this was described in other documents such as the product registration and change control however this was not clear in the validation documents.

3.2.3 The re-qualification described in equipment list [redacted] v [redacted] for [redacted] stated that requalification for filter integrity tester [redacted] was required. It was explained that this was incorrect and was a document error.

3.2.4 The extent of data integrity controls was inadequate where monitoring data that was important to the process in that data was being recorded manually by transcribing from equipment displays, such as temperature and agitator speed readings from mobile vessel [redacted] that was used in the preparation of the emulsion.

3.2.5 No preventive actions were considered for interrupted QC chromatography sequences due to power supply issues, as evidenced by laboratory incident investigations [redacted] and [redacted] from 2021.

Reference EU GMP C1.4(xiv), A11.1, A15.1.8, A15.2.3

3.3 The [redacted] BMR was ambiguous as to how it was ensured that the pre-sterilisation bioburden sample would be taken immediately prior to sterile filtration in that the process could potentially allow a hold of almost 8 hours in an

intermediate vessel following bioburden sampling but prior to the second sterilising filtration. It was acknowledged that routinely that product was not intended to be held prior to the secondary/sterilising filtration.

Reference EU GMP C4.3

D4 COMMENT

4.1 Line I and Line II, terminally sterilised products and large volume sterile products were no longer within the scope of this inspection as they no longer applied to the UK or EEA markets. Therefore, it was discussed with the site that they would be removed from the GMP certificate.

4.2 The inspectors found useful the site's brief presentation of the [redacted] manufacturing process that was delivered immediately after the opening meeting and before the initiation of the document review. This may be useful this presentation to be included for future inspections to aid the understanding of the manufacturing process.

4.3 Line IV was being commissioned at the time of the inspection with qualification activities incomplete. It was not inspected and was discussed with the site that [redacted] would require a future inspection.