Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

OFFICIAL - COMMERCIAL

[redacted]

MHRA
151 Buckingham Palace Road
London SW1W 9SZ
United Kingdom

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19th September 2016

Ref: Insp GMP/IMP 14023/4574-0017

Subject: **THE HUMAN MEDICINES REGULATIONS 2012 (as amended) (SI 2012/1916)**
MANUFACTURER'S LICENCE NO. MIA 14023
THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004
MANUFACTURER'S LICENCE NO. MIA (IMP) 14023

Dear [redacted]

May I thank you and your colleagues for the courtesy and co-operation shown to us during the inspection of your premises at Swindon (Zydis facility) on 13th to 15th September 2016.

During the inspection a number of failures to comply with the guide to Good Manufacturing 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.

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.

Yours sincerely

[redacted]

GMDP Inspector
Telephone: [redacted]
Email: [redacted]

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Inspection Date: 13-15 Sep 2016
Company: [redacted]

FAILURES TO COMPLY WITH THE GUIDE TO GOOD MANUFACTURING PRACTICE

1 CRITICAL

None

2 MAJOR

None

3 OTHERS

3.1 The inspection of equipment is not robust in that:

3.1.1 There is no process to ensure that Mixing vessels are routinely assessed to confirm that the surface finish is satisfactory for GMP manufacture. e.g. the [redacted] mixing vessel was severely pitted when viewed during the inspection.

3.1.2 There is no evidence that the purified water tanks are routinely inspected for rouging as part of the maintenance schedule.

3.1.3 Scraper bars are not robustly inspected for damage before use as several were seen in mixer room 10 and 11 which showed evidence of damage and could potentially result in contamination of the batch.

Reference: EU GMP 1.8 iii, 3.34, 3.39

3.2 The Purified Water maintenance reports generated by [redacted] did not include confirmation that the concentration of the DBNPA sanitising agent had been tested. There was also no confirmation during the ring main sanitisation that there was no residual DBNPA present after flushing the system.

Reference: EU GMP 4.8

3.3 There was a time difference between the wall clock in the mixing rooms and the time on the mixer control panel. In mixer room 10, the time difference was around 1.5 minutes and in mixer room 11 around 5 minutes (0953 vs 0958).

Reference: EU GMP 3.41

3.4 Some of the sampling points in purified water system number 2 were not protected with plastic caps which could impact the effectiveness of sanitisation prior to sampling.

Reference: EU GMP 1.9i

3.5 The procedures for validation were inadequate as there was no requirement to label bottles of clear and brown liquid used for validation of the Microbiology autoclave.

Reference: EU GMP 4.29

3.6 The calibration record approved on 06-Jun-16 for the API walk in freezer temperature controller and chart recorder was missing a record of the ambient temperature during calibration. The document had been reviewed and approved without comment in spite of the missing temperature record.

Reference: EU GMP 1.9 iv

4 COMMENTS

4.1 It is noted that some batches for use in future clinical trials are manufactured prior to the IMPD/clinical trial application being prepared and/or submitted. It is therefore important that you specifically state in the release certificate that you have released the batch without verification against an approved clinical trial authorisation or finalised and approved IMPD to avoid any ambiguity.

4.2 Please supply information on historical environmental monitoring air sampling results for manned monitoring at the freeze driers to understand the justification for stopping monitoring at the freeze driers in 2015.