



Medicines & Healthcare products
Regulatory Agency



MHRA

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RESTRICTED – COMMERCIAL

[REDACTED]
BAXTER HEALTHCARE LIMITED
UNIT B
TAURUS BUILDING
PETERLEY ROAD
COWLEY
OXFORD
OX4 2TZ
UNITED KINGDOM

Date 24/08/2023

Case No: Insp GMP/IMP 116/525104-0014

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

AUTHORISATION / REGISTRATION NO. MS 116, MIA(IMP) 116

Dear [REDACTED],

Thank you for the courtesy and co-operation shown during the inspection of your premises at the above address on 21/08/2023.

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 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.

File Ref: Insp GMP/IMP 116/525104-0014
Inspection Date: 21/08/2023
Company: BAXTER HEALTHCARE LIMITED, OXFORD

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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


GMP/IMP Inspector

E-mail: 

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

1. CRITICAL

None

2. MAJOR

- 2.1 Precautions to minimise contamination and mix-up were not consistently taken in that:
 - 2.1.1 More than one ampoule was observed to be open at a single time point and sharing (i.e. more than one withdrawal) from an ampoule was observed during manufacture of product number [REDACTED]
 - 2.1.2 The practice of keeping part-used vials for up to 10 days in the refrigerated area in the isolator did not comply with the published guidance in that:
 - 2.1.2.1 Products were not manufactured as a campaign with the patient doses prepared one after each other.
 - 2.1.2.2 Items were permitted to be moved between isolators for example, if VHP cycle was due during storage.
 - 2.1.3 Finished product assessment (release) did not embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing, and compliance with Finished Product Specification (or order) in that:
 - 2.1.3.1 There was no robust justification for immediate release of batches with up to 84-day expiry without prospective review of environmental monitoring conditions.
 - 2.1.3.2 The releasing officers did not review alarm status (from isolator, particle counters, fridge alarms). Note: this also applies to the particle counters of the new PN unit.
 - 2.1.3.3 The releasing officers were unable to accurately review operator authorisations due to reliance on the electronic system [REDACTED] to control training and authorisation status (Operator authorisations on [REDACTED] were observed to not have been revoked when validations were not completed. For example operator [REDACTED] whose validation was due 1/1/23 and [REDACTED] due 23/2/23 were still authorised for manufacturing on [REDACTED].
 - 2.1.4 Control of releasing officers:
 - 2.1.4.1 There was no list of Releasing Officers within the quality system.
 - 2.1.4.2 There were no documented details of the process required to authorise individuals to be able to perform batch release.
 - 2.1.5 Washing did not follow a written procedure designed to minimize contamination of the clean area or carry-through of contaminants to the clean areas in that there was no handwashing required for entry to the isolator facility.
 - 2.1.6 Personnel were not appropriately monitored after critical operations in that fingers dabs taken only once daily despite three distinct shift

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- patterns for manufacturing.
- 2.1.7 Investigation of microbiological Out Of Specification (OOS) results did not ensure product quality in that:
- 2.1.7.1 Moulds and yeasts were not all considered to be objectionable, as per [REDACTED] even when identified in the Grade A area. For example, where a fungus was identified on finger dab plates on [REDACTED]
- 2.1.7.2 There was no requirement to consider the impact on batch disposition status when an objectionable organism was identified from a manufacturing session.
- 2.1.7.3 The SOP [REDACTED] was not consistently followed as evidenced by no plate photo being available as per SOP where no Grade A identification was available on [REDACTED]
- 2.1.8 Management of isolators and VHP was deficient in that:
- 2.1.8.1 The manner of use of the isolators introduced risk of mix-up and contamination in that:
- 2.1.8.1.1 They were excessively loaded.
- 2.1.8.1.2 They were poorly organised and segregated.
- 2.1.8.1.3 Different drugs and strengths of drugs were stored in a large plastic bag throughout the manufacturing session with the operator required to rummage to find the correct items for manufacture.
- 2.1.8.1.4 The DTP hatch was observed to have remained open during manufacture.
- 2.1.8.2 In operation classification of the grade A area in the isolator was not routinely demonstrated.
- 2.1.8.3 There was no requirement for reconciliation of BIs for VHP cycle qualification.
- EU GMP C5.10, C6.3, A1.7, A1.18, A1.19, A1.21, A1.41, A1.64, A1.70, A11.11
Reference: MHRA Guidance for 'Specials' Manufacturers
<https://www.gov.uk/government/publications/guidance-for-specials-manufacturers>
- 2.2 The arrangements for introduction of the new PN facility were deficient in that:
- 2.2.1 Validation and qualification activities remained outstanding or were deficient. For example:
- 2.2.1.1 Process validations to ensure accuracy via chemical testing of PN bags had not yet been completed.
- 2.2.1.2 The practice of adding [REDACTED] or [REDACTED] to broth for incubation did not meet the pharmacopoeia requirements for [REDACTED]
- 2.2.2 Some equipment or IT was not yet in place. For example:
- 2.2.2.1 There was no provision for the [REDACTED] manufacturing control system to link to the [REDACTED] compounders.
- 2.2.2.2 There were no barcode scanners present in the Laminar Airflow (LAFs) to allow for identification of products via the [REDACTED] system.

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2.2.3	Sterility assurance was deficient in that:
2.2.3.1	Critical connections remained outside the grade A zone during manufacturing. For example, [REDACTED] 3000ml bags.
2.2.3.2	The operator was observed to be continually reaching out of the Grade A cabinet, for example, to collect components.
2.2.3.3	When the operator moved their hands into the Grade A cabinet there was frequently either:
2.2.3.3.1	No sanitisation of hands or,
2.2.3.3.2	No appropriate contact time for the sanitising agent (IPA 70%).
2.2.3.4	Poor aseptic comportment was observed in the Grade A cabinet. For example, poor cleaning technique and excessive movement of hands.
2.2.3.5	The location of the Non-Viable Particle (NVP) counter in the grade B room was not based on a formal risk analysis or the results of room classification.
2.2.4	Gowning and washing arrangements were not designed to minimize contamination in that:
2.2.4.1	Gowning instructions were not on display.
2.2.4.2	Single wrapped sterile clothing was available for use.
2.2.4.3	There was no assurance that clothing did not gather contaminants in that the Grade B clothing was permitted to be worn in the unclassified area on exit.
2.2.4.4	Handwashing used a general hand soap rather than a bacteriostatic agent, there was no drier and towels were stored open on a window ledge.
2.2.5	Good documentation practices were not consistently adhered to in the validation and qualification of the PN facility in that:
2.2.5.1	Results that fail to meet the predefined acceptance criteria were not recorded as a deviation within the PQS to allow for traceability, for example the investigation relating to the bubbling of the floor.
2.2.5.2	It was unclear what documents were still valid after a major change to set-up.
2.2.5.3	The specification and alarm limit set in [REDACTED] for the 'support grade C area' to 'change 1 D/C' area did not match the specification set in the site diagrams. [REDACTED] was set at +5Pa and the site map required +10Pa.
2.2.5.4	There was no process for the updates of the site maps. There were two different diagrams for the TPN facility, with different layouts of the HLAfs and with the same revision number and approval date [REDACTED] from 14 Mar 2022).
EU GMP	C1.8(iii), C3.34, C4.3, C5.10, C5.24, A1.3, A1.8, A1.41, A1.45, A1.53, A1.64, A1.66, A1.73, A1.81, A15.2.1, A15.2.3, A15.2.8, A15.5.3 British Pharmacopoeia C2.6.1 Reference: MHRA Guidance for 'Specials' Manufacturers https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

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3. OTHER

3.1 Deviations

3.1.1 CAPA did not always address all factors found to contribute to an incident. For example:

3.1.1.1 In the case of [REDACTED], concerning a TPN bag released with the incorrect name on the label, workload issues were identified during the investigation, particularly after a bank holiday but there were no actions to address this.

3.1.1.2 In the case of [REDACTED] concerning the release of an incorrect strength of product, the CAPA focussed on errors made during order entry but did not cover the error made at release.

3.1.1.3 In the case of [REDACTED] concerning potential cross contamination, the CAPA did not address the actual cross contamination issue involving the re-use of a syringe.

3.1.2 Investigations were not conducted in a timely manner. For example, in the case of [REDACTED] interviews with operators were carried out one month after the incident was discovered.

EU GMP C1.4(xiv), C8.18

3.2 Recall arrangements were deficient in that the control of a field safety notice was lacking in that the recalled batches of CADD cassettes were still available on [REDACTED] rather than under quarantine.

EU GMP C8.28

3.4 Distribution

3.4.1 There were no formal records to verify distribution.

3.4.2 The Dispatch Room displayed dispatch condition notices (signage) for all conditions rather than that assigned for the current day as required by [REDACTED]

3.4.3 It was not clear within [REDACTED] when an independent verification check by a second operator was required for packaging and distribution.

3.4.4 An independent verification of packaging was carried out on 06/07/23 at [REDACTED] however, it was unclear why this was carried out on this one occasion and the verification used an uncontrolled copy of the packaging verification form.

EU GMP C1.8(ix), C4.3, C4.28

3.5 Training

3.5.1 There was no ongoing training and periodic assessment for personnel involved in operations or release to ensure competence.

3.5.2 The on-the-job training records for the Aseptic product manufacture of chemotherapy for a production technician [REDACTED] gave access to [REDACTED] approximately 3 weeks before the final assessment of

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- competence was recorded.
- 3.5.3 There were some gaps in the required fields within training records eg section [REDACTED]
- 3.5.4 An individual listed as a QA releaser did not have a completed record for [REDACTED]
- 3.5.5 There was no documented requirement for a QA releaser to have eg at least 2 years relevant GMP experience. For example, [REDACTED] did not have any experience of GMP prior to employment at Baxter in February 2022.
- 3.5.6 The site did not assure themselves that [REDACTED] [REDACTED] were sufficiently trained in GDP.
- EU GMP C2.3, C2.11, C7.5
MHRA Guidance for 'Specials' Manufacturers
<https://www.gov.uk/government/publications/guidance-for-specials-manufacturers>
- 3.6 Control of cross-contamination was deficient in that there was no assessment of the risk of transfer of adventitious human pathogens associated with using blood products in the same isolator as TPN when [REDACTED] clinical trial was introduced.
- EU GMP C5.18
MHRA Guidance for 'Specials' Manufacturers
<https://www.gov.uk/government/publications/guidance-for-specials-manufacturers>
4. **COMMENT**
- 4.1 The company is requested to provide a target date for CAPA [REDACTED] and confirm that a mock recall will be carried out to check the effectiveness of improvements to the recall process.
- 4.2 The company is requested to provide assurance that the particle counter probes in the Grade A cabinets in the TPN unit are fitted in accordance with the manufacturers instructions with reference to bend radii.
- 4.3 The site MS licence requires to be updated to include Quality Control Testing, microbiological: Non-sterility.