Medicines & Healthcare products
Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Baxter Healthcare Ltd
Aseptic Compounding Unit,
Mount Vernon Hospital,
Rickmansworth Road,
Northwood,
Middlesex
HA6 2RN

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Re-Inspection on behalf of the MHRA IAG

Licence or Reference Number: MS 116

Licence Holder/Applicant: Baxter Healthcare Ltd

Details of Product(s)/ Clinical trials/Studies: Various Specials products

Activities carried out by company:	Y/N
Manufacture of Active Ingredients	N
Manufacture of Finished Medicinal Products – Non-sterile	N
Manufacture of Finished Medicinal Products - Sterile	N
Manufacture of Finished Medicinal Products - Biologicals	N
Manufacture of Intermediate or Bulk	N
Packaging – Primary	N
Packaging - Secondary	N
Importing	N
Laboratory Testing	N
Batch Certification and Batch Release	N
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: *Specials and IMP reconstitution*	Y

Section 40

Name and Address of site(s) inspected (if different to cover):

Site Contact: [redacted]

Date(s) of Inspection: 9th May 2019

Lead Inspector: [redacted]

Accompanying Inspector(s):

Case Folder References: Insp GMP 116/28970-0025

Section B General Introduction

B1 Background information

The aseptic manufacturing unit is part of Baxter Healthcare and operates within the Baxter Corporate structure. The unit moved to its current location in 1998/9 and is on the Mount Vernon Hospital site in a separate purpose-built building.

Section 40 & 43

The site provides aseptic compounding services under an on-going contract with [redacted] for the provision of chemotherapy to [redacted] Hospitals

Manufacturing was patient specific at the time of inspection for [redacted] products, [redacted] and also reconstitution of Clinical Trial products.

Following the inspection in August 2018 (which resulted in a critical finding) volumes were capped by the IAG at [redacted] patient doses per day.

This was a focussed inspection on behalf of the IAG to review current ways of working and process improvements put in place since the last inspections. This report should be considered in addition to the report from August 2018 and January 2019.

Previous Inspection Date(s): 15/16th January 2019
7-8th August 2018

Previous Inspectors: [redacted]

B2 Inspected Areas

Introductions, site overview, changes.
Quality Systems: Deviations, Investigations and CAPAs; Rejected batches; Release processes
Production Processes: Sanitisation; storage, compounding, labelling
Validation and Sanitisation practices
Environmental Monitoring
Training
Distribution

Limitations / exclusions to inspected areas

Multiple areas not covered due to focussed nature of inspection, including (but not exclusively)

- Complaints, Recalls
- Warehousing, storage and stock control
- Self-Inspection, Outsourced activities

B3 Key Personnel met/contacted during the inspection

Name	Position
[redacted]	

Section 40 & 43

[redacted]

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	SMF04L; 30th Jan 2019	N
Compliance Report	02 May 2019	Y
Comments: The SMF continues to reflect the use of Bank isolators which is no longer the case on site.		

Section C Inspector's Findings

C1 Summary of significant changes

Detailed changes are recorded in the pre-inspection compliance reports held in the case folder.

Changes since previous inspection which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

After the production cessation in January 2019; operations restarted at [redacted] doses per day in March and has since increased to [redacted] doses per day in late April 2019.

Future planned changes which are of particular relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

A new contract has been agreed with the local [redacted] until Q1, 2020; with fewer emergency doses agreed and with most orders being placed 48 hours in advance.

C2 Action taken since the last inspection

Whilst improvements were noted, there were still deficiencies of a similar nature to previous inspections, indicating a lack of appropriate improvement, especially given the current company managed reduction in volumes being processed.

The company also reported during the inspection that several actions from the previous inspection had been delayed; relating to the update of the Requalification [redacted] and to the reduction and control of rouging [redacted]

C3 Starting Materials

General

Not reviewed; assessed during 2018 inspection. {The starting materials used were either licensed products or products purchased from other specials manufacturers.}

Compliance with TSE Guidelines

Not applicable

API Compliance

Not applicable

C4 Pharmaceutical Quality System

Section 43

A CAPA related to the under consumption of [redacted] during sanitisation was reviewed; where this had occurred on [redacted] occasions. There was no information of which runs were implicated or any further assessment, see Section D.

Rejected batches were reviewed; there had been 6 since the last inspection in January 2019.

- [redacted] related to an air gap in the [redacted] which was subsequently scrapped. This was down to incorrect technique; however, it had not been escalated to the Deviation as there was no trend.
- [redacted] related to a small grey particle; details were lacking; See Section D

The processes for release of products via Quality checks within the manufacturing area was reviewed and considered acceptable. Appropriate Customer Order forms were available, although the addition of [redacted] details was not signed and dated.

C5 Personnel

Training and approval of releasing officers to conduct QA releasing activities was reviewed in detail.

Upon discussions with the named Quality Controller, there did not appear to be appropriate systems in place for them to approve Releasing Officers and there was a lack of awareness over what systems they actually had in place. Sign-off records consisted of supervising a number of doses depending on previous experience.

In order to ensure releasing officers were aware of any ongoing quality system issues or environmental monitoring issues that could impact release of product, all releasing officers were expected to attend or read minutes of quality management review meetings. However, there was no evidence provided of signed minutes by releasing officers.

Operator Qualification was reviewed for technical [redacted]; via involvement in a process simulation in March 2019. This was considered acceptable however there was no strong system in place to manage the routine schedule for requalification. Operation validation was an agenda item for the monthly quality and management reviews but there were limited details or control measures.

C6 Premises and Equipment

Though trays for holding vials during sanitisation cycles were noted to be improved with respect to rust on joins; some trays were noted to have significant yellow scaling and still available for use. This was not considered acceptable as the scaling could act as potential trapping points for contamination and be difficult to clean.

[redacted] were set for a sanitisation cycle, however components were not adequately separated, and equipment was not located as per the validated plan. Portable transfer units were not identified in any consistent permanent or formal manner. Forms and records were not completed prior to equipment progression through sanitisation cycles or usage. Deficiencies were raised, see Section D

The warehousing area had been improved via a replacement ceiling and stock management within the fridge, eliminating overloading of shelves.

C7 Documentation

Validation records for a new sanitisation cycle ref. [redacted] was ongoing; records showed poor traceability of pages and sections.

Section 43

Logbooks and equipment status forms still only recorded minimal data which did not allow a full traceability of activities undertaken. Stock movement records were not accurately manually recorded; although the errors were not duplicated in the [redacted] control system. The Daily checklist ([redacted] had not been filled in for the [redacted]

The Aseptic Process Simulation Requirement document; [redacted] did not include any detail on the issue or effective dates for the document.

The site had transitioned from [redacted] this was not appropriately overseen from a site or UK perspective and had not been previously communicated to the MHRA as a change in operating practices. See comments in Section D.

C8 Production

During production some issues of concern were noted regarding manufacturing practices. One example was that the critical zone with the production isolator was congested which increased the risk of mix-up. [redacted] was also not physically removed from reach during processing of a [redacted] increasing the risk of incorrect withdrawal. Also, there was no formal control over the number of times an infusion bag port could be pierced for withdrawal or addition. This was not described in the media fill rationale provided ([redacted] Risk assessments to support multiple piercing of [redacted] also did not consider the risks of potential coring of the bung; which had been a noted issue recently with rejections of product.

Deficiencies were raised, see Section D

Labelling processes were reviewed and considered acceptable.

C9 Quality Control

No prospective QC testing was conducted due to the nature of the products (aseptic short-expiry patient-specific doses).

Microbial trending reports covering the last quarter since the previous inspection did not indicate any significant adverse trends of concern.

C10 Outsourced Activities

Not reviewed during this inspection.

C11 Complaints and Product Recall

Not reviewed during this inspection.

C12 Self Inspection

Not reviewed during this inspection.

C13 Distribution and shipment (including WDA activities if relevant)

At the time of inspection, there was only one customer which was the Mount Vernon hospital cancer unit, within a few minutes' walk of the site. Individual patient doses were packed into chemotherapy transport bags and sealed. However, local procedure [redacted] or distribution of doses was silent on how doses should be transported in order to ensure that storage and transport was adequately controlled.

C14 Questions raised by the Assessors in relation to the assessment of a marketing authorisation

Not applicable

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

1. CRITICAL

None

2. MAJOR

2.1 **Production controls were deficient in that**

2.1.1 Equipment still showed an unacceptable level of rouging, as indicated by visual inspection and by the discoloration of cleaning cloths.

2.1.2 Vial trays for sanitisation had yellow scaling and there was no record of assessment to confirm that trays were suitable for use as part of an ongoing maintenance programme.

2.1.3 Sanitisation processes were still deficient in that items were adjacent to or occluded by equipment. Air samplers were not located as per validated loading patterns resulting in hanging bags being pushed into a compressed space. Glove sleeves were not extended or positioned to avoid occluded surfaces.

Section 43

2.1.4 Isolators were used prior to the completion of daily start up checks e.g [redacted]

2.1.5 The critical processing area was cramped, and on one occasion it was noted that [redacted] were in the processing area despite not being required for manufacture of a [redacted] batch.

2.1.6 Active containers were disposed of prior to second checking to confirm correct volumes had been withdrawn.

2.1.7 Withdrawn volumes of components, including active products, were not appropriately checked to ensure the absence of air bubbles.

2.1.8 There was no control over how long materials, components, products and supporting items were held under sanitised conditions.

2.1.9 There was no formal control over number of times an infusion bag may be pierced.

2.1.10 There was no risk assessment in place with respect to the number of times components could be re-used, as such there was no consideration of the risk of contamination with coring of bung as a result of repeated uses.

2.1.11 Picking lists were amended e.g. for batch details without signature or date, and lines were subsequently crossed out post picking/checking without explanation or justification.

EU GMP C1.4(viii), C1.8(vi), C3.8, C3.34, C4.9, C5.9, C5.38, C5.40, A1.78, A1.85
MHRA Guidance for 'Specials' Manufacturers:
https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

3. OTHER

3.1 The Investigational and CAPA Systems were deficient in that:

3.1.1 Investigation [redacted] did not include any assessment or examination into the source or root cause of the particulate contamination and no detail on the level of repeat finding.

3.1.2 [redacted] with respect to [redacted] consumption levels during sanitisation did not clarify the extent of the low usage versus total runs within the time frame and did not address if the low usage was equipment specific.

EU GMP C1.4(ix), C1.4(xiv), C1.8(vii)

Section 43

3.2 Documentation and checks were not recorded correctly in that:

3.2.1 The isolator form [redacted] was not completed for Pre-Filter wash details.

3.2.2 Transfer [redacted] units were marked with leak test and expiry dates that were not appropriately permanent with data wiped off ID sheets.

3.2.3 Transfer [redacted] units were marked with unofficial notice for ambient conditions.

3.2.4 Validation document records for individual protocol runs included the incorrect protocol number and pages were not identified, version controlled or dated.

3.2.5 Performance Qualification Timings were recorded incorrectly for [redacted]

3.2.6 Printed copies of formal documents did not consistently include the issue and effective dates

EU GMP C4.3, C4.7, C4.8, C5.13

3.3 Releasing officers' training was deficient in that:

3.3.1 There was no formal approval by the QC named on the MS licence to ensure that Releasing Officers had met the GMP experience and knowledge requirements to be a suitable candidate to approve release of product under the MS License.

3.3.2 The number of supervised checks required for sign-off lacked a rationale as to why the numbers were considered appropriate.

3.3.3 There was a lack of evidence that releasing officers were made aware of ongoing quality issues, such as attendance at Quality Management Review meetings.

EU GMP The supply of unlicensed medicinal products 'specials', MHRA guidance note 14.
https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials
MHRA Guidance for 'Specials' Manufacturers
https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

3.4 The process for transportation of patient doses to the local chemotherapy unit was not formalised by procedure.

EU GMP C1.4(xvi), C1.8(ix)
The supply of unlicensed medicinal products 'specials', MHRA guidance note 14.
https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials

4. COMMENT

4.1 Management oversight was lacking in that the site had not notified the MHRA that an updated computer system had been implemented [redacted] via any Interim report or monthly update and no localised Change control was available during the inspection. In addition, the site had not notified the MHRA of two lengthy delayed actions relating to significant deficiencies from previous inspections (linked to rouging and validation oversight controls). This was not considered appropriate and indicated a lack of openness with the MHRA Inspectorate and Inspection Action Group given the current level of MHRA oversight of the site and company group. The company is requested to provide an update on how communications will be managed going forwards to eliminate any potential recurrence.

4.2 Following late discussions on site during the inspection; the site is required to provide information on the introduction of [redacted] on both a site and UK wide basis (as this is a common system). This will be assessed as appropriate during a remote review and may also be considered during future UK inspections of Baxter MS sites.

Section E Site Oversight Mechanism

Site referred or to be monitored by:	Tick (✓)	Referral date	Summary of basis for action
Risk Based Inspection Programme		[redacted]	
Compliance Management Team			
Inspection Action Group	✓	09/08/2018	Continued issues seen on site with progress insufficient at this time.

Section F Summary and Evaluation

F1 Closing Meeting

The site accepted the deficiencies presented without dissention and committed to provide an appropriate remedial action plan.

A discussion was held of the continued process for oversight by the Inspection Action Group (IAG), with a statement that the information could be obtained by following the link that would be in the Post Inspection Letter.

Section 43

F2 Assessment of response(s) to inspection report

A response was received [redacted] which was not considered satisfactory. Additional clarification for several points was requested from the company on 14th June 2019. A final response was received on [redacted] which was deemed to be satisfactory.

F3 Documents or Samples taken

None retained from inspection

Information on the introduction and validation of [redacted] into the UK was supplied post inspection. A review was carried out and additional information requested, to support this process. The company agreed that in future there would be a UK change control, with UK sign off on any global change control deployment. This would be updated into [redacted] (the UK Change Control Procedure), to allow further considerations for local assessment and further actions if deemed necessary.

F4 Final Conclusion/Recommendation, Comments and Evaluation of Compliance with GMP and GDP

The site **does not** operate in general compliance with the requirements of:

Compliance statement	Tick all statements that apply
Directive 2001/83/EC, Directive(s) 2003/94/EC and 2011/62/EU	
GMP as required by HMR 2012 (as amended)	✓
Directive 2001/20/EC	
Directive 2001/82/EC	
Article 84 and Article 85b(3) of Directive 2001/83/EC (GDP) and 2011/62/EU	

and is not acceptable for the products in question.

The site is required to continue providing updates on a monthly basis to include the following: production volumes, staffing levels, Key Performance Indicators, open Quality Management System actions, status of Inspection response actions.

Name and Dated Signature of Inspector (s):

Signed: [redacted] **Dated:** 28th November 2019

Accompanying Inspector: **Dated:** 2nd December 2019

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

	May 2019		Jan 2019 (focussed) + Aug 2018 (full scope)
Critical deficiencies this inspection:	0	Last inspection:	0 + 1
Major deficiencies this inspection:	1	Last inspection:	4 + 0
Other deficiencies this inspection:	4	Last Inspection:	3 + 0

(b). Provisional Rating based on Inspection Output (✓ applicable box)

Risk rating level	Input from current Inspection Findings (last inspection findings applicable to rating V only)	Provisional rating – this assessment	Final rating last assessment
0	Serious triggers outside the inspection cycle	[redacted]	[redacted]
I	Critical finding		
II	>/= 6 Major findings		
III	<6 Major findings		
IV	No critical or Major findings		
V	No critical or Major findings from current or previous inspection and <6 other findings on each.		

Section 43

(c). Risk Assessment Inputs – discriminatory factors (✓applicable box)

[redacted]	None relevant (default)
	Significant concern over robustness of quality system to retain adequate control
	Significant failures to complete actions to close previous deficiencies raised at the last inspection
	Complex site
	Significant changes reported in Compliance Report
	Significant mitigating factors applied by the site
	Higher risk rating identified by other GxP and considered relevant to the GMP site
	Relevant site cause recalls, notifications to DMRC or rapid alerts since last inspection
	Nature of batch specific variations submitted since the last inspection give concern over the level of control
	Regulatory action related to the site
	Failure to submit interim update and/or failure to notify MHRA of significant change or slippage in commitments from post inspection action plan
	First Inspection by MHRA (does not require counter-signature for RR II)
	Other discriminatory factor (record details and justify below)

(d). Inspectors Comments Related to Discriminatory Factors

None

(e). Risk Rating Result Incorporating Discriminatory factors (✓ applicable box)

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (✓)
0	Immediate (as soon as practicable)	[redacted]
I	6 monthly	
II	12 months	
III	24 months	
IV	30 months	
V	30 months with 50% reduction in duration of the next inspection	

Section 43

(f). Basis for risk-based acceptance of specific matters arising during the inspection

[redacted]

(g). GMP or GDP certificate conditioning remarks required as a result of risk-based decisions noted in section (f) above

Not applicable

(h). Conclusions

[redacted]

(i). Expert/ Operations Manager / Compliance Management Team (CMT) Comments (Risk rating level 0, I, II):

[redacted]

(j). Confirm Agreed Risk rating following this inspection:

Risk Rating:	Next Inspection target date:
[redacted]	

Notes regarding re-inspection and GMP certificate validity

1. The inspection schedule is based upon risk and resource. This date may change at any time due to factors not pertaining to your site.
2. The GMP certificate does not 'expire' it is provisionally assigned 3 year validity date. For external questions regarding your validity thereafter; please advise that this can be confirmed by contacting the inspectorate at gmpinspectorate@mhra.gov.uk