Medicines & Healthcare products Regulatory Agency

MHRA

INSPECTION REPORT

BAXTER HEALTHCARE LIMITED

CAXTON WAY

THETFORD

IP24 3SE

UNITED KINGDOM

Head Office:
Inspection, Enforcement & Standards Division, MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

Telephone: 020 3080 6000
Email: info@mhra.gov.uk

Section A Inspection Report Summary

Inspection requested by: IAG Request

Scope of Inspection: Full-scope inspection

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Licence or Reference Number: MS 116

Licence Holder/Applicant: BAXTER HEALTHCARE LIMITED

Details of Product(s)/ Clinical trials/Studies: The site manufactures a range of [redacted] under the Specials License.

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	Y
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	Y
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: Specials	Y

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

BAXTER HEALTHCARE LIMITED
CAXTON WAY
THETFORD
IP24 3SE
UNITED KINGDOM

Site Contact: [redacted]

Date(s) of Inspection: 26-28/02/2019

Lead Inspector: [redacted]

Accompanying Inspector(s): None

Case Folder References: Insp GMP 116/18507-0047

Section B General Introduction

B1 Background information

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The compounding unit aseptically produces a range of [redacted] products in [redacted] and [redacted]. It also aseptically assembles the [redacted] product, this process aseptically connects a [redacted] device to a [redacted]. The unit also produces total [redacted] products.

At the time of the inspection the [redacted] product was in the process of being transferred to the Baxter site in [redacted]. This had been delayed from the previous timeline of October 2018, but was now expected to have been moved over and ceased during 2019.

The compounding unit shares the same building and some facilities with the terminal sterilisation business, although the two units operate as separate businesses and quality management systems.

Previous Inspection Date(s): 16/10/2018[redacted]

Previous Inspectors: [redacted]

B2 Inspected Areas

Pharmaceutical Quality Systems
Recall
Customer Complaints
Deviations
Change Control
Capacity Management
Product Quality Review
Training
Qualification of aseptic operators
Cytotoxic, non-cytotoxic and [redacted] manufacturing areas
Manufacturing equipment
Order Receipt
Production Activities
Quality Control
Outsourced activities

Limitations / exclusions to inspected areas

Manufacture of [redacted] was not observed due to the facility being shutdown at the time of inspection.

B3 Key Personnel met/contacted during the inspection

[redacted]

[redacted]

B4 Documents submitted prior to the inspection

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Document	Version /Date of document	Reflected activities on site?
Site Master File	[redacted]	Y
Compliance Report	Feb 2019	Y
Comments: None		

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. No significant major changes had been reported since the previous inspection.

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

None relevant.

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

Replacement of the existing [redacted] was anticipated during 2019.

C2 Action taken since the last inspection

Change controls raised to complete actions from the previous inspection were open, but revised completion dates had been submitted to the Inspectorate by the Interim compliance report.

C3 Starting Materials

General

The site uses licenced medicinal products or products supplied from other MS licence holders as starting materials

Compliance with TSE Guidelines

Not applicable.

API Compliance

Not applicable.

C4 Pharmaceutical Quality System

Deviations were designated as non-conformances, and escalated to [redacted] if more serious issues or trends were detected. Microbial issues were treated as OOL results and documented on a separate form type. As the procedure had been assessed in detail at previous site inspections, examples of [redacted] were reviewed in detail.

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Notably, an out of limit result was concerning, whereby microbial OOL report [redacted] for an operator validation media fill failure of one broth growth in five bags filled. The [redacted] was determined as [redacted] however the site had failed to alert DMRC of the media fill failure, and had not stated the failure in the relevant section of the pre-inspection compliance report. Looking into the details of the investigation, there was a lack of detailed product impact assessment done to a detailed level to assess whether any further action or risk reducing measures were needed. The site at first had suspected that the failure might be due to sterilised multipack [redacted] lacking container integrity, and had undergone some informal testing in-house of the bioburden testing, using unvalidated methods in uncontrolled conditions. This had yielded results where some different organisms (i.e [redacted] had been detected. However further bioburden testing done by the [redacted] did not indicate any growth. This appeared to be inconclusive as a potential root cause, however the handling of this investigation was considered to be deficient and several points were raised. The site was also requested to keep the Inspectorate / DMRC updated on any progress or further issues.

Several other [redacted] were reviewed and issues were raised with these. For example, [redacted] lacked evidence on the extent of hands-on training that was performed for the operator [redacted] for a [redacted] failure lacked a formal documented impact assessment despite having been closed out and [redacted] root cause analyses lacked detail and identified human error as a root cause without adequately addressing whether system or process issues were potentially at fault.

Issues such as manufactured product defects were designated and investigated as CPIs. Though these were lacking detail, for example the type of particles detected, to adequately determine potential root causes based upon trends. Investigations into supplier issues did not always result in follow-up to confirm that the supplier had performed what was requested of them, for example [redacted]

C5 Personnel

The site had recently transferred over to a new training software system at the time of this inspection. The training records for a new operator was reviewed, and included activity competencies and knowledge training. It was noted that there was no formalised GMP refresher training for QA releasing officers.

Capacity planning was also assessed and did not indicate that capacity was being breached. There had not been a substantial increase in workload or transfer from other sites. The way capacity was being monitored was under review.

C6 Premises and Equipment

The facility layout remains the same to that noted at the previous inspection. The site differentiated between [redacted] and the other [redacted]. The manufacturing area for the latter was referred to as the isolator area. The [redacted] manufacturing room was in a different location within the site to the other manufacturing areas. Each area has separate stores for starting products and components. The Baxter ERP system was used for stock control and product status. The site had made changes to the process flow to rectify the issue around deboxing raw materials in the Grade D prep room Isolator area and moving that process to the unclassified areas.

The racks used to hold components during [redacted] sanitisation were also present in the prep room. The appearance and condition of the racking was much improved in the cytotoxic room, however in the [redacted] the racking still in use was starting to rust at the joins and not considered acceptable. The site should ensure that the processes for confirming that racking was appropriate for use are robust.

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Each isolator has a work station which is connected to the electronic [redacted] designated as [redacted] This system is connected to balances which are used for weight checks. Operators could not move onto the next stage of the process if the weights were not within limits, or if appropriate volume checks had not been done.

The validation of [redacted] in the flexible film isolators was reviewed. These included placing [redacted] at a number of locations within the isolator, considered worst-case, using a simulated worst-case load, with [redacted] in triplicate at each location.

Maintenance records were reviewed for isolators, LAFCs and the cleanrooms. The accuracy limits of + or – [redacted] applied to recorded pressures lacked a rationale as to why these were considered appropriate in the [redacted]. In addition, there was no control over the number of [redacted] repairs that would be allowable following detection of a [redacted] hole during routine maintenance.

C7 Documentation

Procedures in use appeared to be within their review dates at the time of inspection.

C8 Production

Production was observed for both the isolator cytotoxic area and the [redacted] area. Observation of aseptic technique, particularly in the [redacted] area highlighted a number of weaknesses that could have an impact on sterility assurance. Notably, one dispensing isolator were overloaded with consumables and items during the manufacturing session and had not been arranged in accordance with procedures. Supervisors of sessions would perform volume checks, however there was no recorded check done on the first filled reconstitution of a vial with a vehicle, to confirm that the volume being added was correct.

Review of CCTV footage indicated that [redacted] areas were very congested with too many trolleys in the area, nearby pass-through hatches, meaning operators had to brush past the trolleys to pull out trays from the hatch. Some other practices included not regularly sanitising the computer screens in the Grade A area that were regularly touched. Another practice that was not considered adequate were consumables such as unwrapped [redacted] were stored in single wrap packs, wrapped up with a rubber band once opened in the Grade B and were reopened several times in the [redacted] to remove the required numbers of [redacted] A hold time of up to 24 hours was applied, without further justification; and was considered a contamination risk.

Storage and quarantine areas were inspected and no issues were raised regarding these areas in general, however the quarantine cage logs did not uniquely identify each quarantined consignment to aid differentiation.

C9 Quality Control

Quarterly reviews of environmental monitoring and personnel monitoring were prepared by the micro department and reviewed at the quality management review meeting. Environmental sampling strategies were consistent with previous inspections, and did not indicate ongoing trends. However, it was noted that the annual report for the [redacted] facility did not discuss changes in annual trends, for example the [redacted] and [redacted] respectively. Also the monthly January 2019 report, for [redacted] detected for Grade A contact plates did not have the required level of detail to explain this trend. [redacted] samples were also QC tested for micronutrient levels such as [redacted]

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C10 Outsourced Activities

Technical agreements were in place for outsourced activities, including maintenance and courier firms.

C11 Complaints and Product Recall

Complaints procedure [redacted] covered the various aspects, timelines and risk assessments for complaints; though issues were noted, it was acknowledged that these were being addressed as per commitments to previous inspections within the company group at different sites. Examples were reviewed including complaint [redacted] regarding precipitation of a desferrioxamine pump documented a root cause of inadequate tightening of the hub, but had not been addressed with any CAPA. Also not all complaints were being recorded appropriately within their three day timeline. Processes for recall call were considered to be adequate, however no mock recalls had been conducted since 2017.

C12 Self Inspection

Self-inspections had last occurred in 2017. However, there had been no [redacted] raised within the site's QMS to account for this, despite a high-level risk assessment having been done.

C13 Distribution and shipment (including WDA activities if relevant)

Finished products were distributed throughout the UK and Ireland to customers. Baxter contract vehicles or courier transport was used to distribute products. [redacted] products were transferred to the Northampton Baxter site for further distribution to [redacted]

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

D1 Critical

None

D2 Major

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2.1	Pharmaceutical Quality Systems were deficient in that:
2.1.1	[redacted] for an operator validation media fill failure of one growth in five bags filled (Species ID: [redacted]) in Nov 2018 was lacking in that:
2.1.1.1	There was a lack of detailed product impact assessment done to a detailed level to assess whether any further action or risk reducing measures were needed.
2.1.1.2	The issue was suspected to be due to a potential contamination of [redacted] however the investigation lacked detail around the consideration of other issues such as equipment or transfer sanitisation issues.
2.1.1.3	The analytical test used by [redacted] to test the potential contamination of [redacted] had not been validated, which called into question the validity of the bioburden results for example two of [redacted] contaminated with [redacted] The rationale for this sample size was not clear.
2.1.1.4	The ongoing issue had not been reported to the Inspectorate or DMRC prior to this inspection and was not stated in the pre-inspection compliance report.
2.1.2	[redacted] lacked evidence on the extent of hands-on training that was performed for the transfer sanitisation process.
2.1.3	[redacted] for a [redacted] filter failure lacked a formal documented impact assessment despite having been closed out.
2.1.4	[redacted] root cause analyses lacked detail and identified human error as a root cause without adequately addressing whether system or process issues were potentially at fault.
2.1.5	[redacted] did not include an impact assessment of not having completed a mock recall since 2017.
2.1.6	[redacted] lacked detail, for example the type of particles detected, to adequately determine potential root causes
2.1.7	[redacted] supplier's report did not have evidence that an effectiveness check by the supplier had been done.
2.1.8	Investigations into re-qualification sanitization failures in [redacted] did not have a robust investigation to prove why the [redacted] were considered to be rogue.
2.1.9	Complaint [redacted] regarding precipitation of a [redacted] documented a root cause of inadequate tightening of the hub, which had not been addressed with any CAPA.
2.1.10	Complaints were not always being reported within the 3 day reporting requirement.
2.1.11	The annual report for the [redacted] facility did not discuss changes in annual trends, for example the [redacted] and [redacted] respectively. Also the January 2019 report, for [redacted] detected for Grade A contact plates was not adequately reviewed.
2.1.12	There was no [redacted] raised within the site's quality system for the self-

inspection delay; the last of which had occurred in 2017.

EU GMP — C1.4(viii), C1.4(xi), C1.4(xiv), C1.4(xvii), C1.5, C1.6, C1.8(vii), C1.12, C1.13(i), C1.13(ii), C8.13, C9.1
The Human Medicines Regulations 2012 (as amended) SI 2012/1916. Part 3, regulation 36, 37(2)

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2.2 Sterility assurance and process design was deficient in that:

2.2.1 Consumables such as unwrapped syringes were stored in single wrap packs, wrapped up with a rubber band once opened in the Grade B and were reopened several times in the [redacted] to remove required numbers of [redacted] A hold time of up to 24 hours was applied, without further justification.

2.2.2 One operator did not re-sanitise the [redacted] compounder screen located in the [redacted] on a number of occasions, to reduce the risk of microbial contamination.

2.2.3 Some isolators were overloaded with consumables and items during the manufacturing session and had not been arranged in accordance with procedures.

2.2.4 On review of CCTV videos, the [redacted] area was noted to be very congested with too many trolleys in the area, nearby pass-through hatches, meaning operators had to brush past the trolleys to pull out trays.

2.2.5 A small patch of rust was noted on one of the [redacted] racking.

2.2.6 There was a lack of rationale to support how the [redacted] process simulation could be considered representative of the actual [redacted] process.

EU GMP — C1.8(v), A1.46, A1.61, A1.64, A1.82

D3 Others

3.1 Production controls were deficient in that:

3.1.1 Records of usage of [redacted] containers for product transfer were not kept up to date. For example, [redacted] had been logged on an isolator record for 25th Feb 2019 as connected to one of the chemotherapy isolators, however [redacted] was actually connected to the isolator at the time of inspection.

3.1.2 Not all vials had been loaded and oriented onto the vial racking in the same direction in accordance with procedure and validation, as noted during an observed in-process [redacted] sanitisation cycle.

3.1.3 There was no recorded check done on the first filled reconstitution to confirm that the volume being added was correct.

EU GMP — Chapter 5 Principle, C4.8, C5.43

3.2 The quarantine area log record did not uniquely identify each quarantined consignment to aid differentiation.

EU GMP — C5.13

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3.3 Maintenance of critical equipment was deficient in that:

3.3.1 The accuracy limits of [redacted] applied to recorded pressures lacked a rationale as to why these were considered appropriate in the [redacted] report.

3.3.2 There was no control over the number of [redacted] repairs that would be allowable following detection of a [redacted] hole during routine maintenance.

EU GMP C3.35, A15.4.2

3.4 There was no formalised continuing training programme for QA releasing officers

EU GMP C2.11

D4 Comments

4.1 Please keep the Inspectorate and DMRC updated with progress into the media fill investigation.

4.2 Some issues were discussed which had already been raised as deficiencies at the other company sites. It is expected that the company continues to make improvements across the 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	✓	Ongoing	A report of the deficiencies was provided to IAG as part of the ongoing company referral of Baxter Healthcare Ltd.

Section F Summary and Evaluation

F1 Closing Meeting

The deficiencies were presented to the site and verbally accepted.

F2 Assessment of response(s) to inspection report

A response to the post-inspection letter was received on 04/03/19, however clarification was required on some points. The 1st RFI response was received on 29/03/2019 which needed clarification and a further acceptable response received on 17/04/2019.

F3 Documents or Samples taken

None

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

The site operates 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 acceptable for the products in question.

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Name of Inspector (s):

Lead Inspector: [redacted]

Date:
10/05/2019

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	2	Last inspection:	1
Other deficiencies this inspection:	4	Last Inspection:	0

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

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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]	
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.		

(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)

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(d). Inspectors Comments Related to Discriminatory Factors

[redacted]

(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	

(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 n

[redacted]

(h). Conclusions

[redacted]

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[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