Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

BAXTER HEALTHCARE LIMITED

ASEPTIC COMPOUNDING UNIT

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: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MS 116

Section 40 & 43

Licence Holder/Applicant: Baxter Healthcare Limited

Details of Product(s)/ Clinical trials/Studies: Aseptically prepared sterile specials – [redacted] both on a named patient basis and as batches.

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	Y
Importing	Y
Laboratory Testing	Y
Batch Certification and Batch Release	Y (Release)
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): As cover page.

Site Contact: [redacted]

Date(s) of Inspection: 03-06 Dec 2019

Lead Inspector: [redacted]

Accompanying Inspector(s): Not applicable

Case Folder References: Insp GMP 116/18507-0049

Section B General Introduction

Section 40 & 43

B1 Background information

The compounding unit aseptically produces a range of [redacted] and [redacted] products in [redacted] and [redacted] It also previously aseptically assembled the [redacted] product, however this product has now been transferred to a sister site in [redacted] and is no longer handled at the Thetford facility. The unit also produces [redacted] products.

The compounding unit shares the same building and some facilities with the terminal sterilization business, although two units operate as separate business units. The commercial operations were inspected at the same time as this inspection (Ref Insp GMP/GDP 116/18507-0048) however these were managed as separate inspections.

Previous Inspection Date(s): 19-21 Jun 2018 (full scope inspection)
16 Oct 2018 (focussed inspection at [redacted])
26-28 Feb 2019 (full scope inspection)

Previous Inspectors: [redacted] (19-21 Jun 2018)
[redacted] (16 Oct 2018)
[redacted] (26-28 Fen 2019)

B2 Inspected Areas

Introductions, site overview, changes, future plans, completion of actions from last inspection review of licences.
Quality System: management review, capacity planning, complaints, recall, deviations, CAPA, technical agreements, TSE, vendor assurance, OOS, batch records, release procedures, sterility assurance, training, self-inspection.
Facility Tour: dispensing, manufacturing [redacted] distribution, microbiology laboratory.

Limitations / exclusions to inspected areas

The following were not reviewed in detail:

- change control process
- validation master plan
- storage areas for incoming materials for Specials manufacture

B3 Key Personnel met/contacted during the inspection

[redacted]

Section 40 & 43

[redacted]

* Staff listed were present at the closing meeting

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	[redacted]	Yes
Compliance Report	Dated 26 Nov 2019	Yes
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.

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

The [redacted] product had been transferred from the site to a sister site in [redacted]

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] cabinets was initially planned during 2019 however due to issues with the [redacted] this has been delayed until early 2020.

The company provided a position paper on the status of introduction of prospective sterility testing for products with extended shelf lives approaching 90 days. An update on this was requested by the end of January 2020 (ref Comment 4.1).

C2 Action taken since the last inspection

Actions from the previous inspections had mainly been addressed, however some items remained open and others were not fully addressed. Specifically:

- The introduction of prospective sterility testing was not complete (see above and Comment 4.1)
- Data generated relating to the 15-minute contact time applied for the sporicidal disinfectant used rather than the manufacturer's recommendation of 60 minutes did not fully support this reduction.

Section 43

C3 Starting Materials

General

Not applicable as licensed or unlicensed products are only used.

Compliance with TSE Guidelines

A TSE statement was present on the certificate of conformance of each unlicensed product.

API Compliance

Not applicable.

C4 Pharmaceutical Quality System

Deviations

[redacted] described the process for managing deviations, which were described as non-conformances [redacted]). More significant issues were designated as serious non-conformances [redacted] If an issue could be resolved via the respective SOP controls, then this was raised as a [redacted] and not escalated to an [redacted] unless it was a repeat incident. Appropriate review periods for repeat incidents were applied depending on the frequency of the concerned activity. Issues that were not deemed significant such that an [redacted] was required were documented as CPIs (Quality Incidents). Issues related to microbiological contamination were raised separately as micro OOL reports.

Several [redacted] were selected for review within the [redacted] system and whilst generally comprehensive, some issues were noted. Examples reviewed:

- [redacted] – Incorrect component on batch [redacted]). Raised as an [redacted] due to repeat issue. Although the investigation was generally acceptable, a number of CAPAs were raised with excessive lead times. For example approximately five months to raise a change proposal for an additional transfer hatch and approximately six months for an update to the sheets for process adjustment.
- [redacted] – wrong barcode label applied to [redacted] Appropriate actions were implemented.
- [redacted] – One of three [redacted] failed during [redacted] requalification. [redacted] raised due to several similar incidents during 2019. The requalification cycle was run at a shorter exposure than the routine production cycle and each time the production cycle duration was also successfully challenged. An action to change from [redacted] to [redacted] was in progress.
- [redacted] – Non-compliance with media fill process. Isolated to several operators noted to not hang larger bags outside the [redacted] cabinet.
- [redacted] – five mould [redacted] within a five-day period. These were noted to be all from the same batch of [redacted] plates and the contamination was observed only on the outside edges of the plates, including one finger dab plate which did not correspond to the dab indentations. The report did not include any reference to consideration of any remaining stock of products that remained within Baxter control and whether these should have been quarantined pending the investigation.
- [redacted] – trend in missed / invalid EM samples. The apparent increase was due to multiple invalidated results for an expired buffer used for swab monitoring, so this was not a general increased trend and considered a on-off event.
- [redacted] – Flush bag sent for electrolyte testing in error. The investigation did not include any review of trend data for the [redacted] as part of the justification to accept release of batches.

Section 43

Cancelled [redacted]

- [redacted] – objectionable organism isolated. Cancelled as it was managed within the micro OOL procedure.
- [redacted] – spike in complaints for leaking blue caps. Cancelled as the record was duplicated in the system. In addition, this was covered by an 'umbrella investigation' ref [redacted]
- [redacted] – [redacted] filters failed integrity testing. Cancelled as the result was within the procedural repair limits.

[redacted]

- [redacted] Missing digit from human readable number on temporary label. Barcode correct as mix-checks were acceptable.
- [redacted] – 17 minutes of missing data from FMS. The documented [redacted] had not considered what activity was ongoing at the time of missing data and the potential impact – e.g. whether open or closed activity was being performed.
- [redacted] – OOS for sample bag electrolytes – flush bag sent for testing in error. Escalated to [redacted]

Management review

SOP [redacted] described the management review process and this included a detailed breakdown of data from [redacted] Quality Incidents not raised as [redacted] in order to determine emerging issues or trends.

Batch release

The batch release process was generally comprehensive and procedure [redacted] described the process observed in the processing areas.

C5 Personnel

The staff met during the inspection were knowledgeable of the procedures and processes applicable to them.

A comprehensive form was in place for the approval of delegated releasing officers which included both a record of observed activities and detailed questions and answers. The observation part of the form included provision for three observed sessions, however if any of the activity was not applicable to the specific observed session, there was no provision to document whether this was acceptable or whether specific tasks required additional assessment.

The capacity planning process detailed in SOP [redacted] was generally comprehensive and data reviewed showed that the site was routinely operating within appropriate capability. The spreadsheet used included the capability to simulate additional workload to determine stress points in advance of accepting additional activity.

Section 43

C6 Premises and Equipment

The [redacted] product had been transferred out of the Thetford site by the time of this inspection. Two main manufacturing areas remained, with PN manufactured in one of two grade B suites containing grade A horizontal [redacted] cabinets and the [redacted] products within a grade D suite containing multiple grade A flexible-walled isolators which were subject to [redacted] gassing.

Deboxing of materials had been moved to a stage prior to the grade D area following previous inspections.

The manufacturing areas were generally well maintained and issues highlighted at previous inspections such as damage being evident on racks used for [redacted] sanitisation in the isolator suite being corrected. It was however noted that the fatigue mats used in the grade B [redacted] suite were worn. These were removed during the inspection. The cleaning process for the area was observed via CCTV footage and it was confirmed that these mats were moved appropriately during the cleaning and sanitisation activities. The cleaning and sanitisation [redacted] was however unclear in some areas, including the use of mop heads, the quantity of disinfectant to use and the duration or surface area to be covered prior to replacement. In addition, it was noted that there was no periodic sporicidal disinfection of the transfer hatches supporting the isolator area.

[redacted] for the [redacted] cabinets were requested for review, however only static studies were available for inspection and these did not include components or ongoing activity within the grade A areas. It was also noted that the available studies demonstrated better air clearance if the containers of alcohol wipes were placed away from the side of the cabinet however this had not been translated into the routine procedures.

Each workstation in both the [redacted] and isolator areas was connected to the [redacted] electronic batch record system and barcodes were used to maintain traceability from ordering through to release checks.

C7 Documentation

Master formulations were created by the customer services group and these were sent back to the customer for approval. Once approved, these were entered into the [redacted] and orders were placed against the respective product code in the [redacted] system. This process was reviewed and no specific issues were raised.

It was noted that during processing in the isolator areas, the first volume checks were performed but not documented as there was no provision for this within the [redacted] batch record system.

During observation of activities in the [redacted] area, an operator was observed to acknowledge a particle alarm on the monitoring system. The alarm condition had triggered the alarm at 15:06 on 03 Dec 2019 and was acknowledged at 15:40, when the operator entered "using swabs" into the system as the reason for alarm without confirming this activity with the manufacturing suite.

A database system [redacted] was used for recording of environmental monitoring data within [redacted] which utilised direct data entry of results as plates were read. It was noted that zero counts were populated for all monitors at the time of incubation and creation on the system, with these being updated as applicable when the plates were read which was not appropriate.

C8 Production

Activity was ongoing within the [redacted] cabinets during the inspection. Operators were observed to appropriately sanitise hands and surfaces regularly however some rapid movement was observed, particularly when removing the alcohol impregnated wipes from the containers

Section 43

placed in the grade A zone. Several issues relating to sterility assurance were noted and collectively raised as a major deficiency – refer to section D.

The overall media fill process design had been reviewed following deficiencies previously raised. The original target date for completion of this review was 30th May 2019 which was extended to 28th November at the last interim update submitted to the inspectorate. The process was discussed and appeared to cover all aspects of the routine processes in a more robust manner. The expected 'go live' date was 15th January and full implementation across all processes was expected by the end of March 2020.

Where pooling of starting materials was required, the company employed a practice of opening up to five [redacted] at a time before drawing these up into a [redacted] which was not in line with the UK Specials guidance. In addition, the site's rationale and supporting risk assessment for the practice of pooling of up to five ampoules at a time was not sufficiently detailed to fully understand and mitigate the associated risks. In addition, the associated procedures were not sufficiently detailed to ensure consistency of the activity between operators. The practice was observed several times during the inspection, both during ongoing activities and via recorded CCTV footage. In all examples, operators were observed to conduct the pooling activity in a controlled manner and did not perform any activities directly over the open [redacted] however as it is expected that [redacted] are withdrawn immediately after opening to minimise the risk of contamination, a deficiency was raised.

C9 Quality Control

The environmental monitoring programme was generally comprehensive, including settle plates, air samples, contact plates, and sessional fingerdab monitoring.

[redacted] were used for monitoring some locations, however the supporting report for recovery efficiency using a streaking out technique had only considered stainless steel surfaces and did not demonstrate effective recovery.

At the time of inspection, only contact plates included [redacted] for as a [redacted], however a protocol had been implemented at the end of November 2019 to expand this to fingerdab and swab plates.

The site 'microbial control schemes' for the [redacted] and isolator compounding unit [redacted] were generally comprehensive however these stated that alert level reviews were performed bi-annually and that the schemes would be reviewed at a minimum of quarterly which in practice was not done. In addition, [redacted] documents were available which included a defined maximum number of personnel for classified areas, however these were not formally included in the media fill programme.

The alert level review for 2018 [redacted] was generally comprehensive and no specific issues raised. The report included a statement that if the calculated limits showed an increase in the alert level then this would not be implemented and the previous limits would remain.

The manufacturer's recommended contact time for the sporicidal wipes used for the first stage decontamination process was 60 minutes, however a contact time of 15 minutes was used. A study had been conducted (document [redacted] for the 15-minute contact time, however the target log reduction from the protocol had not been achieved.

Microbiology OOL report [redacted] for a count of [redacted] in a [redacted] cabinet, was reviewed. The product impact assessment had included that only closed operations were ongoing during the session, however an inappropriate statement that the count was 'only one [redacted] and nothing from other monitors' had also been included despite the recovery being from a grade A location.

Section 43

C10 Outsourced Activities

Some unlicensed products used as starting materials were sourced from the [redacted] The written agreement was reviewed and this included appropriate detail with respect to provisions for recalled products and the supply of TSE/BSE statements. It was noted that the agreement was approved by [redacted] and Baxter in Dec 2014 and Jan 2015 respectively despite the document stating a three year validity period.

C11 Complaints and Product Recall

Recall SOP [redacted] was generally comprehensive, however the instruction to print and check all Class 1 to 3 recall notices for impact to manufactured products was not routinely followed, with only Class 1 and 2 recall notices printed. In addition there was no provision for verifying the effectiveness of the recall procedure in an out-of-hours situation.

C12 Self Inspection

No internal audits were conducted in 2018 due to an elevated level of regulatory inspections. It was discussed that self-inspection should not be substituted by external audits or inspections.

It was also stated that it had been identified during a previous corporate audit that the allocated time for internal audits was not sufficient and that this was to be addressed via the CAPA system. This may be of interest at future inspections.

C13 Distribution and shipment (including WDA activities if relevant)

All [redacted] products were distributed under refrigerated conditions, using pack out plans with cool packs in boxes. There was no reference to overnight storage by the contract courier used within the respective written agreement and the courier's depot was not listed as a storage site on the site's MS licence (it was noted that an appropriate WDA(H) was held by the contract courier).

Temperature studies had been conducted for the refrigerated [redacted] products using the insulated shipping containers. These had been accepted despite multiple excursions below 2ºC, with the lowest being recorded as 0.3ºC. Ranges for the upper temperatures did not appear to approach the limit of 8º with maximum readings of approximately 5ºC.

The customer approval process was managed by Baxter Head Office and customer accounts were set up on the [redacted], with the respective sites adding the customers to the [redacted] system locally. No specific deficiencies were raised in relation to this process however it was noted that [redacted] only covered activities under the WDA(H) and RP responsibilities, with no reference to unlicensed medicines as described in MHRA Guidance Note 14 or distribution under the company's MS licence.

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

None

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

Section D List of Deficiencies

D1 Critical

None

D2 Major

Section 43

2.1 Systems and processes to assure the sterility of aseptically prepared sterile products were deficient as evidenced by:

2.1.1 The contents of ampoules were not withdrawn immediately after opening in all cases. The site's rationale and supporting risk assessment for the practice of pooling of up to five ampoules at a time was not sufficiently detailed to fully understand and mitigate the associated risks. In addition, the associated procedures were not sufficiently detailed to ensure consistency of the activity between operators.

2.1.2 Data to support the applied 15-minute contact time for the sporicidal sanitisation step versus the manufacturers recommended 60 minutes did not fully support this reduction. *[Note: this is a continuation from deficiency 2.1.2.1 from the inspection conducted in June 2018].*

2.1.3 Operators were observed to move rapidly on occasion during activities within the grade B area and [redacted] units, in particular when pulling alcohol wipes from the container within the grade A zone.

2.1.4 Items were observed to be stored on trolleys at the level of the extract vents in the grade [redacted] area.

2.1.5 With respect to air visualisation (smoke) studies:

2.1.5.1 Air visualisation studies available for review only considered the 'at rest' state and did not include any in-process activity.

2.1.5.2 The available studies demonstrated that the position of the container of sterile alcohol wipes within the [redacted] cabinet impacted the clearance of air at the side of the cabinet, however this had not been specified in the relevant operating procedures.

2.1.6 Goggles worn in the grade B area were sanitised using alcohol-based disinfectant only and were not subjected to any sporicidal disinfection or sterilisation.

2.1.7 The cleaning and sanitisation procedure did not clearly describe the quantity of disinfectant to be used to soak the sterile mop heads used in the grade B area nor the maximum surface area that should be cleaned prior to replacement.

2.1.8 It was not required for all jewellery to be removed before entry to clean areas in that 'plain' wedding bands were permitted.

2.1.9 A particle alarm from [redacted] on 03 Dec 2016 was observed to be acknowledged at approximately [redacted] with the comment "using swabs", however this was not verified with the personnel operating within the respective [redacted] cabinet before the comment was logged.

2.1.10 The maximum number of personnel in the [redacted] area as defined in

Section 43

	the [redacted] was not formally challenged during the media fill process.
2.1.11	There was no routine sporicidal cleaning conducted in the transfer hatches to the isolator area.
EU GMP	C4.3, A1.20, A1.40, A1.40, A1.42, A1.54, A1.61, A1.64, A1.67, A1.73, A1.77, A1.81 MHRA Guidance for 'Specials' Manufacturers (3.5.18) https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

D3 Others

3.1	Management of deviations and CAPA was deficient in that:
3.1.1	Investigations did not always include appropriate information with respect to product / patient risk assessment. For example:
3.1.1.1	[redacted] relating to 17 minutes of missing particle data from a [redacted] cabinet did not consider what activity was ongoing during the period of missing data, for example whether closed or open system activities were in progress.
3.1.1.2	[redacted] relating to several incidents of mould contamination had not considered whether any products remained under the control of the site and whether these should have been quarantined pending the investigation.
3.1.1.3	[redacted] relating to a flush bag being sent for QC testing instead of the sample bag did not include any review of trend data for sample bags from the respective compounder.
3.1.2	CAPA timelines were excessive in some cases. For example, [redacted] was closed on 30 Jul 2019 however a timeline of approximately five months was assigned to raise a change control for an additional transfer hatch and another was assigned approximately six months for an update of the documents for the process for adjustment.
EU GMP	C1.4(xiv)
3.2	Microbiology QC processes and methods were not appropriately controlled as evidenced by:
3.2.1	Data available to support the recovery efficiency for the practice of plating out swab monitoring samples were only applicable to stainless steel surfaces and not all representative surfaces monitored. In addition, the available data did not demonstrate effective recovery.
3.2.2	The [redacted] system used for recording environmental monitoring data was inappropriately populated with zero counts at the time of entry and then amended if counts were observed during observation of the plates.
3.2.3	Reviews were not always conducted in accordance with local procedures. For example:
3.2.3.1	The alert level review for environmental monitoring was conducted annually despite the [redacted] stating [redacted]
3.2.3.2	The [redacted] stated it would be subject to review on a quarterly basis however in practice this was not done.

EU GMP	C4.1, C4.8, C6.15

Section 43

3.3	Systems to ensure products were appropriately stored and distributed were deficient as evidenced by:
3.3.1	Studies for temperature-controlled shipper boxes did not adequately support the stated storage conditions for refrigerated products in that excursions below 2°C were observed for all sizes of bag. *[It is acknowledged that temperatures below 0C were not observed however the stated storage and transportation conditions of 2-8°C were not maintained].*
3.3.2	[redacted] was not named as a storage site on MS116 despite some cold chain products being temporarily stored at the company's depot during the shipment process.
EU GMP	C1.4(xvi) MHRA Notes for applicants and holders of a Manufacturer's Licence (Guidance Note 5)
3.4	Documentation and records were not appropriately controlled in that:
3.4.1	The first volume checks conducted in the isolator area were not documented as part of the manufacturing record and were therefore not appropriately traceable.
3.4.2	Checks on the final labelled product were not all performed against the batch document, with only the first item checked as a reference and the other items being checked against this therefore increasing the risk of error.
3.4.3	The training and approval documents for delegated releasing officers for unlicensed medicines did not include any comments or justification for tasks that were not performed during the three observed release sessions to justify whether this was acceptable or if additional observation was necessary to assess practical effectiveness.
3.4.4	The technical agreement with [redacted] for supply of unlicensed medicines as starting materials was approved in January 2015 and had not been updated despite the document stating that it was valid for three years.
EU GMP	Chapter 4 Principle, C2.11, C4.5, C4.8
3.5	Recall procedures were deficient in that:
3.5.1	Only class 1 and 2 recall notifications were printed and signed as reviewed despite the procedure requiring class 1, 2 and 3 notifications to be assessed in this manner.
3.5.2	The recall effectiveness challenge did not include consideration of out of hours processes.
EU GMP	C4.1, C8.30

D4 Comments

4.1 The commitment to deficiency 3.3.2 from the June 2018 inspection regarding prospective sterility testing of products with a shelf life near to 90 days had not been completed at the time of inspection. A discussion was held regarding the status of the action and a paper was provided to the inspectors. The company was requested to provide a detailed update on the progress at the end of January 2020.

Section E Site Oversight Mechanism

Site referred or to be monitored by:	Tick (✓)	Referral date	Summary of basis for action
Risk Based Inspection Programme			
Compliance Management Team	✓	Ongoing	The ongoing company referral of Baxter Healthcare Limited to IAG has been transferred to the oversight of CMT.
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The closing meeting was held with individuals listed in B3 and the deficiencies were verbally accepted in a positive manner. The company committed to addressing the issues.

F2 Assessment of response(s) to inspection report

A response was received on 06 Jan 2020 which was generally comprehensive. Additional clarification for several points was requested from the company on 13 Jan 2020 and further responses were received on 20 and 24 Jan 2020. An additional request for information relating to smoke studies was sent to the company on 24 Jan 2020 and final responses were received on 29 Jan 2020 which were deemed to be satisfactory.

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.

Section 40

Name of Inspector (s):

Lead Inspector: [redacted] **Date:** 28 Feb 2020

Accompanying Inspector: **Not applicable** **Date:** Not applicable

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0 / 0 / 0*
Major deficiencies this inspection:	1	Last inspection:	2 / 1 / 2*
Other deficiencies this inspection:	5	Last Inspection:	5 / 0 / 4*

*Details included from previous three inspections in June 2018, October 2018 and February 2019 respectively.

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

Section 43

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)

Section 43

(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 noted in section (f) above

[redacted]

(h

[redacted]

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

[redacted]

Section 43

[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