Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: This was a remote inspection of a new site to confirm compliance with GMP.

Licence or Reference Number: MS 15956

Licence Holder/Applicant: N/A

Details of Product(s)/ Clinical trials/Studies: The site was applying for a MS license to extend the 7-day shelf life of products manufactured under the section 10 exemption.

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	Y
Manufacture of Intermediate or Bulk	N
Packaging – Primary	Y
Packaging - Secondary	Y
Importing	N
Laboratory Testing	N
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: *E.g. Development, IMP activities, importation of API*	N

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

Site Contact: [redacted]

Date(s) of Inspection: 22/4/20 -15/5/20 (3 days)

Lead Inspector: [redacted]

Accompanying Inspector(s): N/A

Case Folder References: Insp GMP 15956/30187-0015

Section B General Introduction

B1 Background information

The site was already manufacturing around [redacted] products/week under the section 10 exemption. Compounding was roughly [redacted] monoclonal antibody preparation and [redacted] cytotoxic chemotherapy preparation with the isolator on the lef[redacted] designated for chemotherapy and the isolator on the right[redacted] dedicated for MABs at the present time. Recently 700 cancer patients were added to Healthcare at Home's patient list but there should be no adverse impact on manufacturing capacity. Some of products were prepared in pre-filled syringes rather than infusion bags.

Previous Inspection Date(s): New site

Previous Inspectors: N/A

B2 Inspected Areas

Documentation, qualification, quality systems, [redacted] training.

Limitations / exclusions to inspected areas

This was a remote inspection.

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[redacted]		

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	27/12/19	Y
Compliance Report	N/A	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.

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

N/A

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

The site was planning to link [redacted] dispensing system to avoid transcription errors.

C2 Action taken since the last inspection

N/A

C3 Starting Materials

General

An excel spreadsheet for suppliers was provided. The list contained mainly suppliers of licensed injectable medicines with either direct supply from the manufacture or from a wholesaler such as [redacted]

In [redacted] for approval of suppliers, the RP was responsible for re-verification of suppliers of medicinal products and the buyer decided whether the supplier had met the minimum requirements. New suppliers completed an assessment form which confirmed their email and phone numbers independently, obtained copies of WDA(H) licenses and GMP certificates from MHRA and the Eudra GMP websites. If satisfactory an account was set up and purchase orders raised. The MHRA list of suspended and revoked licenses was checked twice monthly and recorded. The Eudra GMP database was checked monthly for SONC and action taken where required. Suppliers were requalified annually by the procurement team, however the role of quality in supplier approval was not adequately detailed in the SOP.

Product specifications were prepared for each input licensed product which included a photograph of the pack. Finished product specifications were also prepared.

Compliance with TSE Guidelines

N/A as licensed products.

API Compliance

N/A as licensed products.

C4 Pharmaceutical Quality System

[redacted] provided definitions and examples of deviations. A deviation form was completed which included a description of the deviation, an impact assessment which applied a risk score, and if critical, management was informed. Root cause investigation, quality review, CAPA initiation and closure review were also part of the process however it lacked detail on certain aspects as indicated in section D below. There was a CAPA log with assigned completion dates.

[redacted] covered both temporary (duration defined) and permanent changes with examples given. Changes were reviewed by Production and Quality and included a justification for the change, classification (as minor or major or document only), an impact assessment and change effective date. Some deficiencies in the change process are indicated in section D below.

The change control log contained three changes: one for a change in supplier and two for new product introductions with one currently still open.

There were three deviations in the log: for a leaking infusion bag which was spiked from the additive port, an isolator gasket which burst and was replaced, and a balance error message and the balance was returned to the supplier for repair.

There was one CAPA for a switch from [redacted] nfusion bags.

Quality metrics at the site included: Deviations and timeliness for closing CAPAs, Environmental and sessional monitoring data, Capacity including demand forecasting, Staffing numbers and staff training, Facility and equipment status – downtime, servicing and maintenance

Data integrity

Data integrity and data governance was covered in [redacted] The SOP covered the principle of ALCOA and described the various terms used in data integrity. There were separate sections on establishing data criticality and risk, data lifecycle, retention and archiving.

C5 Personnel

Two employees had previously worked as an aseptic compounding and had completed personnel media fill tests and aseptic training and were working independently, unsupervised.

One employee had previously worked as a production operator at Burton on Trent Hospital but had no previous aseptic experience. They had completed personnel media fill tests along with benchwork work (practice with consumables etc.) and aseptic technique training and working under direct supervision to complete training.

Two employees had previously worked at Healthcare at Home but had no previous aseptic experience and were currently still in training, one for support activities and the other in aseptic work.

The releasing Pharmacist is a registered Pharmacist has previously checked and released aseptically prepared parenteral nutrition.

C6 Premises and Equipment

Video viewing of the facility was attempted but discontinued as activities in the isolator were too blurred to allow good visibility.

The materials preparation room had a long bench where materials were assembled for transfer into the grade D room. Layout in the isolator room looked satisfactory with isolators side by side with trolleys around the perimeter of the room. The inspection and labelling room contained a light inspection station. There was on refrigerator or freezer in the room.

Materials came out from the room through a transfer hatch for inspection. The finish in all rooms appeared to be of a good standard. The stores area contained 3 racks with 3 shelves in each rack and appeared to be organised.

The highest overpressure was 60Pa in the Grade C cleanroom which decreased to 40Pa in the Grade D inspection and labelling room and 40Pa in the material preparation room. The second stage change room had a 20Pa differential in the correct direction from the isolator room with a further differential of 20Pa to the first stage changeroom. Doors were interlocked to allow opening of one door at a time.

Qualification

Various qualification documents were selected for review. In general, there were some qualification documentation approval issues, no evidence of data integrity checks and no confirmation that IQ was completed before OQ started which are listed in section D below.

Cleanroom IQ, OQ and PQ.

[redacted] – Same specification list as seen in IQ

[redacted] This confirmed compliance with the URS. [redacted] were used instead of [redacted] due to availability and to avoid delays to the project. Pressure across the filters should be monitored to ensure that the prefiltration provides adequate protection.

Sin the document it was stated that shelving was replaced with a trolley and one fridge was installed instead of two. There was an [redacted] supply in case of power interruption and an [redacted] monitoring system for critical systems such as pressure, particles, temperature and RH. There were two exceptions in the IQ: Two 4-glove pharmaceutical isolators were originally to be supplied by [redacted] and a compressed air supply was to be supplied by [redacted]

Cleanroom testing and commissioning report [redacted] performed by [redacted]

OQ – Particle counts were satisfactory and air changes met the acceptance criteria of 5 – 48 AC/H. The facility should be monitored going forward using limits based on the values and applied range found at initial qualification rather than the wider limit of 5 - 48 AC/H.

All results were above 20AC/H and all HEPA filters passed the integrity test except for filter S4 which passed after it was replaced and retested. Pressure differentials were all above 15Pa with the isolator room having the highest overpressure (61Pa). Temperature results were satisfactory. Humidity was recorded at around 50%RH which was within the specification of NLT 45%. Recovery time was around 6 -10 minutes depending on the room. Smoke visualisation was performed with testing indicating good distribution. Interlocked doors were working satisfactory. It was noted that a deviation was not raised in the report for smoke testing dead spots and an extract not working.

[redacted]

The requirements were for an integrated H_2O_2 generator, PLC control, DTPE port on base to remove waste and one to remove product using sterile DPTE tubing, 316, welds were checked, stainless steel passivated inside, CSM sleeve and Neoprene gloves, wire racks for storage, continuous particle counting, biocontamination airlock (grade B), automatic leak test, DI compliant, integrated H_2O_2 steriliser and hardware to connect to [redacted]

The sterilisation cycle was required to include leak test, de-humidification, gas injection and aeration. Cycles should be able to be stored.

[redacted]

Generally, it was difficult to follow the [redacted] reports and link the results to the printouts as the cycle numbers were not recorded in the report.

The isolator was originally designed for sterility testing and consisted of a chamber for transfer and the main chamber. Cycle development determined the typical load, checked compatibility with the gas, confirmed calibration, temperature distribution, optimisation of empty chamber cycle, testing using BI, and aeration testing. Calibration tolerance of +/- 0.5C at 15, 25 and 50C using a Kaye validator was confirmed.

Temperature distribution mapping of isolator (T/Cs in air) and hatch (empty and full load) using 44 T/C's was performed followed by BI and chemical indicator challenge at the coldest and warmest locations. 5 coldest and 5 warmest locations were challenged for optimisation at the end of stabilisation. No surface monitoring was performed where electrical equipment was close to the isolator frame and may overheat impacting the effectiveness of the VHP.

Optimisation of the bio decontamination cycle using 6 BI's was performed where the stabilisation time was increased or decreased to find the shortest cycle. The site checked the efficacy of decontamination at 6 locations (coldest and warmest) in the transfer hatch and incorporate a safety margin of 20%. An aeration check to ensure residues were below 5ppm in the transfer hatch and 1ppm in the main chamber.

It was noted that there was no conclusion which confirmed the final cycle selected for the transfer hatch and isolator and transfer hatch.

[redacted]

This document covered all the expected areas for testing P&ID, utilities, electrical, transfer system, sensor calibration, software, leak test and filter integrity. All results met the acceptance criteria.

[redacted]

Tests included air change rate which had a limit of ≤ 40vol/h in the main chamber and ≤200 vol/h in the transfer hatch.

A pressure regulation check was performed which involved a stabilisation of pressure, recording the pressure generated by sleeve manipulations and when the transfer hatch was opened. The acceptance criteria were met. A functional phase check was performed which confirmed the operation of the isolator when simulating a production run. Other checks were to confirm that the door could not be opened at each phase of the cycle, alarms checks for minimum pressure, gas, power failure, emergency aeration, deflation of gasket at key steps and that the phasing was according to the recipe.

Smoke tests recorded the movement of smoke during the production phase inside the isolator and particle counts confirmed that ISO 5 conditions and recovery were within 4 minutes (limit 20min).

[redacted] **Feb 20**

This was used to test gloves and sleeves. The test cycle had different stages: inflation, stabilisation, testing and de-pressuring steps. There was a self-test function to confirm that there were no leaks. The IQ included documentation review, utility connection checks, installation checks, software verification and a test parameter check. It was noted that the results did not provide values only that the test conformed.

[redacted] **Feb 20**

Testing included a check to verify that reports were correctly displayed, mechanical function of the test plug, the cycle self-check test, emergency stop and that non- conforming cycles are detected using a known leaking glove.

[redacted] **Installation Qualification Feb 20**

This covered software and hardware installation, label printing, balance checking and stability, barcode scanning and operation of the camera. Two incidents were recorded where touchscreens were not tested in the isolator room. The SQL server version was higher than expected and [redacted] will update to a newer version.

[redacted] **Operational Qualification Feb 20**

This covered confirmation of formula body surface area calculation, leucocyte calculation, number of digits after the decimal point, dose modification rules, user groups, working syringe volumes, tolerances for withdrawal, administration permissions, therapy plans, Pharmacist verification, set up preparation, gravimetric preparation (there was a warning if the wrong volume was removed), correct label printing, volumetric preparation, remainders (if product left in stock vial). Remainders were used for the work session in which they were generated and stored on a shelf in the isolator in anticipation of a further order before the session ended. A remainder number was raised by the [redacted] system which was written on the vial and weighed the remainder vial. As remainders were controlled through the [redacted] system with bar code verification and with a unique identity and weight in the isolator for a session. This was considered appropriate mitigation for the vial to remain for the session however the process was not defined in an SOP.

Use of the system in practice will be reviewed at a physical inspection. The system also generated a preparation report, the audit trail could be reviewed and there was a timer for glove changes. Photographs were presented which showed the Pharmacist review of products on the BD Cato system.

The [redacted] identified four main process requiring qualification: small or large volume hand fill syringes, small or large volume hand fill infusion bags. These were designed as worst-case situations in terms of the number of starting materials, manipulations and output products. PV was performed three times initially then 6-monthly in different isolators using different operators. The method for each product type was clearly defined in the SOP.

Environmental monitoring (EM)

The EM data for the period 22/1/20 – 28/3/20 was reviewed. Limits were in accordance with Annex 1 with alert limits set at 50% of the action limits for grade B, C and D. Action limits were currently 50% of GMP limits and all limits will be reviewed when 3-month data was available. Air sample, settle, contact plate results (not in operation) and all isolator monitoring results were zero.

Monitoring locations were mainly located at door entry points, work surfaces, on the floor and change room benches. Locations in the isolator room included; inside isolators, on floors, transfer hatches and benches. Locations inside the isolator were at each end and included the single gassing transfer hatch. The rationale for the selection of the monitoring locations was not formally documented. See section D below.

Building monitoring

The site monitored the temperature of the facility and storage areas using the Tutela system. Temperature excursion alarms are managed with the Tutela call centre contacting nominated site personnel, with escalated contacts if no response. Overpressures and humidity were monitored using the internal cleanroom ECO2 monitoring system.

C7 Documentation

SOP's were simple and clear although short and various SOP's were selected for review:

SOP for [redacted] and checking medication orders – COMP005_01. There was a check for accuracy of order entry into [redacted] from a prescription with a second checks performed on patient data. The status was then changed from planned to confirm. A username and password were required to use the system.

SOP for [redacted] The process involved printing medication labels, picking materials as per the parts list and attaching labels to materials. After scanning the barcode of materials, the status changed to green and the tray could be used.

SOP for [redacted]

Stage 1 - Support to Material Prep. The date of opening of IMS pouches was recorded and could only be used for 24 hours. The hatch/tray was wiped with overlapping strokes and discarded after each item. Dust caps were removed with attention paid to the sanitisation of folds.

Stage 2 - From material prep – isolator room. The first sterile outer was removed and placed in a previously wiped tray. A new wipe surface was used for each stroke.

Stage 3 - Isolator transfer hatch. The tray was placed into the isolator room trolley and logged into the isolator software. The trolley was loaded using sterile gloves with touching of critical parts avoided. Loading patterns were defined for hooks and on the mesh with gaps required between components but the exact placement of components without a visual representation was unclear.

A leak test was performed before the VHP cycle started (Cycle time 1 hour 10 minutes).

SOP for [redacted] Completion status was indicated by a change in colour and the trolley was pulled into isolator where the components were unloaded and hung on hooks or on shelves and the transfer door closed.

SOP for [redacted] Settle plates were exposed during the work session for a maximum of 4 hours with 3 plates positioned at the isolator ends and middle. Finger dabs and contact plates were taken at the beginning and end of the session which increased the risk of subsequent contamination of products in that session and only end of session testing should be performed.

End of session media fills were performed where broth was aseptically transfer into two syringes which was considered representative of the manufacturing process. Sterility samples were also taken at the end of the week where WFI was drawn into a syringe and injected into a 500ml Saline bag.

SOP for [redacted] The operator logged into the preparation section and scanned the product barcode to confirm identity when prompted and photos were taken of the container before adjustment, the correct volume confirmed on the balance and a photo taken after adjustment.

SOP for [redacted] Syringes were supplied in triple wrapped packs with stoppers to maintain sterility when the pack is opened however there was a risk of contamination of the pack with repeated operator access Caps were supplied in interlocked strips to maintain sterility. For syringes, operators were required to ensure that there was no liquid in the piston thread after manufacture.

SOP for [redacted] Product was transferred through a DTPE port to a sterile bag and heat sealed. The [redacted] was positioned not to obscure the vehicle name, lot and expiry on the bag.

SOP for [redacted] The [redacted] was checked for light intensity before use (2000 - 3750 Lux) with a light meter. Product was checked for damage and inspected for contents on a white and black background with any rejects marked with a black cross and separated. The inspection was confirmed in [redacted] the product scanned, and a questionnaire completed to confirm inspection. The labels were then printed.

SOP for [redacted] Product and sleeve were labelled after inspection. Elastomeric infusers required a supplementary flow label and Vinca alkaloids required a warning that the product must be administered by the IV route.

SOP for [redacted] Logs were checked to confirm that there were no alarms, the final check was performed in [redacted] the barcode scanned, the final questionnaire completed, and the prescription, correct order, patients and product details and absence of particles confirmed.

SOP for [redacted] New operators must pass three media fills which involves 51 manipulations: 10 vials and 10 syringes initially then every 3 months thereafter. Product was then incubated for 14 days. The media fill process reflected the maximum number of manipulations for each product, however there was no process to confirm this for new products.

SOP for [redacted] Monitoring used settle plates, active air, contact plates weekly at appropriate monitoring locations. SDA plates were used every 1 in 4 weeks.

SOP for [redacted] defined the cleaning agents to be used (peroxide, IMS), the cleaning schedule and sequence of cleaning (ceiling, walls then floor). All surfaces were cleaned with overlapping strokes.

SOP for [redacted] This SOP covered the first (entry/exit to compounding unit), the second (entry/exit to the isolator room) and was satisfactory.

SOP for [redacted] using the compliance 100 moping system which was described in the procedure. Floors were cleaned daily and the five separate cleanroom areas walls and ceilings cleaned weekly on rotation.

[redacted] for cleanroom working and behavioural practices covered personal hygiene, use of airlocks, wearing of garments, movement and avoiding surface contact.

C8 Production

Capacity planning was detailed in SOP [redacted] The total capacity in production and quality was based on the number of available personnel and adjusted for sickness, holidays, training and leave. The timings for each activity were assigned and capacity of the isolators established which were used to calculate the maximum available capacity for each job role. The capacity against demand was then assessed to identify bottlenecks. Each week the production schedule was reviewed to assess if capacity was exceeded and patients rescheduled if possible. There was an escalation process to the Clinical Director when safe operational capacity was exceeded. It was noted that there was no requirement to raise a deviation if production capacity was exceeded.

The product validation SOP [redacted] ensured that the instructions for preparation complied with the SmPC, that the product was compatible with the primary container, stability and sterility were established. A finished product file, which was reviewed annually, was prepared to bring all the documents together.

There are [redacted] cameras in the facility: Isolator room (x2), material preparation room, inspection and labelling room and in support/stores area

Each [redacted] workstation also had a camera that took a photograph of each preparation at each step of the compounding process. These were reviewed by a Pharmacist as part of the final check/release of the compounded product.

C9 Quality Control

A list of product current shelf life (s10), stability shelf life (which would be used for products manufactured under the MS license) and references was provided. The data was based on the manufacturers SmPC, QCNW data and recognised textbooks. Some issues were noted in section D below concerning the validity and relevance of the stability data presented.

Data for the following products below was selected for review:

[redacted] in syringes – This information came from data supplied by the [redacted] The study was undertaken at [redacted] using an HPLC stability indicating method. The assay was not less than 95% when the product was stored in the dark for up to 168 days, so they used 50% of this value.

In the SPmC [redacted] was stable for up to 28 days in saline and Glucose in LDPE or PVC when stored at 5^0C and 25^0C and protected from light.

C10 Outsourced Activities

The technical agreement with [redacted] dated 2/12/19 covered the incubation of EM monitors, process validation, end of session media fills, sterility testing, media growth promotion, reporting of microbiology results and identification of microorganisms in grade A and B (performed to species level).

The site also had a service contract in place for the isolators and were working on a technical agreement with the cleanroom supplier ([redacted] for on-going maintenance.

C11 Complaints and Product Recall

The [redacted] form included details of the complaint, the initial investigation considered falsification and any implicated batches. A deviation report was raised, previous complaints were reviewed, they responded to the complainant. Complaints were approved by quality and reviewed at monthly meetings. There was a separate process for service complaints

[redacted] Some deficiencies were noted in section D below. A mock recall was performed.

C12 Self Inspection

Not reviewed.

C13 Distribution and shipment (including WDA activities if relevant)

[redacted] indicated that a specific ambient or refrigerated temperature box was used for shipment which were stored at the appropriate temperature before despatch. All products were shipped in GDP compliant temperature-controlled vehicles with refrigerated compartments.

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

N/A

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

D1 Critical - None

D2 Major

2.1 Qualification of the facility and equipment were deficient as evidenced by:

2.1.1 Some qualification documents were not approved by appropriate personnel.

2.1.1.1 The [redacted] only had a single approval by the quality manager who was performing the function of project manager rather than by an independent reviewer.

2.1.1.2 The [redacted] was not approved by the site.

2.1.2 Some dead spots were identified during airflow visualisation in the [redacted] below lights #5, with one extract #5 not functioning, however, a deviation was not raised for these two issues.

2.1.3 The [redacted] did not link the results to the printouts as the cycle numbers were not recorded in the test scripts and it was therefore difficult to determine if the acceptance criteria were met on review.

2.1.4 The adsorption of the sanitising agents into the starting materials was confirmed with the manufacturer however this data was not included in the isolator qualification reports.

2.1.5 Surface temperature monitoring was not performed to determine if surfaces were at a higher temperature which could impact the effectiveness of the VHP cycle.

2.1.6 There was no conclusion in the [redacted] to confirm the final cycles selected for the transfer hatch and isolator and transfer hatch sanitisation.

2.1.7 In the [redacted] test sheets, there was a statement that the IQ was completed but there was no formal signature in the document that this had been performed.

2.1.8 There was no approval of the [redacted] documents by Healthcare at Home personnel.

2.1.9 [redacted] report did not record any test values obtained only that the test conformed.

2.1.10 Data integrity checks were not incorporated into qualification studies.

2.1.11 The media fill process reflected the maximum number of manipulations for each product, however, there was no formal check that the media fill remained valid when new products were introduced.

EU GMP A1.67, A15.1.8, A15.2.2, A15.2.3, A15.2.7, A15.2.9, A15.2.10

2.2 The clarity and content of SOP's was deficient as evidenced by:

2.2.1 The 'remainder' vial process was not defined in an SOP.

2.2.2 The role of quality in supplier approval was not adequately detailed in [redacted]

2.2.3 There was no requirement to raise a deviation in the capacity planning [redacted] if production capacity was exceeded.

2.2.4 [redacted] did not provide enough clarity on the loading of the isolator trolley for sanitisation to ensure that it was consistent with the loading patterns used during qualification.

EU GMP C1.8(iv), C4.3, C4.30

D3 Others

3.1 The quality system was deficient as evidenced by:

3.1.2 The deviation process lacked detail in that:

3.1.2.1 There was no requirement to review previous deviations as part of the investigation.

3.1.2.2 The closure time for critical deviation was 28 days and 3 months for other classifications which was too long to ensure that any CAPA would prevent reoccurrence.

3.1.2.3 The default period of 3 months for the effectiveness review of deviations and CAPA was not considered appropriate as it was not based on the individual requirements of the deviation or CAPA.

3.1.3 There was no target completion date for change controls actions to ensure effective control of the quality system.

3.1.4 The recall [redacted] was deficient in that:

3.1.4.1 It was stated that any recall would be influenced by the impact on supply however this should be determined by MHRA/DHSC and not by the site to influence the recall decision.

3.1.4.2 The SOP did not consider that other batches may be impacted in a recall, and there was no requirement to identify these.

3.1.4.3 There was a lack of detail on how service users should be contacted in the event of a recall. The SOP did not indicate the appropriate method, or the number of attempts required to contact patients e.g. phone.

3.2 Environmental monitoring was deficient as evidenced by:

3.2.1 Finger dabs and contact plates were taken at both the beginning and end of the work session which increased the risk of product contamination and reduction of zone protection when taken at the beginning of the session.

3.2.2 There was a lack of detail as to how finger dabs should be taken in [redacted] as it stated to roll each digit and it was unclear if this included the thumb.

3.2.3 The rationale for the selection of the environmental monitoring locations was not based on a formal documented risk analysis.

EU GMP A1.8, A1.18

3.3 The stability data used to justify expiry dates for some products did not include any related substance testing only assay testing and it was therefore inappropriate to use this data to justify expiration dates.

D4 Comments

4.1 It was noted that SOPs were short in length and the site should consider if any could be combined to reduce the total number of SOP's requiring to be controlled.

4.2 The pressure differential across the U15 filters instead of U14 filters should be monitored to ensure that the prefiltration is adequate to protect the filters.

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			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The persons listed in B3 attended the close out meeting and the deficiencies were accepted.

F2 Assessment of response(s) to inspection report

The response was received on 20th May 2020 and satisfactorily addressed the deficiencies identified

F3 Documents or Samples taken

Documents are in the case folder.

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.

Name and Dated Signature of Inspector (s):

Signed: [redacted] **Dated:**
Name

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	N/A
Major deficiencies this inspection:	2	Last inspection:	N/A
Other deficiencies this inspection:	3	Last Inspection:	N/A

(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]	
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)

(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). Conclusions

[redacted]

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

Expert / Operations Manager / CMT (delete as appropriate)
Risk Rating:
Comments:

[redacted]

Signature:
Name: [redacted] Date: 20/5/20

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

Risk Rating:	Next Inspection target date:
[redacted]	13/5/21

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