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

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Unannounced, Routine Re-Inspection

Licence or Reference Number: MS 116

Licence Holder/Applicant: Baxter Healthcare Limited

Details of Product(s)/ Clinical trials/Studies: Aseptically prepared sterile specials – CIVAs, cytotoxics, PN), 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
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): N/A

Site Contact: [redacted]

Date(s) of Inspection: 30th October – 1st November 2023 (2.5 days)

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

Case Folder References: Insp GMP 116/18507-0054

Section B General Introduction

B1 Background information

The compounding unit, established around 1998, aseptically produces a range of cytotoxic and antibiotic products in syringes and infusion bags. The unit also produces parenteral nutrition (PN) products. The compounding unit shares the same building and some facilities with the licenced business (terminal sterilization), although they operated as separate business units. The commercial operations were inspected at the same time as this inspection (Ref Insp GMP/GDP 116/18507- 0053) however these were managed as separate inspections.

Previous Inspection Date(s): 3rd-6th December 2019

Previous Inspectors: [redacted]

B2 Inspected Areas

Deviations
Change controls
Production (PN and cytotoxics)
Facilities and equipment
Calibration
Maintenance
Qualification
Capacity
Recall arrangements
Quality Control
Sterility assurance

Limitations / exclusions to inspected areas

Self-inspection
Outsourced activity
Training

B3 Key Personnel met/contacted during the inspection

Name	Position
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	[redacted]	Y
Compliance Report	01/11/23	Y
Comments: As the inspection was unannounced, documents were not received in advance but were received retrospectively.		

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:

New cabinets in 2022

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

New unit with an area taken over from plant/commercial team

New hatches to be installed in 2024 with active air supply and since current hatches in the PN suite did not seal.

C2 Action taken since the last inspection

Replacement of the existing LAF cabinets was initially planned during 2019 however due to issues with the HEPA filters, was delayed until early 2020 and was finally completed in 2022.

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 but at the time if inspection there had been no action on this and a further update was requested.

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 at the time of inspection in 2019. Insufficient supporting data was available at this inspection.

C3 Starting Materials

General

Licenced starting materials were used. Where this was not possible the site sourced unlicensed medicines from an authorised supplier or importer, as authorised.

Compliance with TSE Guidelines

Licenced starting materials were used.

API Compliance

Not applicable.

C4 Pharmaceutical Quality System

Deviations and CAPA

'Deviations' was procedure [redacted] Rev AA (Mar 2023). Deviations were recorded on [redacted] and they were classified as NCR (non-conformance) or SNCR (serious non-conformance). The procedure provided instructions for the classification and this classification was independently confirmed by QA. SNCRs required a more detailed root cause analysis. 385 deviations had been raised since Jan 2021 out of which 31 were SNCRs.

SNCR [redacted] was raised to investigate a mould recovery on a grade A in the TPN facility. SNCR [redacted] (Aug 2022) was raised to address a trend on recoveries in the grade A of the TPN facility. This SNCR had been raised over a failed effectiveness check ([redacted] Oct 2021) from a previous NCR. The new investigation was raised as an SNCR as part of the escalation process that included the review of repeated occurrences.

The site operated a separate system for 'quality incidents'. These were recorded under a different system and were trended independently. Quality incidents included out of specification results. Quality incident [redacted] (May 2022) was raised over an out of specification on a finger dab in a grade A area.

Changes

[redacted] described the process which involved a change request being submitted to the change review board for discussion along with a risk assessment for the proposal. The board met once per month for all UK and Ireland sites. If accepted, an owner, actions and timescales were assigned via [redacted] Extensions to timelines were applied via [redacted] and approved by the change review board. The requirement to perform an effectiveness check was determined as part of the initial impact assessment. Records could be closed when all actions were completed which meant the effectiveness check was often a separate record.

The following records were reviewed:

[redacted] – Raised to document new LAFs

[redacted] – Raised to document the addition of stools to the PN room

[redacted] – Raised to document addition of mesh grille to PN cabinet HEPAs.

No comments were made.

New Product Introduction

There had been no new product lines added for over two years but [redacted] described the process to be used. New brands of raw materials were assessed via [redacted] which included a stability and compatibility assessment review. The overall system was heavily reliant on the [redacted] software.

C5 Personnel

Capacity

Around 180 staff were employed in the compounding facility including approximately 20 for quality, 17 releasing officers, 110 for manufacturing across three shifts, 8 customer service/planning, 11 dedicated training staff and 18 for warehouse and packing.

Capacity was calculated and monitored separately for the isolator and PN suites and was noted to be regular breaches of the 80% target without corrective action or prospective QA approval.

Training

Not specifically inspected but it was noted that a dedicated training team was employed who also dealt with routine validations.

C6 Premises and Equipment

Validation of VHP cycles.

[redacted] was document [redacted] ev A (Oct 2023). The protocol included definition of the loads, loading patterns and diagrams. 18 biological indicators were added to the load of the isolator and their positions were described in the protocol.
There was a description of the acceptance criteria for the VHP cycle and this was also present in the procedure for routine use. The validation cycle was the same as the one used for routine manufacturing but with a most challenging load (more units).

[redacted] was document [redacted] rev BA (Oct 2023).

Biological Indicators were checked for population prior to their use. This was outsourced to [redacted] There was a process in place for the reconciliation of these biological indicators that entered the manufacturing areas.

Validation of VHP cycles in the RGP chambers
There were 3 RGP chambers that were connected to 6 of the 10 isolators. Each chamber connected 2 isolators. These RGP chambers were used for the sanitisation and introduction of new materials into the isolator without breaching its integrity.
[redacted] was document [redacted] rev A (Jan 2023). All loads were revalidated annually. [redacted] and [redacted] had only 1 recipe and [redacted] had 2 loads defined. Each load was revalidated separately. The overall process was similar to the validation of the VHP cycles for the isolators.

Temperature mapping of storage areas
[redacted] was document [redacted] ev 00 (Aug 2022) and [redacted] was document [redacted] rev 00 (Sep 2022). 17 additional probes were placed for the mapping exercise. Hot and cold spots were discussed and identified. The protocol discussed the suitability of the chamber loading at the time of the mapping as the store was mapped 'as found'. Operating conditions were simulated and traced (door openings). The store was mapped annually and continuously monitored via FMS. A similar process was in place for [redacted] that held the finished products.

Cleanrooms and air clean devices
[redacted] was document [redacted] from Mar 2023 and applied to all 4 UK

sites: [redacted] Room classification was limited to the 'at rest' condition only. There was no consideration of area classification 'in operation'.

In the TPN facility, all 10 HEPA filters in the grade A (10 LAFs) were integrity tested on a monthly basis. For the isolators integrity testing was performed every 6 months.
Air velocity was confirmed every 6 months, and this was performed by the site. The portable anemometers were cross-checked with the anemometer in the LAFs for continuous reliance on the built in instruments.

Every 6 months, portable particle counters (3x) owned by the site were brought into the LAFs and into the isolators for area classification. However, this was limited to the 'at rest' state only.

Each LAF had an built-in particle monitoring probe and there were three additional probes in the grade B background room. However, there was no documented rationale for their locations.

Warehouse
There was a warehouse that was exclusive for starting materials for manufacturing under the MS licence. The warehouse included a walk-in fridge (2°C – 8°C). Both areas were continuously monitored and routinely remapped. The remapping frequency was 18 months to account for seasonal changes.

Materials were unloaded on the main loading bay of the site and transported into a goods-in area where they were reviewed against an order and a specification. Materials were not given a new batch number, the manufacturer's batch number remained the identification number for the material. Materials were loaded into the system and assigned a location in the warehouse. Some materials would be added to the system 'in quarantine' until a full release had been performed by the QC lab (microbiology plates). This release process was performed on the system.

There were segregated areas for defective materials in both room temperature and the cold store.

C7 Documentation

[redacted] was used for logging, processing and trending. The Baxter bespoke system [redacted] was used to generate batch documentation and labelling along with barcode labels for relevant products (part-used vials and PN)

C8 Production

PN products were manufactured in one of two grade B suites each containing five grade A horizontal LAF cabinets and the cytotoxic / CIVAs products were manufactured within a grade D suite containing 10 grade A flexible-walled isolators which were subject to VHP gassing. Three shift patterns were employed to allow for manufacturing to take place between 6am to 2am daily.

Isolator suite – around [redacted] doses per day

Materials were transferred from a small warehouse via two transfer hatches to the preparation room. When loading a chamber prior to VHP, the operator was not required to wear a mask which should be addressed in the CCS. Form [redacted] "Gassing sheet" documented the sanitisation cycles with each being valid for a two-week period, unless breached, in which case the isolator would be re-sanitised with VHP.

A batch of [redacted] in [redacted] infusor devices was observed being manufactured in isolator [redacted] (one of the dedicated [redacted] solators). The operator was noted to be working directly over the open syringes with stock solution in them. The method for production was in the relevant SOP which was not available to the operator. The operator had to remember the order of additions to the infusor. The site should consider adding this detail to the [redacted] system. Similarly, the operators were able to choose the manufacturing equipment and method and a deficiency was raised. No ampoules were used in the isolator suite.

DTP drums were available to transfer items between isolators if required and this process might be employed up to 20 times per day. The site should ensure that this activity is minimised as far as possible. Manufactured items were removed from the isolator via DTP tubes and sleeves. This process was observed with sealing and cutting operations to protect the Grade A environment.

Finger dabs were only taken once daily at the end of the second shift (9pm) and a deficiency was raised.

PN suite – around [redacted] bags per day

The process employed [redacted] compounders interfaced with the [redacted] system. Pooling operations were routinely undertaken with appropriate control such as pre-programmed [redacted] hours expiry. Routine batch size was [redacted] to allow for 1 QC sample. See section D for deficiencies raised around the material transfer process.

The material transfer process was observed with deficiencies raised – see section D.

PN release was a three-stage process comprising document review, visual inspection, and [redacted] release with check back to original order, all of which were observed. [redacted] and the associated SOP [redacted] incorporated FMS checks three times daily and operator validation checks. However, pressure or particle excursions would not always be captured and a deficiency was raised.

End of session media fills were carried out daily for each operational cabinet as per [redacted] There were three options for PN media fill; 2 [redacted] configurations and one manual configuration.

C9 Quality Control

Chemical – the middle bag of certain PN batches were tested for potassium, sodium and glucose concentrations. The testing was carried out by the commercial team with limits were set at [redacted] The results for recent batches were reviewed with no comments raised.

Environmental monitoring

[redacted] was document [redacted] (Rev 00 from Oct 2017 and rev B from Feb 2021). This EMPQ exercise was routinely done every 5 years and was used to confirm the locations for routine monitoring.
Trend reports were issued on an annual, quarterly and monthly basis. [redacted] was document [redacted]

Microbiology laboratory
The microbiology laboratory was shared with the commercial side of the business. However, they operated under different teams and different procedures. The team for specials was formed of 5 members. [redacted]

The laboratory processed environmental monitoring samples (settle plates, contact plates and air samples) and also the media fills. No sterility testing was performed onsite. Identity testing was outsourced. All isolates from grade A were identified.

All media (plates and broths) was purchased. No media was prepared onsite. All deliveries of media underwent growth promotion test which included the 5 compendial organisms and one in-house isolate. Two walk-in rooms were used for incubation of the plates, one at 20°C -25°C and another at 30°C-35°C. The rooms were mapped periodically and continuously monitored.

There was a system in place for the rotation of the plates and media fill samples to ensure the minimum incubation days were completed at each temperature. The labelling of the plates was found to be lacking consistency across different samples observed during the inspection. All samples randomly selected were followed up and traceable to a batch, a location and an operator. However, the system lacked robustness for some of the samples and, in particular, given the large number of samples that were handled at a single time. The site indicated they were currently working on a new barcode system for the samples.

Environmental plates from critical areas were not routinely read by a second operator for the compounding area although they were for the commercial operation. This should be standardised.

C10 Outsourced Activities

Not inspected.

C11 Complaints and Product Recall

Two recalls had been carried out in the previous period. [redacted] related to particles in a raw material which had been used for manufacturing and [redacted] related to vaporised hydrogen peroxide below the required concentration.

C12 Self Inspection

Not inspected.

C13 Distribution and shipment (including WDA activities if relevant)

Completed orders were sent to [redacted] via a validated transport procedure with appropriately pre-conditioned cool packs.

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

1 CRITICAL

None

2 MAJOR

2.1 Arrangements in place to ensure that microbial and particulate contamination was prevented in the final product were deficient in that:

2.1.1 Operators repeatedly moved their hands in and out of the LAF cabinet during manufacturing, for example to collect ancillary items, remove multiple wipes, or to discard items such as used needles. This is a repeat deficiency.

2.1.2 Operators were frequently working over open syringes in the isolators.

2.1.3 The manner of use of the isolators introduced risk of mix-up and contamination in that they were excessively loaded.

2.1.4 Personnel were not appropriately monitored after critical operations in that finger dabs were taken only once daily despite three distinct shift patterns for manufacturing

2.1.5 The material transfer process was not adequately controlled in that:

2.1.5.1 For the LAF suite, a process involving four individual wiping wipes rather than two sprays and two wipes was used. Therefore, there was no assurance of appropriate contact for all surfaces

2.1.5.2 There was no contact time for IPA at the last stage of the sanitisation process which was into the Grade A cabinet.

2.1.5.3 The method used for sporicidal wiping was observed to have excessive use of single wipes, no defined overlapping strokes, and shared wipes between the surfaces and the items to be transferred.

2.1.5.4 There was no robust evidence to support the employed 15-minute contact time for the sporicidal agent where the manufacturer recommended a 30-minute contact time. Note that this is the third time this deficiency has been raised.

2.1.5.5 Verification of the transfer process did not demonstrate that the process was capable of producing items with an acceptable bioburden profile in the Grade A areas in that samples were taken only in Grade D and C.

2.1.6 There had been no consideration, in the contamination control strategy (CCS) or otherwise to the need for additional gowning such as a facemask being required in grade C and D areas when performing activities considered to be a contamination risk. For example, when manually loading the VHP chamber.

2.1.7 Manufacturing did not consistently take place in Grade A because ingredients such as large bags were situated in the grade B room rather than the Grade A cabinet. During manufacturing these items were observed to be moved along a rail to an area which was directly in front of the [redacted] compounder and therefore would have no clean airflow.

2.1.8 Production did not consistently follow clearly defined procedures in that operators were able to choose the method of manufacture. For example, to use a repeater pump or syringe pusher or not. The information on the method chosen was not recoded anywhere.

2.1.9 Aseptic Process Validations did not demonstrate effective control in that:

2.1.9.1 The media fill validation ([redacted]) indicated that aseptic pools could be transferred between work sessions/cabinets.

2.1.9.2 Incubated broth did not meet the pharmacopoeia requirements in that:

2.1.9.2.1 [redacted] was used as a diluent.

2.1.9.2.2 Dilutions were incorrect to ensure double strength TSB was of the appropriate strength on incubation.

2.1.9.3 Incubation dates differed on manufacturing paperwork compared with the [redacted] micro control system.

Reference: EU GMP Chapter 5 Principle, C5.10, C6.7(ii), A1.4.2, A1.7.13(iv), A1.8.10, A1.8.130, A1.9.22, A1.9.25, A1.9.26, A1.9.29,

British Pharmacopoeia C2.6.1

MHRA Guidance for 'Specials' Manufacturers

https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

2.2 Cleanroom and clean air equipment qualification, maintenance and monitoring did not ensure continuous working conditions in the Grade A & B areas, as evidenced by, but not limited to:

2.2.1 For the Total Parenteral Nutrition suites (TPN):

2.2.1.1 Cleanroom classification was not carried out in the 'in operation' state and was limited to 'at rest' only

2.2.1.2 The maximum time interval for requalification of grade A & B areas (12 months) was greater than the one stated in the guidance (6 months)).

2.2.1.3 There was no assessment whether the particle counters were oriented appropriately and positioned as close as possible to the critical locations to ensure that samples were representative.

2.2.1.4 There was no clear differentiation of cleanroom qualification (including classification) from operational environmental monitoring. For example, when HEPA filters failed integrity testing, batch release relied on routine particle counts and environmental monitoring plates.

2.2.2 For the isolators:

2.2.2.1 Area classification was not carried out in the 'in operation' state and was limited to 'at rest' only

2.2.2.2 There was no periodic monitoring exercise at the timeframes suggested by the guidance (3 months) to demonstrate continued compliance with the requirements

2.2.3 Passthrough hatches were not designed to protect the higher grade environment in that they were not sealed, were noticeably worn and scratched and had no active filtered air supply.

2.2.4 Airflow pattern studies were not performed under conditions representative of current situation in that:

2.2.4.1 There was no consideration whether the 'in operation' condition considered all ingredients and components present in the clean areas.

2.2.4.2 There had been no consideration of the impact on new mesh in the grade A or the new cabinets in the grade B.

***Reference: EU GMP A1.4.12(ii), A1.4.15, A1.4.24,* A1.4.29, A1.4.32, A1.5.9,**

MHRA Guidance for 'Specials' Manufacturers

https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

3 OTHERS

3.1 Finished product assessment (batch release) did not embrace all relevant factors, including production conditions in that:

3.1.1 The releasing officers were not aware of recent environmental monitoring results, particle alarms during production as evidenced by the routine handover being verbal only.

3.1.2 The releasing officers were not aware of authorisation status of operators of because [redacted] authorisations were not appropriately revoked when required such as in the case of operators [redacted]

3.2 There was no prospective QA approval when capacity breached the 80% target such as on several occasions in 2023.

3.3 Storage conditions were not consistently appropriate. In particular, they were not clean and dry and maintained within acceptable temperature limits as evidence by the Storage of 3 sleeve gassers in a portacabin like building with obvious water ingress, condensation and ripped packaging.

Reference: EU GMP C3.19, C6.3, A11.12.1, A11.12.3

MHRA Guidance for 'Specials' Manufacturers

https://www.gov.uk/government/publications/guidance-for-specials-manufacturers

4 COMMENTS

4.1 There had been no documented consideration of the BP requirement to not use [redacted] stored in glass for PN compounding for all customers, only those which proactively asked for formulation change. The site are required to confirm no further use of affected products.

4.2 There has been no action from the 2019 commitment to move towards routine sterility testing programme for products with stability supporting expiries towards 90 days. The site are required to confirm how this will be progressed in a timely manner.

4.3 The site are required to update licence to reflect current status in terms of Contact, [redacted] and the need for authorisation to manufacture Biological medicinal products.

4.4 Several repeat deficiencies were identified during this inspection.

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 closing meeting was attended by personnel listed in B3 and the deficiencies were accepted.

F2 Assessment of response(s) to inspection report

The post- inspection letter was sent on 06/11/23. and a response received 04/12/23. There were several common issues across the Oxford and Thetford compounding sites and these were dealt with concurrently. A final RFI (number 4 for Oxford and number 1 for Thetford) was received and accepted on 13/03/2024.

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
GMP as required by the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	✓
The Medicines for Human Use (Clinical Trials) Regulations 2004	
Regulation 5 of the current Veterinary Medicines Regulations	
Regulation C17 of the Human Medicines Regulations 2012 (as amended) and the Human Medicines (Amendment) Regulations 2019	

and is acceptable for the products in question.

Name of Inspector (s):

Lead Inspector: [redacted] **Date:** 15/03/2024

Accompanying Inspector: [redacted] **Date: 21/03/2024**

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:	1	Last Inspection:	5

(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):

[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