INSPECTION REPORT

Rx Extraction Limited
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UK

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: First full inspection of new site (first inspection was not completed due to the site withdrawing their application).

Licence or Reference Number: API 55392

Licence Holder/Applicant: Rx Extraction Limited

Details of Product(s)/ Clinical trials/Studies: Cannabis extracts

Activities carried out by company:	Y/N
Manufacture of Active Ingredients	Y
Manufacture of Finished Medicinal Products – Non sterile	N
Manufacture of Finished Medicinal Products - Sterile	N
Manufacture of Finished Medicinal Products - Biologicals	N
Manufacture of Intermediate or Bulk	N
Packaging – Primary	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: *None*	N

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

Site Contact: [redacted]

Date(s) of Inspection: 11th December 2024 and 7th and 8th January 2025
(the inspection was split into two parts [redacted])

Lead Inspector: [redacted]

Accompanying Inspector(s): Not applicable.

Case Folder References: Insp GMP 55932/25925977-0002

Section B General Introduction

B1 Background information

This was the second inspection of a new site that intended to manufacture cannabis related products (the first inspection was not completed as the site had applied for the incorrect licence/registration and the GMP experience of staff was not considered appropriate). The site intended to manufacture whole cannabis plant extracts and individual cannabis extracts (APIs) using [redacted]

This site also intended [redacted]

Previous Inspection Date(s): 27th to 28th June 2023 (1 day – no PIL issued as the licence application was withdrawn)

Previous Inspectors: [redacted]

B2 Inspected Areas

Deviations, Change Control, CAPA, Complaints, Management Review, Licence applications, Validation Master Plan, Equipment Qualification, OOS/OOT, Stability, Outsourced Activities, Training, Resource, API manufacturing equipment (including drying, CO_2 extraction, distillation, purification, and crystallisation), vault, Specials manufacturing (packaging) area - note that this was not part of the scope of this inspection

Limitations / exclusions to inspected areas

CAPA, Process validation (had not been completed at the time of the inspection).

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[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] 25 Nov 2024	Yes
Compliance Report	Not applicable as first inspection of site.	N/A
Comments: None.		

Section C Inspector's Findings

C1 Summary of significant changes

This was the first inspection of a new site.

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

This was a new site.

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

No compliance report was provided, as this was the first full inspection of the site.

C2 Action taken since the last inspection

Not applicable, as this was the first full inspection of the site.

C3 Starting Materials

General

The site identified that they were considering [redacted]

The starting material for the API extraction was to be sourced in the [redacted]

The Supplier Audit Procedure was reviewed, [redacted] version [redacted] dated 8th December 2023. The audit findings were classed as Critical/Major/Other/Comment. The QP and QAM were the only personnel allowed to carry out audits. The audit assessment form was [redacted] version [redacted], dated 4th June 2024. It was not clear whether the audits were required to be on-site or remote. The definition of Critical/Major/Other were different in the Audit SOP and the Audit Assessment SOP. The form was a checklist. An audit response of 28 days was typically required, but this was not based on risk. There was no requirement to consider a recall in the event of a critical deficiency being identified. There was a reference to another company and personnel in the form.

The [redacted] SOP was reviewed [redacted] version [redacted] dated 8th December 2023. A change control was required to be raised to add a new supplier. On-site audits were required for the supply of goods/services if these have the potential to adversely affect the product. The risk assessment to determine if a site was required to be audited contained errors and inconsistencies e.g. the scoring of continuous monitoring in section [redacted] There was a financial element that could impact the overall scoring of GMP critical materials to reduce the likelihood of audit if the commercial value was low. Any supplier that fell into the high-risk category required auditing every 24 months, but it was not clear what the expectation was for suppliers with Medium or Low risk ratings. There was no consideration of increasing audit frequency if there were issues identified with the supplier. There was no requirement to do periodic checks of supplier licences/registrations. There was no guidance of whether packaging materials, solvents, etc were critical materials.

The [redacted] version [redacted] was reviewed, dated 4th June 2024.

Incoming goods checks were covered by [redacted] version [redacted] (draft – version [redacted] was issued at the time of inspection). **There was no requirement to confirm the security seal numbers.** Materials were held in quarantine until released (no status label is placed on the

containers when in Quarantine status). A Goods Receipt Number (GRN) form [redacted] was used.

A draft specification for cannabis biomass was reviewed. The API process involved [redacted] version [redacted] draft (version [redacted] was issued). The testing was discussed as being carried out by [redacted] or [redacted] The SOP gave a high level overview of the requirement to release starting materials, but didn't explain how this done routinely. Review of the Certificate of Analysis was carried out and it was identified that there was no mention of shelf-life, storage conditions, example label, how controlled, who can release the material, the records.

Compliance with TSE Guidelines

There was no consideration of TSE risk in the audit questionnaire.

API Compliance

This was an API manufacturing site, so not applicable.

C4 Pharmaceutical Quality System

PQR

The PQR procedure was [redacted] version [redacted] dated 08 December 2023. The review period was identified as being from January to December each year. The PQR was required to be completed within 90 days. The PQR was based on drug products with Marketing Authorisations and required to be rewritten. The PQR only required the review of Critical deviations.

Deviation

The deviation SOP was [redacted] version [redacted] dated 08 December 2023, with a review date of 08 December 2024.

The initial risk assessment to determine the investigation timelines included the Likelihood, and therefore this had the potential to reduce the risk, despite the incident already have happened. Delays to the completion of the investigation required an extension to be approved. Only one extension was allowed. There was no requirement in the deviation form to consider if a recall was required.

The associated deviation notification form was [redacted] There was a separate deviation investigation form [redacted]

There had been one deviation raised at the time of the inspection [redacted]. The deviation was classed as a Minor, but was actually a Notification. There were a number of blanks in the form where no entry had been entered.

CAPA

This was not reviewed in detail during the inspection.

Change Control

The change control SOP was [redacted] version [redacted] dated 8th December 2023. Changes could be temporary or permanent. Changes could be classed as Minor, Major, or Critical. There was a requirement to carry out a post implementation review of the change. The change control form was [redacted] dated 04 June 2024. There was no 'Critical' as an option in the Change control form.

There had been two change controls raised at the time of the inspection. [redacted] and [redacted] There were no checks in the change control form to consider if certain actions were required e.g. stability, training, equipment qualification, updated SOPs etc. The change control risk assessment actions were required to be formally tracked.

Cleaning Validation/Verification

The [redacted] was [redacted], version [redacted], dated 12 December 2023. The procedure was written for finished drug products. A number of equipment cleaning SOPs were reviewed. The [redacted] cleaning procedure was reviewed. There were no cleaning batch records in place, there was a cleaning log. The batch details of the solvents used for cleaning were not recorded. The cleaning process of the extraction unit was a pre-programmed cycle. The process included cleaning the basket exterior with soapy water, however the [redacted] would into contact with the outside of the basket, and this was therefore going to be replaced with a suitable solvent.

Management Review

The management review SOP was [redacted] revision [redacted] dated 6th December 2024. Management reviews were defined as being carried out every 3 months. The associated form [redacted] was reviewed.

Risk Management

The QRM SOP was [redacted] version [redacted] dated 08 December 2023. The risk assessment process included a reference to FMEA, however the site only considered Severity and Occurrence and not 'detectability', which was part of FMEA.

Validation Master Plan

The site VMP was [redacted] version [redacted] dated 03 December 2023. The Project validation plan was [redacted] version [redacted] dated 12 Jan 2024 was reviewed

Process Validation

The process validation had not been completed at the time of the inspection. The site were requested to provide a copy of the report when available.

Analytical Method Validation

All testing was outsourced.

Batch Release

The batch release procedure was [redacted] version [redacted] dated 08 December 2023. The SOP referred to adherence with the MA i.e. for a launched drug product. There was no information regarding the release of APIs.

The batch release checklists [redacted] version [redacted] version [redacted] [redacted] version [redacted] [redacted] and [redacted] version [redacted] [redacted] were reviewed. The detail in these forms was not applicable to APIs or Specials products.

C5 Personnel

Training

The training SOP was [redacted] version [redacted] (draft). There was a training matrix in place. The SOP mentioned GDP training requirements rather than GMP training. The training was required to be carried out annually. The initial training the refresher training was to be carried out by a contract company. There was a test on the GMP induction training, but there was no pass mark identified, or model answers recorded.

The training records for the Health and Safety manager was reviewed. The training record had a number of omissions and it was not clear whether these were required or not. There was no training record/plan for the new QAM who was only recently in post. The training record for the senior extraction manager was reviewed.

Staff Numbers

The SMF identified the following organisation:

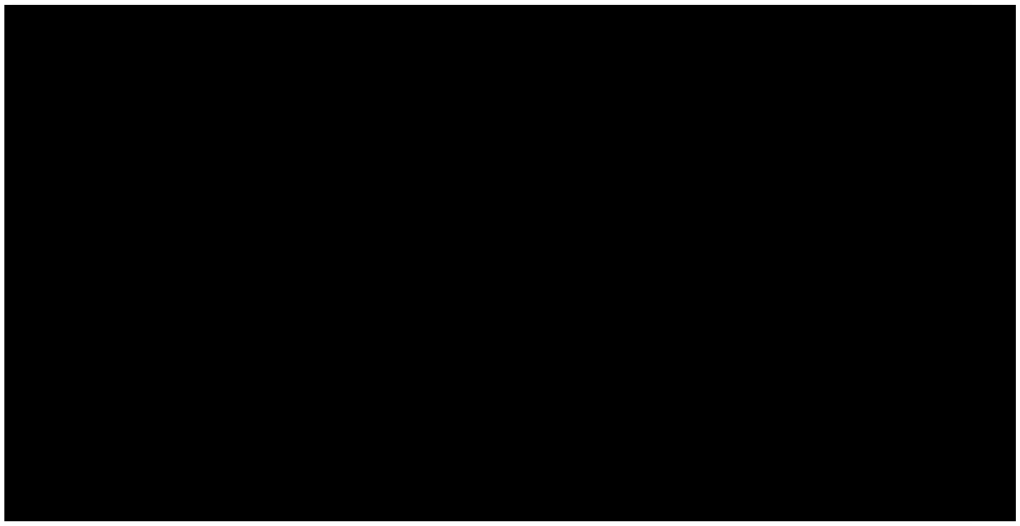
The [redacted] members of staff highlighted in the above organisation chart were based at the site.

C6 Premises and Equipment

The SMF identified the site was over two floors, had an area of [redacted] square fee ([redacted] square meters), comprised of the following key areas:

- Warehouse, Secure vault, Manufacturing room (Plant room and extraction), Clean rooms (distillation room and crystallisation), QC Lab, Specials suite, Board Room

The following simplified plan was also included.



Maintenance and Calibration

There was a combined maintenance/calibration SOP. The SOP was [redacted] version [redacted] (draft). Equipment could either be critical or non-critical to determine the calibration requirements. Calibration could be carried out inhouse or by contractors. It was described that all calibration was to be carried out externally at present. There was no identification of what to do if the calibration due date was exceeded. The expectations of the calibration were not included e.g. the range over which the calibration was to take place, the minimum number of points etc. There was no requirement to review and sign that the certificates had been reviewed. There were no QTAs with the calibration providers. There was no requirement to have like for like changes. There were draft preventative maintenance checklists in place.

Equipment Qualification

The manufacturing equipment had been subject to [redacted] (the equipment had already been purchased and installed, as identified in the previous inspection).

The URS for the [redacted] dated 6 February 2024, was reviewed. A number of URS requirements were checked at the subsequent qualification stages.

The PQ records were also checked. It was identified that gaps in data were present in the batch records e.g. [redacted]

C7 Documentation

Batch Record

The batch records for the PQ distillation activity were reviewed, batches [redacted] The batch record template and master were available to the person carrying out the processing activity. It was discussed that the pages were not initialled by a QA person to minimise the inherent risk of this situation. The batch record did not record the batch number or expiry date. The weight measured to the number of decimal places of the balance was not recorded, it did not record the ID of the balance, it did not confirm that the balance was within calibration date. There was no printer attached to the balance. There was no defined space to attach printouts. There was information missing on the weight of the sample required (the layout did not minimise the risk of data being missed.

Data Integrity

Not covered in detail in this inspection.

Document Control

There was a master document register in place ([redacted] that listed out all the documents in the PQS. A number of documents had a review date of the 8th December 2024, however these were in the process of being updated.

C8 Production

API Production

The process involved [redacted] and was reviewed in detail. [redacted]

C9 Quality Control

OOS/OOT

The OOS/OOT procedure was [redacted] version [redacted] dated 8th December 2023. The procedure detailed the process to follow for OOS. There was no specific detail on how to identify or how to handle an OOT. The OOS process was aligned with the MHRA guidance and required 5 retests when the root cause could not be assigned and there was no manufacturing explanation for the OOS.

Stability

There was no procedure in place relating to stability expectations. There were batches on stability from the trials.

There was no procedural requirement to place batches from production on stability each year.

C10 Outsourced Activities

Manufacture

No manufacture was to be outsourced.

Analytical Testing

The company intended to outsource the testing of the products to [redacted] The contract testing lab was described as being able to subcontract the microbiological testing.

Technical Agreements

Technical agreements were not in place for all outsourced activities.

Qualified Person

There was no requirement to have a QP, however the site had engaged a contract QP to assist them in preparation of the PQS.

C11 Complaints and Product Recall

Complaint

The complaints SOP was [redacted] version [redacted] dated 08 December 2023. The procedure identified timelines related to the level of risk. The form did not have all the investigation elements identified in the deviation procedure.

Recall

The recall SOP was [redacted] version [redacted] dated 08 December 2023. The recall procedure referenced where RX Extraction Ltd were the MAH. The SOP discussed Clinical Trial materials and made mention of [redacted] The DMRC address was incorrect and the procedure identified that yellow-card website could be used to log the initial data. There was no requirement proceduralised to carry out a mock recall. The recall form was [redacted] version [redacted] dated 04 June 2024. It was discussed that the form could be updated.

C12 Self Inspection

The self-inspection SOP was [redacted] version [redacted] (draft). The audit schedule was required to be generated covering Jan to Dec each year. Actions were required to be entered into the CAPA system. The risk assessment for determining the frequency of audits contained errors and was overly complex.

C13 Distribution and shipment (including WDA activities if relevant)

This was not reviewed during the inspection.

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 **Batch manufacturing and cleaning records were deficient as evidenced by:**

2.1.1 The manufacturing distillation batch records [redacted]

2.1.1.1 There was no record of the batch numbers or expiry dates of the raw materials used in the process.

2.1.1.2 There were no printouts from balances included in the batch sheet (not all balances had printers).

2.1.1.3 The batch records had been signed off despite there being information missing (it was noted that the formatting of the document did not assist accurate and full data entry).

2.1.1.4 The weights entered into the batch record at the same place were inconsistently rounded to one, or zero decimal places.

2.1.1.5 There was no record of the balance used, or a confirmation that they were within their calibration date.

2.1.1.6 There was no requirement to confirm the integrity of the mesh filter pre- and post-use.

2.1.2 There were no cleaning batch records in place, therefore, there were no records confirming:

2.1.2.1 That all required steps had been completed and in a consistent manner.

2.1.2.2 Batch numbers or expiry dates of solvents used

2.1.3 The requirement to identify the cleanliness status of the equipment was not proceduralised, and the majority of processing equipment was not clean at the time of the inspection, with no status indication in place.

Reference: EU GMP Part II 2.15, 6.10, 6.20, 6.30, 6.41, 6.51, 6.52,6.70

2.2 **The batch release procedure and associated forms were deficient, as the content of the procedure was not applicable to APIs (the process was targeted to commercial drug products).**

Reference: EU GMP Part II 2.14, 2.32.6.71, 6.72

2.3 **The sourcing and control of materials was deficient, as evidenced by:**

2.3.1 Raw Material Suppliers

2.3.1.1 The audit procedure contained an audit template that included details of a different company and personnel that were not related to Rx Extraction.

2.3.1.2 The procedure had contradictory information to determine whether an on-site audit was required.

2.3.1.3 The consideration for onsite audit of GMP materials was impacted by the material value of the order and could override the GMP considerations

2.3.1.4 The risk assessment to determine if an audit was necessary contained errors in the assignment of risk and was overly complex for staff to understand.

2.3.1.5 The proceduralised re-audit dates were not based on risk

2.3.1.6 The definitions of critical/major/other findings were different in the SOP and the audit template.

2.3.1.7 The audit response time was not based on risk

2.3.1.8 There was no requirement to consider a recall in the event of a critical finding being identified

2.3.1.9 There was no guidance on what constituted a critical material e.g. container contacting final product

2.3.2 Raw materials

2.3.2.1 The procedure for the release of starting materials had no detail of how this activity would be carried out, for example;
2.3.2.1.1 There was no record of who could, or had carried out the release activity
2.3.2.1.2 There was no control of status labels, or definition of what was to be recorded on them.
2.3.2.1.3 There was no requirement for a shelf life to be assigned.
2.3.2.1.4 There was no record of storage controls required.
2.3.2.1.5 There was no procedural requirement to consider the risk of TSE

Reference: EU GMP Part II 2.17, 2.32.2, 6.71, 7.10, 7.11, 7.24, 7.50, 9.31

2.4 **The Pharmaceutical Quality System (PQS) was deficient, as evidenced by:**
2.4.1 Deviation procedure and process
2.4.1.1 The likelihood of the deviation occurring was included as factor in the initial impact risk assessment (despite the deviation already having occurred).
2.4.1.2 There was no requirement in the deviation form to consider if a recall was required.
2.4.2 PQR
2.4.2.1 The procedure was written for commercial drug product manufacturing activities, rather than for API manufacturing operations.
2.4.2.2 The PQR only required the review of Critical deviations.
2.4.3 Recall process and procedure:
2.4.3.1 There was reference to a site in the SOP that was not related to the company.
2.4.3.2 The procedure incorrectly identified the process where the company was the MAH.
2.4.3.3 The address details of the DMRC were incorrect.
2.4.4 Document control and good documentation:
2.4.4.1 The batch record masters were available to the person carrying out the manufacturing activities, with no additional issuance controls in place.
2.4.4.2 There were a number of examples of data entries being missed on approved records e.g. deviations and PQ records.
2.4.4.3 There were unexplained gaps in the training records for personnel.
2.4.4.4 There was no training record generated for the new temporary Quality Assurance Manager.
2.4.4.5 The training SOP frequently mentioned ‘GDP’ rather than ‘GMP’

Reference: EU GMP Part II 2.60, 13.16, 15.13, 15.15

3 OTHERS

3.1 **There was no SOP on stability in the Pharmaceutical Quality System. Additionally, there was no procedural requirement to place routine production batches on stability each year, and it was noted that the change control procedure did not require the site to consider placing batches on stability after significant process changes had been implemented.**

Reference: EU GMP Part II 11.50, 11.54,

3.2 **The calibration and maintenance SOP and processes were deficient, as evidenced by:**
3.2.1 The calibration requirements were not defined e.g. required range or acceptance criteria
3.2.2 There was no guidance on what to do when a calibration date was not met.
3.2.3 There was no requirement to review calibration certificates received from an external company.
3.2.4 There was no requirement for changes to be ‘like for like’, or the impact to be thoroughly assessed if not.
3.2.5 There were no Quality Technical Agreements (QTA) in place with the providers of external services.

Reference: EU GMP Part II 5.10, 5.30, 5.33, 5.34

3.3 **The self-inspection process was deficient as evidenced by there being errors in the risk assessment relating to detectability. It was also noted that the current risk assessment was not appropriate to the scale of operations carried out at site.**

Reference: EU GMP Part II 2.21

4 COMMENTS

4.1 **The site was requested to provide a copy of the completed process validation report when available (it was not expected to be completed prior to responding to the 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	✓	[redacted]	[redacted]
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The closing meeting was attended by those persons identified in B3 and all deficiencies were accepted as presented.

F2 Assessment of response(s) to inspection report

The Post Inspection Letter was sent on the 10th January 2025, a response was accepted on the 3rd March 2023, after one set of RFIs (Requests For Information).

F3 Documents or Samples taken

None.

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

Based on the information provided, the facilities observed, and the commitments made, the site is considered to operate 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	

Name of Inspector (s):

Lead Inspector: [redacted] **Date:** 03 March 2025

Accompanying Inspector: N/A **Date:** N/A

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	N/A
Major deficiencies this inspection:	4	Last inspection:	
Other deficiencies this inspection:	3	Last Inspection:	

The inspection was ceased at the request of the company and no Post Inspection Letter was sent.

(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

[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