Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Clinigen Healthcare Ltd
Idis House,
Churchfield Road
Weybridge,
KT13 8DB
[site 93802]

This report also covers activities at the Byfleet site
Unit 3, Canada Road
Byfleet
KT14 7JL
[site 362376]

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

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

Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MIA 31644, MS 31644, MIA(IMP) 31644 WDA (H)/ 31644 WDA(V) 31644

Licence Holder/Applicant: Clinigen Healthcare Ltd

Details of Product(s)/ Clinical trials/Studies: The site carried out a wide range of activities and was a supplier of unlicensed medicines. The site continued to procure and source unlicensed medicines as well as being involved in sourcing of materials for clinical trials, handling some of their own licensed medicines and wholesaling.

The Weybridge and Byfleet sites mainly supplied products to the UK and EEA markets. In addition, there
was limited supplied to the Rest of the World.

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	N
Manufacture of Finished Medicinal Products - Biologicals	N
Manufacture of Intermediate or Bulk	N
Packaging – Primary	N
Packaging - Secondary	Y
Importing	Y
Laboratory Testing	N
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: *Over labelling of imported unlicensed medicines and comparators for clinical trials*	Y

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

Site Contact: [redacted]

Date(s) of Inspection: 27th – 29th February 2024 (Weybridge: site 93802)
05 March 2024 (Byfleet: site 362376)

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

Case Folder References: Insp GMP/GDP/IMP 8733/93802-0021 & Insp GMP/GDP/IMP 31644/362376-0012

Section B General Introduction

B1 Background information

Previously Idis (1987), Clinigen was founded in 2012 and acquired Idis in 2015. Clinigen acted as a partner with pharma companies for support of drug shortages, support of clinical trial and comparator sourcing. There were approximately 350 employees based in the UK.

The company were involved in multiple activities including:

- Clinical Trials: Importation, comparator/NIMP sourcing
- Unlicensed Medicines: Import, storage, supply, export of both non-clinical trial stock or non-UK licensed medicines for unlicensed use. In addition, secondary packaging and release under the MIA(IMP) or MS license.
- Commercial Medicines: Virtual Marketing Authorisation Holder and oversaw subcontracted GMP activities.

The company operated across three different sites, which included two administrative sites (Weybridge, Surrey and Burton, Staffordshire). There was one operational site (Byfleet) for storage, distribution, import, certification and secondary packaging activities. There was no physical stock received, stored or distributed from Weybridge or Burton where activities were limited to procurement and supply administration only. There was no manufacture of drug product, primary packaging activities, QC testing, randomisation or blinding activities for IMP products.

Clinigen provided services for products that had been manufactured by another site on a contract basis. All secondary packaging was either for unlicensed supply on a named patient basis, or of commercial comparators for clinical study. The company was authorised to conduct secondary packaging (excluding blinding and randomisation) of clinical stock also but was not conducting such activities at the time of inspection.

Clinigen was in the process of [redacted]
Approximately [redacted] of its business was related to such activity at the time of inspection.

During the inspection it was difficult to identify which product had been imported under which licence. The provision of documentation was slow.

Previous Inspection Date(s): 1st – 3rd December 2019

Previous Inspectors: [redacted]

B2 Inspected Areas

Starting materials
Pharmaceutical Quality System
Change Controls
Deviations
Quality Management Reviews
Product Quality Reviews
Supplier Management
New Product Introductions

Import and Distribution
Training
Premises & Equipment
Production
Component Sampling
Artwork Checks
Quality Control
Outsourced Activities
Complaints and Product Recall
Self-Inspection
Distribution & Shipment

Limitations / exclusions to inspected areas

There were no limitations to the inspection.

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[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	February 2024*	Y
Comments: *A GDP pre-compliance report was submitted only.		

Section C Inspector's Findings

C1 Summary of significant changes

Taken from pre-inspection compliance report

Key Personnel:
- Feb-2020 Add [redacted] as RP of Clinigen Byfleet and Idis House
- Dec-2021 Add [redacted] as RP of Clinigen Byfleet and Idis House
- Dec-2021 Add [redacted] as RP of Clinigen Head Office
- Jun-2022 Add [redacted] as Responsible Person for Import

Licensing Activity
- Jun-2021 Include 2.4 Export to Clinigen Burton, Clinigen Follingsby and Clinigen Byfleet
- Jun-2021 Include 2.6 import to all sites
- Mar-2022 Include 3.1.4 Radiopharmaceuticals

Facilities/Premises
- Feb-2020 Removal of Clinigen Stretton warehouse
- June-2020 Add of [redacted] as a third party storage site
- Sep-2020 Removal [redacted] and [redacted] as a Third Party Site
- Sep-2020 Add new Clinigen Follingsby site
- Dec-2021 Removal of Clinigen Follingsby site
- Jun-2022 Removal of [redacted]

Organisation:
- Jun-2021 Divestment of [redacted]
- Apr-2022 Clinigen acquired by international private equity company [redacted]
- Oct-2022: Interim CEO appointed following departure of previous CEO
- Nov-2022: Clinigen acquires [redacted]
- Mar-2023: Clinigen divests [redacted]
- Jun-2023 New CEO is appointed

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

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

Clinigen was in the process of [redacted]
Approximately [redacted] of its business was related to such activity at the time of inspection.

C2 Action taken since the last inspection

Actions appeared to have been completed from the previous inspection.

C3 Starting Materials

General

Qualification of starting materials was the responsibility of the contract giver.

Compliance with TSE Guidelines

It was described that responsibilities for TSE compliance lay with the product manufacturer, however **processes for ensuring TSE compliance at Clinigen were not reviewed in detail and may be of interest at the next inspection.**

API Compliance

Responsibilities for assuring API compliance lay with the product manufacturer.

C4 Pharmaceutical Quality System

The pharmaceutical quality system (PQS) did not appear to be in a state of control, with multiple document types overdue for close-out and review, some dating back from 2021. The site were asked to provide a list of current overdue documents at the point of the inspection (Table 1). Note, the table does not include all documentation types e.g. overdue SOPs, quality technical agreements and supplier qualifications etc. A total of 199 investigations and change control were overdue. The impact and root cause analysis of these overdue documents had not been documented. It was discussed during the inspection that this issue had been raised during client audits but CAPA/actions plans had not been raised and improvements not instigated.

Table 1: Overdue Investigations and Change Controls At Time Of Inspection

	number overdue	number open	%overdue
Non-conformance	18	19	95
CAPA	26	67	39
Change requests	54	175	31
Complaints	8	31	26

Change Control

Change control [redacted] and [redacted] were reviewed which concerned the expiry extension of [redacted] and [redacted] respectively. The expiry dates for both products were extended, upon request from the sponsor. The main stockpile, held by Clinigen, had the expiry updated and then reversed back to the original expiry, once the work order had been complete. Clinigen's approach is to raise a change control each time stock requires an expiry update, in order to release a work order, as opposed to updating the expiry date of the entire stockpile. These changes were reviewed without comment.

Deviations

Investigations, [redacted] and [redacted] were reviewed. [redacted] was reviewed concerning the mix-up of [redacted] in a container labelled as containing the [redacted] strength. DMRC were notified and the root cause from Clingen's investigation concluded the [redacted] stock decanting process was not sufficiently documented to prevent this issue from recurring again. Initially, Clingen decanted [redacted] stock as part of the incoming goods stock check. Clinigen raised an action to stop all decanting activities out with the production area, where there were better physical control measures to accommodate this activity. The opening of [redacted] stock is now controlled via [redacted]

Quality Management Review

The Quality Governance Policy [redacted] detailed requirements for Quality Management Review which defined monthly Site Quality and Quality Committee Reviews and a quarterly Quality Council. The Site Quality Meeting minutes were reviewed for January and February 2024 and deficiencies raised. There was no ongoing review and trending of investigations to identify process improvements. CAPA plans were not identified or implemented. There was an acknowledgement of overdue documentation, but no improvement plans identified.

Product Quality Reviews

Product Quality Reviews (PQRs) were governed by [redacted], the scope of the procedure applied to products where the company acted as the Manufacturing Authorisation Holder (MAH). PQRs were provided by the product manufacturer and reviewed by Clinigen Quality. PQRs for [redacted] for review periods 2021 – 2022 and 2022 – 2023 were reviewed without comment.

Supplier Management

The vendor approval process was controlled by [redacted] When onboarding a new vendor, Clingen perform a vendor checklist, which includes a cross-check of their licences and any appropriate HO CD licences.

Clinigen held a monthly vendor approval board meeting to review the status of all vendors and any outstanding actions from supplier complaints, in addition, quality technical agreements are reviewed as part of the board meeting. It was explained that Clingen's main challenge was getting suitable responses from suppliers, as many of their products were not sourced directly from the original manufacturers.

In addition to the vendor approval board, all vendors were checked every 2 weeks to ensure they still held a valid licence (both MHRA and Eudralex databases checked).

New Product Introduction

New product introduction was managed through Quality Technical Agreements with clients.

Importation and distribution

The following importation activities were undertaken at the site:

- Import of IMPs from a listed country (QP oversight process)
- Import of marketed products from EEA
- Import of unlicensed products

The company had not imported IMPs or marketed products from 3rd countries since the last inspection.

During the inspection it was difficult to ascertain which products had been imported under which licence. Provision of import documentation was slow. A major deficiency was raised for importation (see section D).

Importation of IMPs from a listed country QP Oversight process

Import of investigational medicinal products into Great Britian from approved countries was governed by [redacted] Clinigen Healthcare Ltd acted as a QP oversight process contractor. IMPs underwent clinical packaging in Germany or Belgium [redacted] and then imported to the UK. The two-step approval process and clinical trial inventory was managed and controlled by [redacted] CTAs, approvals, amendments, product specification files (PSF), manufacturers GMP certificates and batch certification documentation were managed via [redacted] The clinical trial programme manager was responsible for green light approval and shipping to sites following UK QP certification and release. The import of [redacted] preparation for intravenous infusion [redacted] was reviewed and the following documentation was reviewed:

- QTA between Clinigen Healthcare Limited UK (importer), [redacted] (clinical packager) and [redacted] (Sponsor)
- Clinical Trial Application: amendments had been documented and reviewed by the UK QP. A deficiency was raised as there was no documented evidence that shipping address to [redacted] had appropriate ethics approval. The approved site in the CTA referenced [redacted]
- Batch certification [redacted]
- Regulatory approvals

Import of Unlicenced Medicines

The company imported unlicenced medicines for supply to early access and compassionate use programmes for specific territories. Importation of unlicenced medicines was governed by [redacted] The process included monthly reviews of recently licenced products. The monthly review of January was reviewed. There were no controls in place to ensure the pausing of import or supply under a MS where a manufacturing authorisation (MA) had been granted but the product had not been launched. A 'Programme Processing' document was in place for each product detailing authorised supply territories and local regulatory requirements for export. There was a requirement for the healthcare professional to identify unmet clinical need, however, there was no requirement to ensure that the hierarchy described in Guidance Note 14 for the use off label licenced product had been met. Orders were placed via portal by authorised healthcare professionals for post-trial patients, there were requirements for the patient EUDRA CT ID and eligibility criteria to be included in the order. Physicians were required to undergo an annual validation process. A deficiency was raised as there was no documented process for batch QC review and approval, requirements for this process was not described in an SOP.

The import of [redacted] was reviewed during the inspection, the following documents were reviewed:

- [redacted] programme processing document
- Shipping and import documentation. A deficiency was raised as the 'importer of record' was documented as [redacted]
- Shipping Temperature records. It was noted that temperature excursions were investigated in [redacted] temperature excursion details, however the document had not been completed. The excursion had been accepted based on information detailed in a [redacted] however supporting scientific data had not been provided.
- [redacted] and Clinigen Healthcare Ltd QT vs 12 October 2022. The QTA allowed shipment under quarantine, however, there was no process at Clinigen to allow receipt under quarantine. Responsibilities for transport had not been defined.

- Picking and Distribution records, including proof of delivery
- Customer verification: [redacted]

Procurement of Licenced Products From a Listed Country

Licenced products were procured from a listed country via an RPi process. This process was governed by [redacted] (effective 17 May 2022). Import of [redacted] was reviewed during the inspection. Approval was based on a statement from the WDA(H) [redacted] that batches were sourced within local approved supply chain and that the product had been placed on the market and commercially available within at least one EEA member states. Supplier qualification reviewed which was based on review on EUDRAGMDP. RPi approval was documented via status change in the ERP system.

C5 Personnel

Training

Auditor approval record for the lead auditor was reviewed during the inspection. It documented their relevant experience and provided the certificate for completion of the IRCA QMS Auditor/Lead Auditor 5-day Training Course.

C6 Premises and Equipment

Warehouse

The warehouse facility was located in Byfleet, which required swipe card access to enter. The warehouse was temperature controlled between 16 -24 °C. The warehouse had 7 x 2°C - 8°C walk-in storerooms and 1 small freezer. This included 2 x cold stores for incoming materials for Temperature controls were monitored via the BMS system [redacted] where audible alarms and texts messages were sent to an on-call team in the event of an excursion. Excursions were investigated via a non-conformance and reviewed by the RP. There was a locked cage in one cold storeroom that was used for returned stock.

Incoming goods were checked by an Inbound Goods team against requirements laid out in Work Instruction [redacted] which described requirements for checks on transit temperatures, product information, checks on tamper seals, including supplier numbers, and product licence numbers. Product requirements including licence numbers which described for each product in an item catalog [redacted] which was manged by the Master Data Management Team. Acceptance of deliveries was via a scan into the ERP system, however there was no documented evidence that all inbound checks specified in the work instruction had been conducted. The site also accepted deliveries of [redacted] stock' from manufacturers (blinded stock). Checks on these deliveries were documented on a form which had been implemented since October 2023. Checks of decommissioning of stock was described to be the responsibility of the supplier.

The site held [redacted]
The CD store was inspected which was located within a locked cage which contained additional locked safe storage. Access was limited to 19 CD trained staff, it was discussed that this appeared to be a large number of staff and it was described that this list was to maintain coverage during an early and late shifts. CD inventory was performed daily which required one person counting physical stock and a second operator performing the reconciliation against the documented inventory. CCTV covered all areas of the CD storage area, discrepancies were investigated by the RP and all shipments of CDs were suspended. It was described that there had not been any discrepancies since the last inspection. CD returns were also located in a

safe. It was described that there were no controlled drugs that required cold storage. Returned product was stored in locked cages, paperwork was contained with each returned product. A batch of [redacted] had been returned on 29 Aug 2023, the description of why the product was returned was limited to "courier returned", no other information was provided and an investigation had not been initiated. There was a procedural requirement that returns would be allowed into available stock up to 5 days for ambient stock and 24 hours for cold chain storage if the stock had remained under control of Clinigen. It was described by the RP that cold chain products were not returned to saleable stock as a general process.

Printed componentry were stored in padlocked boxes. Sampling plans were described in [redacted] and based on [redacted] Critical, major and other defects were defined but an acceptable failure rate for higher risk defects was not described.

The management of suspected falsified medicinal products was governed by [redacted] The process did not contain details for requirements on checks on Italian or Greek liveries.

C7 Documentation

Batch Record Review and Certification

[redacted] was reviewed. The product original batch number was tracked throughout the production run and not obscured as part of the assembly activity. This number was traceable through the batch record as week as the final Clinigen generated batch number.

The QP generated a CoC which detailed where the product was to be supplied and if further release steps were required by other territories. There was a regulatory review associated with this that was jurisdiction specific via a Packing customer request and jurisdiction form. This was managed by SOP [redacted] which detailed the country information tables and the local requirements, including version controls. Any onboarding of a new country for compassionate use post certification of a batch was considered via SOPs [redacted] They triggered the regulatory review for the new market and recertification if required of existing stock.

The QA batch review form documented the inspection of finished packs. The review did not evidence assessment of any relevant CAPA. It also did not consider variations or changes to the receipted IMP, in particular to products where the site was responsible for the final certification. For instance, if the comparator was under recall at time of certification or if variations had occurred to update the componentry or manufacturing steps.

<u>Componentry checks for artwork control in line with the MPS</u>

This was managed by work instruction [redacted] It was not evident in section [redacted] when and how the check occurred to confirm that the componentry of the receipted product had not changed or if it had how this would be notified and trigger an update of the MPS.

C8 Production

Ground floor production was adjacent to the warehouse and accessed via a change room in the warehouse area. The production receipt and assembly occurred on the ground floor. There was capacity for it to occur upstairs, but the production room was not typically used. Processes were manual and there was a "Production Information Record" in the room for each batch being assembled to aid the operators, which was a list of the component codes required for the job and images of what the labelled pack would look like on completion of the job. Next to the ground floor assembly room was the QA release review room, where the batches remained until certification was complete. Upstairs there was also a QC componentry check room and the print room. There were three [redacted] printers for smaller labels and a leaflet printer in the print room. It was discussed that only one batch would be printed in the room at a time. There were

processes in place for issuing reprints due to errors or additional requests from the production operators. Typically, a 5% overage was printed and all labels were 100% reconciled.

On the ground floor there was also a cold chain manufacturing room, which was not in use at the time of inspection. This was continuously monitored and maintained at 2-8C.

Sampling of the finished product was based on ISO standards and typically an inspection level 2 was conducted. However, the procedure did not clearly define when greater inspection would be required if at all. This was managed by SOP[redacted]

The process for line clearance was vague and did not detail any specific checks, particularly in the print room. The process for generation of retention samples and avoidance of mix up of the retention samples with the rest of the batch was unclear and not documented.

Incoming Components Sampling

This was managed by work instruction[redacted] There were details on how to inspect preprinted and blank components. However, it could not be evidenced that all the checks required per component were being carried out as there was no documented evidence of the checks conducted or required as exampled by checks for carton code[redacted] and booklet leaflet code [redacted] The procedure also did not clearly define under what circumstances non-conformance with the specification may be acceptable and in what circumstances there could be product quality or regulatory impact.

C9 Quality Control

All analysis was outsourced, either to the CMO or to contract laboratories. The following non-conformance reports were reviewed during the inspection:

[redacted] Unexpected observation reported by[redacted](Low total capsule mass when preparing samples for[redacted] Dissolution test). Raised on 22-Jul-2022, completed 21-Oct-2022. The results were upheld following extensive investigation. All manufactured product was recalled from market. Clinigen subsequently terminated the relationship with the relevant CMO due to discovering extensive issues during a for-cause audit.

C10 Outsourced Activities

Quality Technical Agreements were governed by procedure[redacted] version[redacted]

Vendor management was governed by procedure[redacted] version[redacted] Four statuses were applied for vendor management, approved, pending approval, unapproved and temporary. Vendors were required to be risk assessed during the approval process. This determined the requirements with regard to QTA, audits and questionnaires, as well as the re-assessment frequency.

Vendor auditing was governed by procedure[redacted]version[redacted] The procedure allowed for the completion of remote audits if onsite could not be performed and recommended audit frequency be reduced to mitigate this risk.

Vendor approval form[redacted] for[redacted] Assessed as acceptable to approve on basis of a questionnaire, although[redacted] were a GXP laboratory, they were only performing development work for Clinigen Healthcare Limited. Questionnaire completed by[redacted] on 15-Jul-2021.

Vendor Audit report for[redacted] was reviewed during the inspection. The audit was conducted remotely on 15-Feb-2022 and the report was approved on 15-Mar-2022. One major, one other and 2 recommendations were raised. The audit report recommended that the next audit be performed on-site. All observations were satisfactorily closed. Audit frequency was determined as 3 years.

QTA [redacted]

Quality Agreement between Clinigen Healthcare Limited and [redacted] dated 14-Mar-2023 for provision of QP services.

C11 Complaints and Product Recall

The Class 1 recall of [redacted] was reviewed. This was managed through [redacted] and [redacted] This recall was initiated after an adverse event was raised. Through investigation, it was found that the manufacturer of the [redacted] had been incorrectly taking an average weight of [redacted] when performing in-process sampling – therefore weight discrepancies of active ingredients within capsules were not identified prior to batch release. Batches [redacted] were released by Clingen and immediately were within scope of recall. It was later identified, through further investigation, that only the [redacted] and [redacted] dosages were impacted. The actions performed, through investigation and CAPA's, were to terminate the contract with the manufacturer [redacted] and a new CMO [redacted] were contracted to manufacture this same product. The on-boarding of [redacted] involved an on-site audit. The report from this audit was reviewed and contained specific attention to how in-process weight checks are performed. There is a shared QTA between Clinigen, [redacted] (testing facility), which specifically details that each party to share any OOS results.

Another non-conformance related to a potential product recall, was also reviewed. [redacted] was raised due to an [redacted] containing the incorrect dosage and contradicting the primary packaging label. Clinigen informed DMRC, but did not initiate a recall due to the company having full patient traceability. Full patient traceability was ensured via a product and product container check at a pharmacy level. Details of this were recorded on a checklist provided by [redacted] (manufacturer). The root cause was due to the supplier incorrectly filling [redacted] into the incorrect bottles/containers. The patient traceability process was managed by [redacted]

C12 Self Inspection

Self inspections were governed by procedure [redacted] version [redacted] The inspection plan was generated based on a calendar year (July to June). All QMS and GXP functions were required to be inspected at a minimum of once every 3 years. Inspection completion progress was tracked via an Internal Audit Log within excel. Inspection reports were required to be completed within 30 days of the inspection. Observations were rated on criticality as critical, major, other and comments/recommendations. The procedure allowed for the completion of virtual inspections, as well as in person. Internal auditors were required to have been trained in an IRCA accredited Pharmaceutical Quality Management System Lead Auditor course or equivalent, however, QP and RP roles were deemed to be appropriately trained through there QP and RP training. Internal audits were documented within form [redacted]. The self inspection schedule for Weybridge, Byfleet and Burton, covering 01-Jul-2023 to 30-Jun-2024 was reviewed.

The following self inspection was reviewed during the inspection:

[redacted] covering management review, complaints and recalls, completed between 25-Sep and 25-Oct 2023. 6 minor observations and 6 recommendations were raised.

C13 Distribution and shipment (including WDA activities if relevant)

Distribution and shipment records were reviewed during the inspection as part of importation and distribution of products.

Export

Export was not reviewed as a separate topic during the inspection and may be of interest at the next inspection.

Customer Approval

Customer Verification was governed by [redacted] effective 25 Dec 23. Hospital and Pharmacy establishments were required to be re-verified every 3 years. Wholesale dealers and customers holding other licences were required to be re-verified annually. Customer verification of [redacted] was reviewed without comment.

Introduction (Import for Export)

The company had not imported products from a third country and exported to a third country through 'introduction' since the last 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

Deficiencies were shared in two separate closing meetings and are presented below to indicate which deficiencies were presented on which date:

29/02/2024

1 CRITICAL

None

2 MAJOR

2.1 Pharmaceutical Quality System

2.2 A state of control had not been established and maintained by developing and using effective monitoring and control systems for process performance and product quality as evidenced by;

2.2.1 106 investigational PQS documents were overdue for review. 95% of open of non-conformances (18 out of 19) were overdue for review at the time of the inspection, some dating back from 2021, see further information below:

	number overdue	number open	%overdue
Non-conformance	18	19	95
CAPA	26	67	39
Change requests	54	175	31
Complaints	8	31	26

2.2.2 The impact and root cause analysis of overdue PQS documents had not been documented. It was discussed during the inspection that this had been raised during client audits, but CAPA/actions plans had not been raised.
2.2.3 The site quality review meeting minutes from January and February 2024 referenced overdue PQS documentation but did not identify opportunities for improvement to the quality system.
2.2.4 It could not be demonstrated that full product quality assessments had been conducted of returned stock, for example a batch of [redacted] had been returned on 29 Aug 2023, the description of why the product was returned was limited to "courier returned", no other information was provided and an investigation had not been conducted. It was described that there was no tracker for the investigation of ongoing returns.
2.2.5 There was no trending of investigations such root causes or a formal continual improvement programme as a result of process / product monitoring to identify preventative actions to avoid potential deviations occurring in the future

Reference: EU GMP 1.4(ix), 1.4(viii), 1.4(xi), 1.6
EU GDP 6.3

2.3 Importation Operations

2.3.1 Import of Unlicenced Medicines
2.3.1.1 The company had not taken all reasonable precaution and exercised all due diligence to ensure the safety, quality or efficacy of the medicinal product imported from the third country as evidenced by;
2.3.1.1.1 There was no requirement to ensure suitable GMP compliance of the manufacturer of the imported product. For example, there was no requirement perform an audit of the manufacturing site or obtain Competent Authority inspection reports to ensure products were manufactured to an appropriate level of GMP.
2.3.1.1.2 The QC review and release process was limited to review of transit temperature data. There was no requirement for review of batch release certificates or confirmation of compliance against relevant pharmacopeial monograph requirements.
2.3.1.1.3 There was no procedural process describing the checks required for QC review and release of unlicenced medicine imported from a 3rd country.
2.3.1.1.4 QC review and release of imported unlicenced medicines was not documented formally within the PQS.
2.3.1.2 Controls were not in place to ensure the suspension of import or supply when a Marketing Authorisation of a product had been granted but it had not yet been confirmed as to whether the product had been launched.
2.3.1.3 The procedure for [redacted] did not describe controls to ensure the hierarchy for the use of unlicensed medicines were met.
2.3.2 Import of [redacted] was deficient as evidenced by:
2.3.2.1 The Importer of Record was documented as [redacted] rather than Clinigen Healthcare Limited
2.3.2.2 Investigations had not been completed to a sufficient level to support certification. Fro example, temperature excursion record [redacted] had not been fully completed before release of the product. Required details regarding supplier, and temperature excursion ranges and time periods were not documented.

2.3.2.3 The quality technical agreement with [redacted] and Clinigen Healthcare Ltd [redacted] did not specify responsibilities all steps for outsourced activities such as inbound transport requirements.
2.3.3 Importation of Investigational Medicinal Products and the QP oversight process
2.3.4 Suitable arrangements had not been made to ensure requirements set out in the approved Clinical Trial Application (CTA) for [redacted] were adhered to. For example, there was no documented evidence to support that the shipping address of the clinical trial unit site at [redacted] had suitable ethics approval.

Reference: EU GMP C1.4(iv), C4.4, C4.8, C7.15, A13.40, A13.43, A16.1.7.16, A19.2.2
The supply of unlicensed medicinal products 'specials', MHRA guidance note 14.
https://www.gov.uk/government/publications/supply-unlicensed-medicinal-products-specials
HMR 2012 17 (1a)

3 OTHERS

3.1 Warehouse Operations

3.1.1 Processes to prevent falsified and counterfeit medicines entering the legal supply chain were deficient as checks of Italian and Greek FMD devices were not subject to security checks via UV lamp exposure.
3.1.2 Freezer [redacted] had not been maintained to minimise hazards to the quality of products, as it had significant levels of frost inside the freezer.
3.1.3 The sampling plan of printed componentry did not consider production methods to ensure that representative samples would be taken of the entire printing run, or consideration of different printing heads used during production.
3.1.4 It could not be demonstrated that initial checks on incoming materials were subject to contemporaneous quality checks.

Reference: EU GDP 3.3, 4.2, 5.4
EU GMP A8.5

4 COMMENTS

4.1 None

05/03/2024

1 CRITICAL

None

2 MAJOR

2.1 **Documentation Management was deficient in that:**

2.1.1 <u>It could not be evidenced records were made or completed at the time each action was taken and in such a way that all significant activities concerning the manufacture of medicinal products were traceable. This was exampled by:</u>
2.1.1.1 No documented assessment of incoming finished products for assuring the printed artwork was at the correct version vs that of the incoming licensed pack, such as for leaflets.
2.1.1.2 Incoming componentry QC sampling checks were not detailed, such as checks for carton code [redacted] and booklet leaflet code [redacted]

2.1.2 Procedures were not always clearly defined and therefore it could not be evidenced that they were effectively adhered to. For example:

2.1.2.1 There was a lack of instruction on how line clearance checks should be performed, particularly in the print room.

2.1.2.2 The process for generation of the retention sample was not formally defined, including controls to avoid mix up of the retention sample with the batch.

2.1.2.3 Batch review processes did not consider the review of any open CAPA for impact to the batch being certified.

2.1.2.4 Batch review processes did not consider Regulatory Variation or changes to receipted material (particularly IMP stock) that could have occurred post receipt but prior to final certification and the impact of those to the final stock.

2.1.2.5 The work instruction [redacted] associated with QC sampling did not consider where there could be regulatory impact of a component's failure against acceptance criteria.

Reference EU GMP: C4.1, C4.8

3 OTHERS

3.1 Retention samples were not representative of the finished product supplied to customers or market.

Reference EU GMP: A19.8.1

4 COMMENTS

None

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

Closing meetings were held on 29/02/24 & 05/03/24 and the deficiencies were verbally accepted.

F2 Assessment of response(s) to inspection report

Insp GMP/GDP/IMP 8733/93802-0021 (27/02/24-29/02/24):Responses were received on 17 April 2024, an RFI was sent on 02 May 2024.
A secondary response was received on 10 May 2024 and was accepted.

Insp GMP/GDP/IMP 31644/362376-0012 (05/03/24):
Responses were received on 11 April 2024 and were accepted.

F3 Documents or Samples taken

None taken

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: 01/07/2024**

Lead Inspector: [redacted] **Date: 02/07/2024**

Accompanying Inspector: [redacted] **Date: 01/07/2024**

Accompanying Inspector: [redacted] **Date: 01/07/2024**

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	3	Last inspection:	1
Other deficiencies this inspection:	2	Last Inspection:	6

(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.		

([redacted] ssessment 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

[redacted]

(h). Conclusions

[redacted]

(i). Expert/ Operations Manager / Compliance Management Team (CMT) Comments

[redacted]

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

[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