Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Chemilines Limited
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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Triggered inpsection

Licence or Reference Number: MIA / WDA (H) 8746 / MIA 19488
Licence Holder/Applicant: Chemilines Ltd & S&M Medical Ltd
ch
Details of Product(s)/ Clinical trials/Studies: Parallel import of ophthalmic, inhalation, parenteral, topical and suppository dosage forms

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	N
Laboratory Testing	N
Batch Certification and Batch Release	Y
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: *Wholesaler*	Y

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

Site Contact: [redacted]

Date(s) of Inspection: 14th – 16th May 2024 (2 days)

Lead Inspector: [redacted]

Accompanying Inspector(s):

Case Folder References: Insp GMP/GDP 8747/18194-0024 Chemilines Ltd
Insp GMP 19488/18194-0023 S and M Medical Ltd

Section B General Introduction

B1 Background information

Chemilines Limited acted as a parallel importer whereby they over-label and/or repack parallel imported medicinal products. The company was established in 1985. The company also acted as a wholesaler and had 1.1, 1.2, and 1.4 selected on their WDA, in addition to export activities. There were no procedures in place for the management of unlicenced medicines (1.2) or export. Chemilines provided a service to [redacted] who were also a PLPI authorisation holder. The latter was a virtual operator.

Previous Inspection Date(s): 27th- 28th July 2021

Previous Inspectors: [redacted]

B2 Inspected Areas

PQS: Management review, change management, risk management, Deviations and CAPA, Reference Master File, PQR, Licence Review

Personnel, Premises and Equipment, Documentation, Production, QC Outsourced activities, Complaints, Recall, Self Inspection, Wholesale

Limitations / exclusions to inspected areas

Customer qualification

Document control was not reviewed in detail

B3 Key Personnel met/contacted during the inspection

Name	Initials	Position
[redacted]		

B4 Documents submitted prior to the inspection

Document	Version /Date of document	Reflected activities on site?
Site Master File	[redacted]	Y
Compliance Report	02 May 2024	Y
Comments: None		

Section C Inspector's Findings

C1 Summary of significant changes

Detailed changes are recorded in the pre-inspection compliance reports held in the case folder.

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

None

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

Personnel changes on licences (Production Manager)

C2 Action taken since the last inspection

Actions from the last inspection were not reviewed in detail during the inspection, it was described that there were no overdue actions to the inspectors.

C3 Starting Materials

N/A

C4 Pharmaceutical Quality System

It was discussed that the PQS was shared between Chemilines and [redacted] However, some procedures were scoped to only apply to Chemilines and it could not be evidenced that the full PQS applied to [redacted] and therefore that the organisation had procedures for all activities.

Management Review

This was managed by [redacted] It did not cover a formal criteria for an agenda. There was no procedure for the [redacted] The Q4 2023 and Q1 2024 reviews were inspected. See section D for deficiency details.

Change Management (including risk assessment)

This was managed by procedures [redacted] respectively. Each change required an initial risk assessment to aid determination of its classification as minor, major or critical. This involved calculating a score for severity and probability of occurrence. It was discussed that the criteria for probability of occurrence was determined based on data already available within the PQS, e.g. number of new product introductions, number of manufacturer changes. However, the procedure did not define this and allowed for subjectivity in how the score for probability would be determined. There was also a section on detectability which was not applied to change control risk assessments and there was no rationale for this.

Change management was a manual process and had an associated annual change log that issued a change number, sequentially to every new change generated.

The change procedure did not detail what actions to take in the event of a change cancellation. Nor was it clear how “implemented successfully?” was assessed as a criteria vs “evaluation of effectiveness.”

The following change controls were reviewed:

[redacted] this was a minor change but listed as major on the change log. There was no rationale for this discrepancy.

[redacted] this was a componentry update due to change in manufacturer. It could not be evidenced that all actions had been considered, including those in line with [redacted]

(Generation of MBR) section 7.8, which required superseding of componentry and email generation for new BPR communication. It could not be evidenced that these actions were conducted. Nor could it be evidenced that it was considered if the superseded master sample pack was removed from the area.

[redacted] This was raised to generate SOPs around temperature mapping and equipment qualification. However, the changes were limited in scope and did not consider if mapping or qualification activities had been conducted or if any reevaluation was required if conducted.

Deviation and CAPA (including risk management)

Deviations were governed by [redacted] was managed by [redacted]

Risk assessments were conducted for all deviations, however the approach differed to that of a risk assessment associated with change in that detectability of an issue would be considered in the final risk score.

It could not be evidenced that repeat occurrences of deviations would be considered when conducting a risk assessment nor did the procedure require this.

The CAPA effectiveness would be conducted five days after CAPA implementation. This approach had been implemented in 2024.

The following deviations were reviewed:

[redacted] Mixed batch- root cause was process not followed. The investigation did not consider if the process needed further improvement, if other products supplied by this supplier was impacted, if other products without FMD labelling would be impacted.

[redacted] Braille label incorrect dimensions. This appeared to be adequately investigated.

[redacted] Missing braille label. The investigation did not consider the print room and no CAPA were identified.

[redacted] FMD sample label in BPR not included. This investigation did not consider appropriate CAPA for the root cause “instructions not followed.”

Reference Master File

Management of the reference master file was sub-contracted to [redacted]. Updates to printwork were managed via call-in lists, and review and comparison of issue dates of foreign patient information leaflets against the granted English leaflet. Where discrepancies were identified, the foreign leaflet was translated via Google and sections 5 – 6 compared for changes against the previous version of the current granted MHRA English leaflet. “In pack date lists” were maintained by [redacted] and emailed every month to QA and RA. Regulatory details were maintained on the “RA report summary” (excel spreadsheet) by [redacted] of the reference master file for [redacted] was reviewed without comment.

BPRs were generated on [redacted] and version controlled by [redacted] under various procedures:

Preparation of Master Batch Packaging Record [redacted] effective 17/08/2023

Batch Packaging Record Generation [redacted] effective 24/04/2024

Patient Information Leaflet and Design Approval Design and approval [redacted] 24/04/2024

PQR

There was no formal approach for PQR generation and no associated procedure. The company had not generated PQRs to date.

Licence Review

Licences for both Chemilines Ltd (MIA 8747 vs 36) [redacted] were reviewed and discrepancies identified. The licences did not authorise non-sterile and sterile batch certification. There were discrepancies on WDA(H) 8747 vs 9 sections 1.2 (relating to unlicenced medicines), 2.4 (export) and 3 (relating to biological products). The company agreed to submit a variation to correct the MIAs and WDA(H).

C5 Personnel

Warehouse and production personnel appeared to have good knowledge of the processes they were operating. Training records for the Goods In work instruction [redacted] was reviewed without comment. The training record for the QP was reviewed, however there was no documented evidence of ongoing CPD training.

C6 Premises and Equipment

Warehouse

The company had a large warehouse that was temperature controlled and monitored with heating and cooling which was controlled via the company's ERP system, [redacted] Temperature excursions generated an alarm and a text message to be sent to the CFO. Medicinal products were received through a loading area where materials underwent initial incoming checks. It was described that these checks were conducted against information contained on the invoice, purchase order and packing list sent from the supplier. It was described that these checks were documented on a checklist and the RPi checklist, however these were not readily available in the warehouse, nor was the Goods In SOP. An uncontrolled version of the Goods In work instruction was provided to the inspector upon request. Goods were scanned for FMD and decommissioned where required. FMD checks on [redacted] stock did not extend to the use of UV and were limited to checks on websites. Cold chain products were required to be checked immediately and had a 1-hour time limit outside of the cold chain storage. Incoming pallets containing mix batches were physically separated before booking into [redacted]. Pick lists were generated by First Expiry First Out (FEFO) or in accordance with customer requirements. It was noted that a large proportion of pallets used in the warehouse were damaged and splintered.

Storage locations and disposition of medicinal products were managed via the company's ERP system, [redacted] The warehouse had segregated locations for quarantined, released and rejected storage. The controlled drug storage area was a secure area with access to 5 people. The company were licenced to procure and supply schedules 2 – 8 products. It was described there was a procedural requirement to conduct stock checks every quarter, but this was only occurring once a year. The warehouse had segregated locations for returned stock and 'damaged by saleable stock'. Three boxes of [redacted] had significant damage to the outer packaging, including tears, and broken tamper evident seals but had a released disposition. There was no documented justification for the released disposition for these packs. Review of batch documentation showed that a member of the sales team dictated the disposition of the batch. Warehouse operatives were able to change the disposition status on [redacted] Other examples of packs with significant damaged outer cartons were also observed in this area. This contributed to a major deficiency for warehouse operations. At the time of the inspection, there were two batches of returned product which had

been received back to the company in April 2024 and were awaiting RP disposition following investigation. There was provision for cold storage at 2 ºC – 8 ºC which was a room with segregated areas for quarantined and released stock. A deficiency was raised as printed componentry containing variable data was stored on racks in plastic storage boxes and not in a secure location.

Temperature mapping

Temperature mapping of storage areas was performed every 3 years unless there is a physical change to the layout of the warehouse. The previous mapping exercise was reviewed and deficiencies noted:

Warehouse 28 July 2022 – 4 August 2022 (summer) – reviewed without comment.

Warehouse 15 -22 March 2022 (winter) – the mapping exercised was not considered to be fully representative of winter conditions with outside temperature being recorded between 2 ºC – 16 ºC.

Cold room 28th July – 4 August 2022 - failure at position 18 with a maximum temperature of 8.96 ºC for 2hr 21 mins 50 s was not investigated or risk assessed (specification 2 ºC – 8 ºC).

Calibration certificates for [redacted] (15th December 2022) – reviewed without comment

Production

There were [redacted] production rooms, and a sperate printing area which had [redacted] label printers including one braille printer / embosser equipment that was located on the mezzanine of the warehouse. Labels and leaflets were printed from an approved computer file and the batch number and expiry date inserted. The production rooms were unclassified but were temperature controlled. There were some equipment for label printing, but the majority of processes were manual. It was noted that there were a few broken ceiling tiles in the production area. There were [redacted] production rooms used for cold chain packaging which was air conditioned.

Equipment Qualification

The validation master plan or any other document did not consider qualification status of equipment and not all equipment could be evidenced to be qualified, including label printers and the braille printer.

The leaflet folder qualification completed in 2021 was reviewed. It did not adequately evidence if leaflets of different sizes were required to be considered as part of the test criteria or if they were used during testing. It also did not include an assessment of the impact to product or the equipment for not qualifying all fold types, only double parallel. The process risks associated with this were also not considered.

C7 Documentation

The site operated a paper based documentation system. A deficiency for management of documentation was raised. Multiple SOPs reviewed did not contain sufficient detail, examples of uncontrolled documents was observed during the inspection in the warehouse and in production areas, relevant SOPs and work instructions were not readily available in various production and warehouse areas of the company e.g. line clearance SOPs, use of balance SOPs, goods in work instructions. An uncontrolled version of the goods in SOP was provided to the inspector in the warehouse when requested. **The generation and control of documentation was not reviewed in detail during the inspection and may be of interest at the next inspection.**

C8 Production

The process for printing of packaging overlabels was governed by [redacted] (effective 30/10/2018). It was noted that the SOP was due for review 29/10/2021 did not contain explicit detail on how to conduct a line clearance. Labels and leaflets were printed from an approved, locked computer file supplied by regulatory and the batch number and expiry date inserted. All leaflets were printed on A3 sized paper and then cut to a size determined by the operator. There was no process in place to ensure that the dimensions of patient leaflets were those described in the licence. Product labels were printed on separate work stations, however line clearance operations were not fully described in an SOP, nor documented in the form of a check-list. Multiple products that were subject to the generation of printed labels were bought into the printing line areas increasing the risk of product mix-ups. All printed componentry were subject to QC checks before issuance to the production areas. These checks included quality of printing, and comparison of dates from the foreign supplied leaflet compared with those from the granted English leaflet. Discrepancies were referred to the Regulatory team for review.

The majority of packaging and overlabelling activities were manual. There were some automatic labelling activities on packs. Reference / guide samples were generated for each manufacturing operation by the supervisor. Product label guides were also used and were issued within the BPR. A deficiency was raised for processes relating to line clearance due to inadequate completion of line clearance documentation and observation of a batch of [redacted] being taken into production room 06 before all components of the previous batch, [redacted] had been removed. Packaging and labelling of cold chain products were conducted in air-conditioned rooms with a maximum time limit of the product allowed outside of controlled temperature conditions being 1 hour. In process checks were conducted every hour where a random sample was taken and compared against the reference sample. It was described that a retain sample was taken from within the batch, at random by QA/RA. It was described that balances were use for weighing of controlled products to ensure full reconciliation and confirmation of the correct number of tablets in each pack, there were no SOPs in place for the use of these balances. Cleaning logs for rooms 07 and 09 had not been completed at the time of the inspection.

Batch release was governed by [redacted] effective 15/04/2024. Batches were reviewed by QA before review by the QP. QP certification was documented on a checklist. There was provision for QP remote certification via scans and photographs of the QP batches.

C9 Quality Control

Reception, sampling, testing and releasing of printed materials was governed by [redacted] (effective 22/07/2021), the SOP referenced a sampling plan based on √N+1 rather than a statistical sampling plan. 'Tail gate' samples were sent from the supplier which were printed with the relevant print head station. Sampling and testing of printed cartons for [redacted] were reviewed without comment. Retain samples of incoming materials were taken by the company.

C10 Outsourced Activities

There was no technical agreement in place between [redacted] and Chemilines yet the latter was providing a service to the former, including repackaging and supply to customers. Nor was there a TA with the [redacted] organisation providing regulatory services.

The self inspection for [redacted] conducted in Dec 2023 was reviewed. It was discussed that this was an external service provider and the use of remote only assessments had not been adequately risk assessed. The scope of the audit was not clear and it could not be evidenced that all activities conducted by [redacted] were audited, including a review of [redacted] There was an associated action plan for deficiencies raised and it was discussed the extended timelines for action completion, e.g. Jul 2024, were not appropriate for all actions identified.

There was no risk assessment for the impact to operating with the deficient process until Jul 2024.

There was no evidence of transport provider audit schedules and it could not be evidenced all service providers were adequately assessed for audit. The 2021 [redacted] was reviewed) and it did not adequately consider all elements, such as storage and control of transport routes.

The [redacted] (related to packaging material audits) was reviewed and the defined process allowed the opportunity for only remote audits to occur of non-printed componentry provider. This was based on provider criticality. The 2024 schedule did not demonstrate which audits were remote and which were onsite. Audits were required every three years. On initial onboarding, a questionnaire was conducted.

The company used five artwork suppliers for printed componentry. The following supplier qualification documentation was reviewed:

Audit report for [redacted] (6 April 2022) – the audit report made no reference or acceptance of the sampling processes employed at the supplier.

Technical agreement between [redacted] and Chemilines effective 19/04/22. A deficiency was raised as there was no mention of sampling requirements.

Customer Qualification

Customer Qualification was not reviewed during the inspection and may be of interest at the next inspection. It was described that all customers were UK based.

C11 Complaints and Product Recall

Complaints

Customer complaints were managed by [redacted] The procedure did not clearly define how to assess for reoccurrence or to assess if any previous deviations could have been a contributing factor to the complaint.

The following complaints were reviewed:

[redacted] to open. The complaint was raised 05/03/2023 and was not investigated until April 2024, with the investigation completed in May 2024. The complaint was closed on 02/05/2024 without any further attempt to receive information from the distributor who was also contacted on 02/05/2024. This was not in line with procedure, which required complaints to be kept open for 4 weeks post communication with third parties.

Recall

The Dec 2023 mock recall was reviewed and it mimicked the circumstances of a class recall. Chemilines evidenced they could conduct their relevant actions within 48 hours. However the system did not challenge out of hours or recall within 24 hours, including class 1 recall.

Recall was managed by [redacted] It did not detail how to assess if the original product was under recall. The 2023 agreement with [redacted] was reviewed. This included a section on national recall and recall information sharing. However, the agreement had both a three year expiry date and “no expiration” documented. The two statements were in conflict.

C12 Self Inspection

This was managed by [redacted] The 2023 and 2024 schedules were reviewed. All inspections were up to date. However, it was discussed that scope of each inspection would

need to be clearly defined. A specific self inspection was not reviewed as it was discussed it would be in the same format and follow the same approach as that of the self inspection of Titanium, see C10.

C13 Distribution and shipment (including WDA activities if relevant)

Distribution and Shipment

Customer orders were managed by work instruction [redacted] There was a process for how controlled drugs would be reviewed for monitoring of unusual transaction. This included maximum monthly quantities that would be supplied to customers prior to assessment. There was a monthly review of these orders and the April 2024 review was inspected. It was completed via [redacted] and it was discussed with the company there was no evidence that the CFO had documented his review approval.

The maximum order numbers were based on NHS data for supply within England.

It was discussed there was limited criteria for how non controlled drugs would be investigated for monitoring unusual transactions. This included the Oct 2023 transaction of [redacted] for which it could not be evidenced that [redacted] as was stated by the customer. This statement was the basis for accepting the large volume order.

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

PLPI assessor [redacted] attended the inspection and conducted an independent review of marketing authorisations.

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

1 **CRITICAL**

None

2 **MAJOR**

2.1 **The Pharmaceutical Quality System was deficient in that:**

2.1.1 It could not be evidenced that the company maintained the required conditions for their manufacturing and wholesale licences, in that, wholesale dealing of unlicenced medicines and export were authorised for which the company did not have the have associated controls in the PQS.

2.1.2 Management review did not identify opportunities for continual improvement of products, processes and the system itself, as demonstrated by the Q4 2023 and Q1 2024 reviews. For instance, not all key performance indicators were identified, not all trends were identified, there was no formally defined agenda, the consideration to review resource capacity or upcoming regulatory changes and actions were not robustly tracked.

2.1.3 The company did not conduct product quality reviews for verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials

and finished product to highlight any trends and to identify product and process improvements.

2.1.4 It could not be evidenced all manufacturing processes were clearly defined within associated procedures as it could not be demonstrated procedures were in place for operations to be carried out on behalf of [redacted]

2.1.5 It could not be demonstrated effective prospective evaluation took place of all changes implemented, including the approach for risk assessment, which did not consider detectability factors as part of risks associated with a change.

2.1.6 The evaluation of changes did not evidence that all actions would be identified and actioned, including those defined in procedures. For example:

2.1.6.1 [redacted] did not identify if any mapping or equipment qualification required revaluation.

2.1.6.2 [redacted] did not evidence consideration of multiple actions, including superseding of componentry and email generation for new BPR communication which were required by [redacted]

2.1.7 It could not be evidenced that an appropriate level of root cause analysis was conducted for investigations and that appropriate CAPA were identified, as exampled by [redacted]

EU GMP: Human Medicines Regulation 2012, Part 3, Chapter 2 (36) & (42), 1.4 (xii), 1.4 (xiv), 1.6, 1.8(i), 1.10

2.2 **Warehouse operations were deficient as evidenced by;**

2.2.1 The wholesale distributor had not ensured the identity and integrity of the medicinal product minimising the risk of falsified medicinal products entering the legal supply chain for example:

2.2.1.1 Three boxes of [redacted] that had significant damaged packaging, including broken tamper evident seals were available for sale and had a 'released' disposition on the [redacted] The decision to change the disposition of the three boxes of product had been taken by a member of the sales team and the disposition changed within [redacted] by a warehouse operative.

2.2.2 Processes for receipt of medicinal products were deficient as evidenced by: (GDP 5.4)

2.2.2.1 There was no documented evidence of checks performed on incoming medicinal products in accordance with the requirements stated in the required work instruction [redacted] It was acknowledged that the a Goods In checklist had recently been updated, however these documents were not being used during the inspection.

2.2.2.2 There was no documented instructions on how to check [redacted] safety features beyond checking relevant Competent Authority websites. There was no requirement for the use of UV devices during verification.

2.2.3 The 2022 temperature mapping exercises in the cold store and warehouse were deficient as evidenced by:

2.2.3.1 The 2022 summer temperature mapping for the cold storage area failed specification of 2°C - 8°C at position 18, with a maximum recorded temperature of 8.96°C for a period of 2:21 hours. This failure was not investigated and there was no consideration on product risk, location of permanent temperature probes, or ongoing product storage locations.

2.2.3.2 The 2022 mapping exercise had not been conducted in accordance with a documented risk assessment.

2.2.3.3 The 2022 winter mapping of the warehouse had not been conducted under representative conditions. The mapping exercise had been conducted in March where temperatures ranged from 2 – 16°C.

2.2.4 Printed componentry were not adequately stored in secure conditions such as to exclude unauthorised access. For example, boxes of issued printed componentry which included variable data were stored in unsecure boxes within the main warehouse.

2.2.5 All equipment impacting on storage and distribution of medicinal prodducts were not maintained to a standard which suited its intended purpose. For example, wooden pallets in use in the warehouse were splintered and in poor condition.

Reference: EU GMP C5.46

EU GDP 3.2.1, 3.3, Chapter 5 Principle, 5.4

2.3 **Outsourced Activities were deficient in that:**

2.3.1 Written contracts had not been written covering all outsourced activities, including for services between [redacted] and Chemilines Ltd, or, for services from [redacted] regulatory group based in India.

2.3.2 It could not be demonstrated that the performance of [redacted] had been adequately assessed, including audit scope, the lack of on-site audits, the lengthy implementation time for actions associated with deficiencies, and the frequency of audits.

2.3.3 Audit scheduling did not allow for adequate monitoring of suppliers, including the fact the 2024 schedule of printed packaging providers did not consider if the previous audit was remote or on site, and schedules were not in place for all service providers.

2.3.4 The system for componentry audits allowed for only remote audits to take place and this was not adequately controlled, or risk assessed.

2.3.5 There was no evidence of audit for [redacted] yet they were a transport provider for multiple years.

2.3.6 The 2021 TA with Arra Transport did not define all responsibilities, including maximum time allowable for handling of products in transit, e.g. if storage by [redacted] was acceptable.

2.3.7 The 2022 TA with [redacted] did not define responsibilities and requirements for sampling.

2.3.8 The 2022 audit report with [redacted] did not define sampling requirements or sampling plans.

Reference: EU GMP C7.1, C7.7, C7.14

3 **OTHERS**

3.1 **Documentation was deficient in that:**

3.1.1 Procedures within the QMS were often ambiguous in information or lacked information, for example but not limited to:

3.1.1.1 The recall procedure, which did not detail how to assess for recalls in Europe.

3.1.1.2 The change procedure, which did not detail what actions to take in the event of a change cancellation. Nor was it clear how “implemented successfully?” was assessed as a criteria vs “evaluation of effectiveness.”

3.1.1.3 The complaints procedure, which did not clearly define how to assess for reoccurrence or to assess if any previous deviations could have been a contributing factor to the complaint.

3.1.1.4 The deviation procedure, which did not detail how to assess for repeat occurrences.

3.1.1.5 The batch release procedure, which did not detail what images needed to be taken for evidence of the retain / QP packs for remote batch certification.

3.1.1.6 The printing and packaging overlabels procedure, which did not detail how to conduct line clearance.

3.1.2 Documents were not designed, prepared, reviewed, and distributed with care, for example:

3.1.2.1 There was no documented procedure for the use of balances in the production area.

3.1.2.2 There was no process or documented procedure for the management of transport risk assessments and none were in place, including for product supplied by [redacted]

3.1.2.3 There was no process or documented procedure describing the requirements for user access controls or the addition of new users for the [redacted]

3.1.2.4 The goods in work instruction could not be easily located during the inspection. An uncontrolled version was printed upon request from the inspector.

3.1.2.5 There was no copy of the procedure for printing and packaging overlabels within the printing area.

3.1.2.6 The procedure for printing of packaging overlabels [redacted] was overdue for review (due 29/10/2021).

3.1.3 Uncontrolled paper was in use for the attachment of broken labels as part of reconciliation during packaging processes.

3.1.4 It could not be demonstrated that reproduction of information would be captured accurately as exampled by the change log vs change control [redacted] which had two different classifications (minor and major).

Reference: EU GMP 1.8(iii), 4.1, 4.2, 4.3

3.2 **Production and Packaging operations were deficient in that:**

3.2.1 There was no clearly defined procedure to ensure that dimensions of patient information leaflets complied with the relevant marketing authorisation.

3.2.2 The risk of mix-ups or substitutions during printing operations were not minimised as evidenced by;

3.2.2.1 Multiple printing jobs of different products were stacked into one box for printing and bought within the printing line.

3.2.2.2 Line-clearance of printing operations were not performed in accordance with an appropriate checklist.

3.2.2.3 It was observed during the inspection that a batch of Oestrogel was taken into production room 06 before all materials for packaging of [redacted] had been removed. The line clearance check for the Oestrogel BPR had not been completed.

3.2.3 Cleaning logs for Rooms 07 and 09 had not been completed.

Reference: EU GMP C3.2, Chapter 5 Principle, C5.49, C5.50

3.3 **Equipment Qualification was deficient in that:**

3.3.1 Not all equipment qualification and validation activities were planned and did not demonstrate that the lifecycle of equipment was taken into consideration. For example, there was no schedule for when equipment would be required to be requalified and not all equipment could be demonstrated as being qualified, including the braille printer.

3.3.2 Testing of the leaflet folder equipment did not demonstrate equipment operated as designed, for instance:

3.3.2.1 The equipment had capacity to conduct multiple different folds, however, they were not tested, nor controls implemented to stop users from selecting a different fold on the equipment.

3.3.2.2 Test criteria did not consider the need to fold different leaflet sizes.

Reference: EU GMP A15.1, A15.3.11(i)

3.4 **Complaints and Recall were deficient in that:**

3.4.1 It could not be evidenced Quality defects would be reported in a timely manner by the manufacturer to the marketing authorization holder as exampled by [redacted] which was initiated in May 2023 and not communicated further until May 2024. The product or patient impact had not been considered in the interim. Nor was the system failure (impact on delay of investigation) considered.

3.4.2 The arrangements for recall could not be evidenced to be fit for function as the 2023 mock recall did not consider out of hours recall or the worst case scenario of a class 1 recall.

Reference: EU GMP: 8.15, 8.30

3.5 **Sampling was deficient in that:**

3.5.1 The number of samples taken for packaging materials was not determined from a statistical sampling plan. The sampling plan was determined from √n+1.

Reference: EU GMP A8.5

3.6 **The QP demonstrated a lack of knowledge and continuous training in processes associated with GMP as exampled by:**

3.6.1 The authorisation of a [redacted] transaction in Oct 2023 without evidence the large quantity ordered by the customer was legitimate.

3.6.2 The implementation of a non-robust strategy for assessing CAPA effectiveness.

3.6.3 The lack of understanding for the requirements of PQR and transport risk assessments.

Reference: EU GMP C1.5, Chapter 2 Principle, A16.1.2

4 **COMMENTS**

None

Section E Site Oversight Mechanism

Site referred or to be monitored by:	Tick (✓)	Referral	Summary of basis for action

		date	
Risk Based Inspection Programme	✓	[redacted]	[redacted]
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

A closing meeting was held and the deficiencies were verbally accepted.

F2 Assessment of response(s) to inspection report

An acceptable response was received on 15/07/2024 following one RFI.

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: 27th August 2024**

Accompanying Inspector: [redacted] **Date: 03rd September 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:	3
Other deficiencies this inspection:	6	Last Inspection:	3

(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		
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)

✓	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

None

(e). Risk Rating Result Incorporating Discriminatory factors (✓ applicable box)

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (✓)
0	Immediate (as soon as practicable)	
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

N/A

(g). GMP or GDP certificate conditioning remarks required as a result of risk-based decisions noted in section (f) above

GMP Certificate: *None* ***GDP Certificate:*** *None*

(h). Conclusions

Inspectors comments on risk rating: None

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

Expert / Operations Manager / CMT (delete as appropriate) **Risk Rating:N/A** **Comments: N/A** Name: Date:

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

Risk Rating:	Next Inspection target date:
III	**May 2026**

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