



INSPECTION REPORT

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Section A Inspection Report Summary

Inspection requested by: MHRA

Scope of Inspection: Routine Re-Inspection

Licence or Reference Number: MIA 14023, MIA (IMP) 14023

Licence Holder/Applicant: Catalent UK Swindon Zydis

Details of Product(s)/ Clinical trials/Studies: Non sterile 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	Y
Packaging – Primary	Y
Packaging - Secondary	N
Importing	N
Laboratory Testing	Y
Batch Certification and Batch Release	N
Sterilisation of excipient, active substance or medicinal product	N
Broker	N
Other: lyophilised tablets, IMP activities	Y

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

Site Contact: [REDACTED]

Date(s) of Inspection: 13th – 15th June 2023

Lead Inspector: [REDACTED]

Accompanying Inspector(s): [REDACTED]

Case Folder References: Insp GMP 14023/4574-0022

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Section B General Introduction

B1 Background information

The company specialise in the manufacture of [REDACTED] [REDACTED] and is part of Catalent Pharma Solutions (CPS) organisation, which is headquartered in NJ, USA. The site acts as a contract manufacturer and [REDACTED] licence for [REDACTED]. The site also had clinical and development production facilities and laboratories. There was no secondary packaging on site, all secondary packaging was provided by customer / sponsor, all packs were sent to the customer / sponsor in the primary packaging.

Previous Inspection Date(s): 17th – 20th February 2020 (3 days)

Previous Inspectors: [REDACTED]

B2 Inspected Areas

PQS: Product Quality Review, deviations, Quality Management review
Premises and equipment: storage areas, sampling, purified water systems, equipment review
Documentation: batch certification and release
Data Integrity
Production: commercial and clinical tours, dispensing, mixing, form fill, lyophilisation, digital print suite
Calibration and planned preventative maintenance.
Quality control: QC laboratory tour, microbiology tour, validation and qualification
Stability Management
Complaints
Product recall
Self-inspection
Training

Limitations / exclusions to inspected areas

Pest control
Distribution and shipment
Starting Materials: supply chain maps, TSE, excipient and nitrosamine risk assessments

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]
[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] dated 2/5/2023	Y
Compliance Report	05 June 2023	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. Line [REDACTED] was introduced since the last inspection.

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:

The company were introducing a [REDACTED]

C2 Action taken since the last inspection

Actions from the previous inspection had been completed.

C3 Starting Materials

General

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Starting materials were not reviewed during the inspection.

Compliance with TSE Guidelines

TSE compliance was not reviewed during the inspection.

API Compliance

It was described that most APIs were supplied to Catalent by the client, where this did not happen Catalent would employ their own Supplier Assurance processes. The supply of [REDACTED] API was reviewed see Section C10.

C4 Pharmaceutical Quality System

The site operated under a global PQS with corporate and site SOPs sitting underneath global policies.

Annual Product Quality Review

Annual product reviews (APRs) were governed by SOP [REDACTED] which required APRs to be reported within 3 months from the end of the review period. The review period was typically set annually or defined by the customer. The 2021 - 2022 APR for [REDACTED] was reviewed. The report highlighted an issue with yields data sets being below the lower control limit, a note was raised to review this in the next continuous process validation report [REDACTED] however, this was not captured in the draft report or CAPA which was due in November 2023. Reviews of technical agreements / statements were limited to a review of the review dates and did not assess the accuracy of the agreement. Data generated for critical process parameters (CPPs), for mixing: pre-mix hot temperature, dosing min and max temperature, dosing max and suspension hold times regularly exceeded lower control limits LCL and UCLs without action or investigation. Process capabilities were reviewed and cpk values calculated, however, cpk values of [REDACTED] for maximum suspension time were accepted without justification or investigation. It was discussed that APRs were not routinely performed for IMP products and there was no process defined for review of clinical data even for long campaigns where multiple batches may be manufactured.

Deviations

Deviation management was managed via [REDACTED] (policy) and SOP [REDACTED] Deviations were categorised as critical, major and minor with a requirement for a risk priority number (RPN) to be calculated, a review of historical deviations was also required. Impact analysis and classification were required to be performed within one business day. There was a weekly meeting to review all deviations raised within the last week to review impact and classification. There had been an upward trend in the number of deviations raised and overdue CAPA since the last inspection, however actions had been implemented and a reduction in the number of deviations and overdue CAPA were started to be seen. The following deviations were reviewed:

Deviation [REDACTED] (Critical) [REDACTED] Use of product [REDACTED] restricted [REDACTED] parts used on [REDACTED] pump rig build There was no documented evidence that MAHs were contacted within 24 hours. The report was spread over a number of documents and was difficult to follow in a logical fashion. The deviation impact assessment did not list out all potentially affected batches.

Deviation [REDACTED] (Minor) Pipette [REDACTED] - The "As Found" calibration did not meet specification. No comments were made during the review of this deviation.

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Quality Management review

Quality management review was governed by [REDACTED]. There were monthly and meetings with representatives from QP and senior leadership. The April 2023 quarterly management review meeting minutes was reviewed without comment.

Change control.

Change control was governed by SOP [REDACTED] dated 11/2/2022, and provision was made for temporary and emergency changes and changes were managed in the [REDACTED] system.

The SOP required a site review board to approve and review the change prior to entering in [REDACTED] except for urgent changes and changes which were routine such as artwork were managed using a proforma.

A selection of change controls was reviewed:

Change [REDACTED] relating to Implementation of [REDACTED] for [REDACTED] opened which was opened on 26 April 2021 and initially due for completion 17 December 2021, equipment included in the change was a [REDACTED] this was considered a major change. A URS was generated however issues were encountered with set up, these were resolved, and a new change control was raised.

Change [REDACTED] raised 15 June 2022 closed 4 November 2022 to cover the use of an alternative spray ball for the mixer temporary change other as the [REDACTED] spray ball had been lost this was to replace the spray ball and it was not clear if the change was a like for like change and why no process validation was required and additionally no implementation date for the change was recorded.

Change [REDACTED] opened 3 December 2020, this change concerned use of TSA media prior to QC approval in parallel with growth promotion test due to an urgent requirement, no comments were raised.

Change [REDACTED] opened 26 April 2021 for introduction of a new [REDACTED] API with enough to manufacture a [REDACTED] this change only covered specifications and a further change [REDACTED] had been raised to cover the process validation which was reviewed and was satisfactory.

C5 Personnel

There were approximately 750 staff onsite with the site running a 24/7 "continental" shift pattern, with 4 shifts on/4 shifts off rolling day/night pattern, including clinical lines.

Certain GMP activities such as cleaning were contracted out. Cleaning was contracted to [REDACTED] the training record of employee [REDACTED] and [REDACTED] who had cleaned Dispensary [REDACTED] on 7 June 2023 were reviewed with no gaps.

C6 Premises and Equipment

Commercial and IMP and warehousing, sampling, dispensing were common areas. The GMP facility rooms were at negative pressure compared with the production corridors. Pressure differentials were monitored electronically with an audible alarm in case of differential limits being reached. It could not be determined during the inspection how often the alarms were checked.

Storage Areas

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It was noted that the number of authorised personnel for the controlled drugs store was approximately 20 people, this was justified by the site as access was required for the 24-hour operation, additionally certain QC staff required access to obtain stability samples.

Sampling

The warehouse contained a booth for raw material sampling, packaging materials including foils were sampled within the warehouse. Sampling of raw materials for QC testing was governed by [REDACTED]. Every API drum was required to be sampled via disposable scoops from the top. An associated risk assessment which was appended to [REDACTED]. The risk assessment conclusion documented that for the freeze-dried tableting process, particle size, including that of micronized material did not impact the process capability and therefore any potential stratification of particle size in a drum was considered low risk. The risk assessment did not support this conclusion with reference to any scientific data. The general sampling risk assessment was also silent in terms of risks of falsification. A maximum of [REDACTED] composite samples were defined. However, the sampling plan /risk assessment for Sampling Process for [REDACTED] specified that composite microbiology sample of [REDACTED] was taken from all drums in a delivery of up to [REDACTED] drums. The risk assessment identified that [REDACTED] was high risk for microbiological growth but did not justify that a [REDACTED] composite sample from up to [REDACTED] drums would identify microbiological contamination from one drum. The microbiological method had not been validated to show that the method was sensitive enough to detect microbiological contamination at a [REDACTED] sample size.

Purified water

The site had [REDACTED] systems for purifying water using reverse osmosis and electrical deionisation. System [REDACTED] (Powder line) had a [REDACTED] filter on the return loop after UV irradiation, it was confirmed that this system was used for cleaning in on the development lines only and there were plans to reconsider the design of this system. The annual water system report for 2022 and 2021 for all purified water systems was reviewed without comment.

Warehouse

Warehouse

The goods in area was adequately protected from inclement weather with a canopy.

The Goods In process for Raw materials was governed by SOP [REDACTED] which did not require that delivered frozen or cold chain goods were in the appropriate store before the temperature data monitor was switched off and hence the potential remained that the goods could be stored outside required limits during this time. Raw materials could be supplied with a pre-delivered "tailgate" sample or sampling could be performed for the raw materials in a sampling booth in the warehouse. This was suitable with an airlock and changing area and only one material at a time was taken into the sampling area. The differential pressure was recorded. An in-use container of [REDACTED] was seen outside the sampling booth and it was disclosed this was not on the company approved cleaning material list. The SOP [REDACTED] for raw materials sampling had not been updated to incorporate use of an alternative source of facemask.

The warehouse had two walk-in cold stores where [REDACTED] was stored, and excursions were automatically notified to relevant staff and to the gatehouse out of hours. A document relating to material code [REDACTED] was seen in Cold store [REDACTED] which did not relate to anything currently stored in that area. SOP [REDACTED] governed Monitoring of temperature and Relative Humidity in warehouse. Trending of data was done on a monthly basis and data was downloaded and saved on a weekly basis, and there was a requirement to raise a deviation if data was missing. There was additionally a six-monthly review check of the whole system and evidence of trending of data was seen.

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C7 Documentation

SOPs were controlled via [REDACTED] and update of changes were documented in the associated change request. Commercial batches were managed via electronic batch records, whereas clinical batches were mainly recorded in a paper batch record.

Batch certification and release

Batch records underwent a two-stage review process; a quality assurance officer (QAO) review and a QP check, certification and release which was managed via [REDACTED] and [REDACTED] respectively. Final release was governed by [REDACTED]. The batch records for [REDACTED] unsealed [REDACTED] sealed batch [REDACTED] and [REDACTED] batch [REDACTED] (clinical) were reviewed during the inspection. QAO checks were documented on a QA amends form [REDACTED], however the data was not retained. QP checks were recorded on a batch disposition check form and final release was recorded on a CoA and CoC on a [REDACTED] global system which also acted as a QP register. The site allowed in process rejections of part loads of a batch, however, was no procedural controls for physical management or part batch / load rejections to minimise the risk of mix ups.

C8 Production

Commercial production was performed on [REDACTED] lines [REDACTED] which consisted of a form filler, freezer tunnel, freeze drier and sealer. Line [REDACTED] had been introduced since the last inspection. Commercial production had [REDACTED] mixers, intermediate storage vessels (ISVs), refrigerated storage cabinets (RSCs) and dry storage cabinets. There was one development clinical production line (Line [REDACTED]). Investigational medicinal products (IMPs) were primary packaged and sent for secondary clinical packaging to contract sites.

Dispensing

There were three dispensing rooms, including an API containment dispensary. The [REDACTED] (electronic batch record) system was used to control the allocation of rooms, dispensing activities, and the required mass of raw materials. The mass of dispensed materials was automatically entered into the batch record via the [REDACTED] system. It was noted that the logbooks for the dispensary documented that vacuum cleaner bags were changed every week which was contradictory to the requirements in [REDACTED] specified that vacuum bags were changed after every excipient or API. The [REDACTED] logbook [REDACTED] did document any changes of the vacuum cleaner HEPA filters. The cleaning was performed by external contractors (see Section C10), the record of the last cleaning performed was seen with no comments.

White powder was observed on the outside of a keg of [REDACTED] in the storage area for dispensed and picked items that was due to be taken back into the warehouse.

Mixing room [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED] Mixing recipes were controlled via the [REDACTED] system and settings on the mixing vessel were manually entered by the operator. Temperature, stirrer speed, vacuum pressure and RPM were continuously monitored via a digital chart recorder. Hold times were defined as 7 days and managed via the [REDACTED] system. ISV temperature was monitored via the digital chart recorder.

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An unlabelled container of clear liquid which was described as [REDACTED] was seen in the Mixer [REDACTED] room during the inspection.

Line [REDACTED]

The form fill sealer was observed for the production of [REDACTED] during the inspection. Suspension / solutions were dosed into pockets formed in plastic or aluminium laminate blister films. IPC weights would be performed at 'first off' and after filling of each load, adjustments to the pumps were made when action limits weights were reached which were recorded in the electronic batch record. Filled trays underwent a 'snap freeze' in a freezing tunnel where the temperature would be quickly reduced using a liquid nitrogen spray. Nitrogen tanks were located outside the facility and filled daily. Two filters were located on the nitrogen line. Temperature sensors were placed at the top and end of the freeze tunnel and recorded on the digital chart recorder. The trace from the digital chart recorder was printed and checked against an approved overlay. Sub loads of frozen trays were placed in refrigerated storage cabinets (RSCs) and transferred to a freeze dryer. Pressure and temperature were recorded on the digital chart recorder. Trays were stored in dry storage cabinets post lyophilisation. Trays were fed into the sealing machine where variable data would be printed via a [REDACTED] map. Print quality checks were performed at the end of every shipper. The line had a pin hole detection system and an overhead vision system checking variable data. Reprocessing of blister packs through the overhead vision system was allowed once as there was a known issue of a high number of false rejects. The control of this was not explicit in the rework SOP [REDACTED]. There was a separate inspection area for IPCs. Leak tests were performed on every shipper.

Line [REDACTED] Wash room and Pump storage room

The line [REDACTED] washroom was inspected, it was observed that a seal on a dedicated intermediate storage vessel for [REDACTED] was torn and had holes in it.

There was a separate storage room for dedicated parts for [REDACTED] as a result of a critical deviation. [REDACTED] pumps and parts were engraved with [REDACTED]

Line [REDACTED] (development / clinical line)

The development / clinical line was located in a different facility to that of the commercial line. There was no manufacture on Line [REDACTED] during the inspection. There was no logical flow, or step over in both male and female gowning areas, the gowning process described in the SOP located in the room was difficult to follow due to the lay out of the room. Materials destined for clinical manufacture were dispensed in the line [REDACTED] in the commercial facility. The mixing room contained a small [REDACTED] mixer. A development flash mixer that was on loan from the manufacturer was located in mixing room, however, it did not have an associated logbook or record of what had been used on it. Uncontrolled documents detailing how to use the flash mixer were observed in the mixing room. Line [REDACTED] had a form filling room and a freeze dryer. Equipment was cleaned using pressure washers in the washroom. It was noted that the cleaning area was very cramped. Deficiencies were identified in this area are and described in section D of this report.

Digital Print Suite.

The site printed selected artwork designs onto primary lid foil laminate. Primary packaging foil used for printing was purchased. The storage of printed primary packaging was in an open area of the warehouse and not under separate secure storage.

New product introduction and cleaning validation

Development Product Cleaning Validation was assessed using form [REDACTED]

The site utilised a worst-case approach for calculating the Maximum Allowable carry over for the API where either the PDE of [REDACTED] or next dose which ever was the worst case and typically

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cleaning would be assessed using three reference runs. Deviations were required to be raised in [REDACTED] or cleaning failures in validation, and if changes were made to process revalidation may be required. Cleaning agent removal was assessed three times and thereafter every two years.

Principles of cleaning validation documented requirements were governed by [REDACTED] version [REDACTED] dated 4 May 2023 required that cleaning validation for manual processes were revalidated every 2 years but had justified why CIP and automated cleaning system revalidation could be extended.

The cleaning of the last API introduced to the facility was reviewed, this was [REDACTED] cleaning validation assessment form [REDACTED]

The site had a PDE assessment from a third party [REDACTED] reference [REDACTED] dated 13 July 2015 with the PDE being assessed as [REDACTED]. It was discussed what the trigger for update of the assessment was, the company stated this would be assessed and changed by the third party however for this product the responsibility had changed the company did not hold a PDE assessment for [REDACTED] API from [REDACTED] despite a requirement for this being detailed to be supplied in the Quality Technical Agreement and furthermore the PDE assessment in place related to weight of [REDACTED] rather than the [REDACTED] specified in the agreement with [REDACTED]

The first stage of introduction to the site required an initial risk assessment was made for onboarding the API where it was confirmed API could be removed, typically using a reference product.

A further risk assessment was made when commercial equipment was used and risk parameters were applied such as solubility, API concentration, Toxicity, lowest therapeutic dose, cleanability and the type of cleaning process (manual vs CIP) to get a risk score for cleaning. This was applied to the existing reference product index and the worst case became the reference product however for other API if risk score was within [REDACTED] other APIs would also be classified as reference products and periodically reassessed. [REDACTED] was classed as a reference product as the [REDACTED] limit was of concern, hence cleaning required validation typically consisting of three runs and periodic revalidation. If a product was not classed as a reference product, then a single cleaning validation was required.

It was not clear how the effects of small changes over time impacted the requirement for requalification timelines for example for cleaning revalidation and this contributed to a deficiency.

The initial validation of [REDACTED] performed in was assessed with no comments additionally the revalidation which was performed in November 2022 for [REDACTED] was reviewed, specifically the data for cleaning the [REDACTED] pumps reference [REDACTED] dated 10 January 2023. The pumps used on the November campaign were set [REDACTED], the site could not demonstrate a robust system to confirm that set [REDACTED] had been effectively quarantined and removed from use following verification of [REDACTED] campaign in November 2022. The procedure [REDACTED] dated 8 December 2022 for control of equipment subject to cleaning validation in use required that a Form [REDACTED] notice was placed on the equipment but the SOP allowed reuse of the equipment for the same product before completion of validation and it was not clear how the company controlled the equipment after it had been reused. SOP [REDACTED] dated 17 May 2023 clearly detailed the swab sites for chemical cleaning validation.

This cleaning of the [REDACTED] pumps had been in accordance with [REDACTED], it was noted that tubing was disposed of after each campaign of product. The SOP allowed a reclean of nozzles with no requirement to raise a deviation and this contributed to a deficiency.

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Out of specification

The management of out of specification and atypical results was governed by SOP [REDACTED]. It was required to raise an investigation within one day. The SOP described all expected investigation steps. A selection of OOS raised were reviewed with no comments, specifically:

OOS [REDACTED] concerning water content for a stability study

OOS [REDACTED] relating to a batch contaminated with mould, the batch was rejected, and the deviation and risk assessment concluded no other batches were impacted.

OOS [REDACTED] concerning an incorrect date format on a blister, this was escalated to a deviation, and it was linked to an incorrect date format supplied by [REDACTED] manufacture.

QC laboratory

The QC laboratory operated on two shifts for finished product testing, other activities were raw material and stability testing.

There were a number of pieces of standalone equipment in the QC laboratory and it was required to take a printout which would form part of the batch record or second check to meet data integrity requirements.

The site disclosed that it was not possible to do a second check for the disintegration test and this had been covered with a risk assessment however the site had no requirement to revisit such risk assessments to check if the compliance gap could now be met and this contributed to a deficiency.

Analytical test methods were held on [REDACTED] system, and a copy could be printed which was valid on the day of printing only.

The laboratory had a separate room which housed [REDACTED] HPLC and [REDACTED] UHPLCs which were linked to an [REDACTED] system, it was seen that two were dedicated for cleaning validation only. The logbook [REDACTED] was reviewed in the area with no comments.

Fridges and freezers used to store reference samples were monitored by a [REDACTED] and excursions were additionally communicated to the gatehouse. Each product had a logbook to record standard usage, it was noted that in-use standards in the fridge were not covered in parafilm once opened, it was stated that this was not required as standards were kept upright, although at the time of inspection several were noted to be laid horizontally.

The site only used primary reference standards. The record for [REDACTED] Standard [REDACTED] was reviewed with no comment.

The site had previously used a [REDACTED] system for handling laboratory data but now used an [REDACTED] system. Legacy data for the [REDACTED] system was held and the [REDACTED] described steps to take if it was found data required further reprocessing and reapproval for example if an error had been noted.

SOP [REDACTED] covered review and approval of chromatographic data in [REDACTED] it covered audit trails and how to review manual integration and was generally comprehensive.

Data held in both systems relating to [REDACTED] cleaning validation and verification was reviewed during the inspection, it was noted for the cleaning verification for [REDACTED] dated 17 May 2023 there was no comment which explained why a reassignment had been performed and there was no record of the manual integration in the workbook as required by the SOP.

The site held a Data integrity risk assessment and remediation plan dated March 2023 reference [REDACTED] where gaps had identified mitigations these had been incorporated into project plans, an unresolved gap was the site were unable to do a second check for dissolution in the QC laboratory as the dissolution was immediate, and an

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assessment had been made which was satisfactory but there did not appear to be a requirement to revisit unresolved gaps and this contributed to a deficiency.

Stability

Stability was managed by an analytical support team; it was required to raise a deviation if stability timelines were not adhered to. Stability rooms were linked to [REDACTED] temperature recorders, and a weekly check was made on all [REDACTED] systems. Controlled drugs were held on stability in the controlled storage area in the warehouse. There were two walk-in rooms 25/60 and 30/75 as well as three further storage areas 25/60, 40/75 and 30/65. Stability studies were assigned a stability study number, it was seen that for more recent set downs improvements had been made to the way samples were labelled.

Stability protocol [REDACTED] packs for [REDACTED] dated 24 August 2020, the protocol was seen, and it was seen how the reconciliation was done for the samples. It was disclosed that this protocol had been regenerated, as the original had been found to be missing, this was linked to an individual leaving the business. No deviation had been raised at the time of discovery and hence it had not been determined if other stability protocols were similarly impacted.

Microbiology Laboratory

The microbiology laboratory tested raw materials, finished products and performed water and environmental testing for the facility. It was required that when predetermined action and alert limits were exceeded that the organisms were speciated.

Sampling of water for QC testing was governed by SOP [REDACTED] it was required that prior to taking the sample the water was run for [REDACTED] minutes to allow at least [REDACTED] litres of water to flow, this was consistent with the instructions for Production use of the water.

Media could be bought in or manufactured in house, control systems for media management were reviewed and the record of preparation of TSA batch [REDACTED] was also reviewed with no comments.

The laboratory had two autoclaves used for media preparation, cycle data was printed out and retained.

Maintenance of the Autoclave [REDACTED] was seen it was required that a service was performed every six months and annual calibration, records were seen for the last service in February 2023 and the calibration and the service in August 2022 with no comments.

Analytical Method Validation

The validation protocol [REDACTED] for assessing cleaning of [REDACTED] was reviewed this detailed swab recovery of data for materials stainless steel, Teflon/PTFE and Ceramic and rinse recovery for the nozzles and appeared suitably detailed. The final report [REDACTED] 172 dated 15 June 2018 was seen, an issue had been raised as an atypical result for a lowest recovery [REDACTED] and no comments were raised with this review.

Examples of the chromatography for the validation exercise from 2018 and the reverification exercise were reviewed with data issues noted for the reverification exercise as there was no commentary which explained why a result had been reassigned furthermore There was no record of the manual integration in the workbook as required by SOP [REDACTED]

Validation and Qualification

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The site had a Validation Master Plan was governed by [REDACTED]. The site adopted a Continuous Process Validation which was governed by [REDACTED]. This process required validation history review to be performed which assessed aspects such as calibration and maintenance, risk of process / equipment, unplanned maintenance and deviations raised during review period. Temperature mapping plan for cold storage and freezer storage was required to be performed every 5 years. The following validation reports were reviewed without comment:

Tray marking system PQ for line [REDACTED] Tray marking system – [REDACTED]
Approved 02 July 21. Validated using 3 batches.

Periodic Temperature mapping freeze tunnel every 5 years November 2022 [REDACTED]
[REDACTED]

C10 Outsourced Activities

Outsourced activities were managed in the [REDACTED] system and changes to Suppliers were subject to change control.

The cleaning of GMP areas was performed by a third-party contractor [REDACTED] this company also managed the activity performed by a third party who laundered the Production garments.

A Quality Technical agreement reference [REDACTED] was in place between [REDACTED] and Catalent Pharma however the agreement was local to the Swindon site, this appeared comprehensive, and no comments were raised.

The site had audited [REDACTED] report reference [REDACTED] on 11 August 2022 for 1 day with 2 auditors and expected areas had been covered.

The Quality Technical Agreement with [REDACTED] who were the MAH for [REDACTED] was reviewed, the agreement was generally comprehensive. (See New Product Introduction),

C11 Complaints and Product Recall

Complaints

Complaints were governed by SOP [REDACTED] complaints were classified as critical, major, minor and complaint not confirmed. Complaints came from the marketing authorisation (MA) holder or the sponsor of the IMP and required complaints to be completed within 30 calendar days. Initial assessment was required to be performed within one business day. There had been 114 major complaints since the last inspection. The following complaints were reviewed during the inspection without comment:

[REDACTED] (major) Contamination red marks on blister [REDACTED].
Red spots found on blister. Customer performed luminal analysis and determined it was blood – confirmed complaints.

[REDACTED] (major) Empty blister for [REDACTED]

Recall

There had not been any recalls in the previous two years.

Mock recall performed between 25th October 2022 – 2nd November 2022 [REDACTED] Foil packaging component issue. The mock recall did not assess the full recall process out of hours, for example it did not document the classification of recall, it did not assess whether relevant personnel such as the QP could be contacted out of hours.

C12 Self Inspection

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Data integrity monitoring was performed as part of the self-inspection programme. The [REDACTED] system was last audited by [REDACTED] 03 Aug 21 and documented on [REDACTED] Digital Cart Recorder (DCR) Network Data Integrity Assessment was last performed on the 6th November 22 and reviewed without comment.

C13 Distribution and shipment (including WDA activities if relevant)

Customer shipping requirements was governed by SOP [REDACTED] and a list of customer shipping requirements was given this included types of documents required, vehicle type, samples, and any specifics for transport for example when the use of thermal blankets to be attached was required. Distribution and shipment were not reviewed in detail as part of this 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

D1 Critical

None

D2 Major

None

D3 Others

3.1 Measures to prevent the spread of cross contamination were deficient as:

- 3.1.1 The technical and organizational measures to prevent cross-contamination in the Line [REDACTED] clinical GMP area were deficient as evidenced by:
 - 3.1.1.1 The gowning process in the male and female changing areas were not laid out in an orderly and logical manner to minimize the risk of confusion, risk of omission or wrong application of the gowning process.
 - 3.1.1.2 The control of development equipment within the Line [REDACTED] suite did not minimize the risk of cross-contamination, for example a flash mixer on loan from the manufacturer did not have an associated logbook detailing which products had been used.
 - 3.1.1.3 A 'line flush' was observed in the Line [REDACTED] equipment store without an asset number and had "do not use" written on it.
 - 3.1.1.4 The stainless-steel holding vessel in the Line [REDACTED] washroom did not have a smooth welding around the drain point inside the bowl.
 - 3.1.1.5 The hot water hose in the washroom Line [REDACTED] was not stored in a manner to allow free drainage.
- 3.1.2 The company could not demonstrate a robust process to demonstrate pump set [REDACTED] had been effectively quarantined and removed from use following verification of [REDACTED] campaign in November 2022.
- 3.1.3 It was not clear how the company controlled the validation restriction for equipment used before approval of validation in the batch.

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- 3.1.4 It was not clear how the effects of small changes over time impacted the requirement for requalification timelines for example for cleaning revalidation.
- 3.1.5 The risk of accidental cross-contamination resulting from uncontrolled release of dust was not appropriately controlled as evidenced by;
 - 3.1.5.1 There was no documented evidence for vacuum bag changes after dispensing a batch of starting material in API containment dispensary line [REDACTED]
 - 3.1.5.2 SOP detailing clean requirements for vacuum cleaners ([REDACTED]) did not specify the required frequency or requirements for HEPA filter changes.
 - 3.1.5.3 White powder was observed on the outside of a [REDACTED] d keg that was awaiting return to stores in material storage from goods in area.
- 3.1.6 Manifolds stored in a clean equipment cupboard in the Line [REDACTED] washroom were not visually clean. It is noted that swabs taken during the inspection and subsequently analysed via FTIR did not show a spectrum.
- 3.1.7 SOP [REDACTED] allowed a reclean of nozzles with no requirement to raise a deviation.

Reference: EU GMP C3.7, C3.8, C3.14, C3.34, C3.35, C3.6 C4.31, C5.13, C5.17, C5.18, A15.10.2, A15.4.2, A16.1.7.1, A16.1.7.12

- 3.2 **Sampling plans for raw materials were not appropriately justified based on a risk management approach as evidenced by:**
 - 3.2.1 The Sampling Process for [REDACTED] did not adequately justify the number of samples which may be blended to form the composite sample. The sampling plan required one [REDACTED] microbiological composite sample to be generated from a potential of [REDACTED] drums despite the requirement of a maximum of [REDACTED] composite samples being specified in [REDACTED]. The sampling plan identified that [REDACTED] was a high-risk product in terms of microbiology and did not confirm the sensitivity of the microbiological method.
 - 3.2.2 The justification for sampling raw material solely from the top of a drum and not performing stratified sampling referenced in [REDACTED] did not consider falsification risks and did not provide reference to scientific studies to justify risks associated with particle size distribution during transport.

Reference: EU GMP C6.12, A8.4

- 3.3 **Pharmaceutical Quality System**
 - 3.3.1 The 2021 – 2022 annual product review (APR) for [REDACTED] was deficient as evidenced by:
 - 3.3.1.1 Quality technical review statements in the APR were limited to a review of the sign off dates and did not verify the appropriateness of the information in the Quality Technical Agreement.
 - 3.3.1.2 Data generated for critical performance parameters, such as pre-mix hot temperature, dosing minimum and maximum temperature and dosing maximum suspension hold time regularly exceeded lower control limits (LCL) and upper control limits (UCLs) without action or out of trend investigation.
 - 3.3.1.3 The report highlighted an issue with yield data sets being below the lower control limit. [REDACTED] was raised to review this in the next continuous process validation report however, this was not captured in the draft report which was due in November 2023 or appropriate CAPA.
 - 3.3.1.4 There was no documented risk-based justification or investigation for accepting Cpk values of below [REDACTED] for maximum suspension hold time and mixing -final mix temperature.
 - 3.3.1.5 There was no procedural requirement for the consideration of product quality reviews for routine manufacture of clinical trial batches.

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- 3.3.2 Deviation management was incomplete as:
- 3.3.2.1 The site had failed to investigate an incident when it was believed a stability protocol had been lost.
- 3.3.2.2 Deviation [REDACTED] did not document evidence that MAHs were contacted within 24 hours as required by the SOP [REDACTED]
- 3.3.3 Change control did not always completely describe the change details and justify validation requirements for example [REDACTED] raised 15 June 2022 for use of alternative spray ball for a mixer did not describe that the spray ball was considered like for like and it was not evident when the change had been made.

Reference: EU GMP C1.4(xii) C1.8(v), C1.8(vii) C1.10(ii), C1.10(xii) C6.9

3.4 Facilities and Equipment management

- 3.4.1 The Goods In SOP [REDACTED] did not require that delivered frozen or cold chain goods were located in the appropriate store before the temperature data monitor was switched off and hence the potential remained that the goods could be stored outside required limits during this time.
- 3.4.2 Printed materials were not stored in adequately safe and secure location to exclude unauthorised access.
- 3.4.3 The seal around the [REDACTED] intermediate storage vessel (ISV) that was located in the equipment store was torn / broken.
- 3.4.4 An unlabeled container of clear liquid which was described as [REDACTED] was seen in the Mixe [REDACTED] room.
- 3.4.5 The approved cleaning list was incomplete as there was no reference to [REDACTED] which was seen in use outside the raw materials storage area.

Reference: EU GMP C3.25, C3.44, Chapter 4 Principle, C5 Principle, C5.2, C5.12, C5.46

3.5 Documentation and Data integrity controls were deficient as:

- 3.5.1 Appropriate controls were not in place to ensure the integrity of all records throughout the retention period as evidenced by;
- 3.5.1.1 Quality Assurance Officer (QAO) batch record amendment forms were not retained to ensure complete data existed for the batch record.
- 3.5.1.2 The laboratory records associated with the cleaning verification for [REDACTED] dated 17 May 2023 were deficient as:
- 3.5.1.2.1 There was no comment which explained why a reassignment had been performed.
- 3.5.1.2.2 There was no record of the manual integration in the workbook as required by [REDACTED]
- 3.5.2 The company did not hold a PDE assessment for [REDACTED] API from [REDACTED] despite a requirement for this being detailed to be supplied in the Quality Technical Agreement and furthermore the PDE assessment held related to weight of [REDACTED] rather than the [REDACTED] specified in the agreement.
- 3.5.3 The Rework procedure SOP [REDACTED] did not specify the location of where blisters for reprocessing should be placed on the line.
- 3.5.4 There was no procedural instructions for physical controls and requirements for when part of a batch (load) was rejected to ensure prevention of mix up.
- 3.5.5 The SOP for raw materials sampling had not been updated to incorporate use of an alternative source of facemask.
- 3.5.6 The site had no requirement to revisit data integrity gaps which had been mitigated by risk assessment for example the disintegration test.
- 3.5.6.1 An uncontrolled document relating to the manufacturer's instructions for the flash mixer was

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seen in the mixing room for Line ■■■

Reference: EU GMP C1.4(viii), C1.4(xi), C1.8(iv), C4.1, C4.3, C4.10, C4.19(h), C7.2

- 3.6** The last mock recall did not assess the effectiveness for all recall process arrangements for out of hours, for example it did not document the classification of recall, it did not assess whether relevant personnel such as the QP could be contacted out of hours.

Reference: EU GMP 8.31

D4 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	✓		
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

A closing meeting was held and deficiencies were verbally accepted.

F2 Assessment of response(s) to inspection report

A response was received 20 July 2023 which was accepted.

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	✓

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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:

██████████

Date: 27 July 2023

Accompanying Inspector:

██████████

Date: 27 July 2023

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Annex 1

GMP Site Risk Rating

(a). Inspection Findings

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

(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

(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

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

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

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

Risk Rating:	Next Inspection target date:

Notes regarding re-inspection and GMP certificate validity

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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