Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

INSPECTION REPORT

Catalent UK Swindon Zydis Ltd,
Frankland Road,
Blagrove,
Swindon,
Wilts.
SN5 8RU

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 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: 17,18,19 & 20th February 2020 (3 days)

Lead Inspector: [redacted]

Accompanying Inspector(s): [redacted]

Case Folder References: Insp GMP/IMP 14023/4574-0019

Section B General Introduction

B1 Background information

The company specialise in the manufacture of [redacted] and is part of Catalent Pharma Solutions advanced drug delivery (ADL) organisation, which is headquartered in NJ, USA. The site is a contract manufacture [redacted] Development laboratories are also located on site.

Previous Inspection Date(s): 13 -15th September 2016

Previous Inspectors: [redacted]

B2 Inspected Areas

Quality systems
Product Quality reviews
Planned and unplanned Change controls
Quality risk management approach
Quality management review and metrics
List of rejected batches in last year
Manufacturing
Warehouse
Line clearance
Cleaning verification
Segregation/ prevention of X contamination
Purified Water system
Batch records
House keeping
Validation
Validation Master Plan
Process validation
Equipment qualification
Computer validation
Quality control, stability testing and Microbiology
Others
TSE
Routine maintenance, ppm, calibration
Technical agreements
Batch record review
Batch/ QP release
Self-inspection
Training /records
Supplier auditing/ approval
Contractor agreements
API GMP compliance

Limitations / exclusions to inspected areas

R&D laboratories/manufacturing areas, engineering, Pest control, Technical transfer

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]
[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	7th February 2020	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 relevance to compliance / risk rating, or which relate to inspection deficiencies are listed below:

The changes are covered in the pre-inspection compliance report and the responses to the previous inspections.

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

It was indicated that the [redacted] system was to be replaced. Technical meetings had been held with [redacted] egarding their [redacted] system and a test system was expected to be available on site in May 2020. A 'User Requirement Brief' had been generated [redacted]

The site was rolling out a change in Chromatography software, from [redacted] to [redacted] as part of a corporate improvement plan for all Catalent analytical laboratories.

A QR code product identification system was undergoing installation and qualification during the inspection. Please refer to section C6 for further information.

C2 Action taken since the last inspection

The actions since the last inspection had been addressed

C3 Starting Materials

Excipient risk assessments had been appropriately conducted in accordance with SOP [redacted] The assessment for [redacted] was reviewed and assessed as satisfactory and followed the EMA guidance.

SOP [redacted] described the procedure for the Assessment of Suitable GMP requirements for excipient suppliers.

The supply chain map for [redacted] was reviewed and found to be generally satisfactory. The API supply was the responsibility of the client however all information as received as required. However, the TSE statement from the client did not reference the EMA guidance document, EMA/410/01 rev 3.

[redacted] supply which was under the purchasing control of Catalent Zydus was reviewed. The Technical agreement with the supplier; [redacted], was reviewed and was satisfactory.

It was noted when sampling was reviewed that Some API's were received with tailgate samples which were transferred directly to the laboratory after the details were checked.

C4 Pharmaceutical Quality System

Deviations

The deviation management process was described in SOP [redacted] Version [redacted] Issues were raised within production as 'PELs' (production event log) which could be classified as either 'events' or 'deviations', with the latter being categorised as critical, major or minor and requiring full investigation and root cause analysis. Personnel responsible for performing investigations were required to attend specific training for this, which was primarily via external courses for the SMEs who then also provided training in-house. An RPN process was used and the process used was generally acceptable however there was no specific provision in the procedure for a 'common sense' clause where high risk issues were noted with low occurrence and high detectability. There was however no evidence that any issues had been accepted on the basis of the RPN calculation in isolation.

At the time of inspection, there were very few overdue deviation investigations and it was acknowledged that this had not been the case in the past, but the site had focussed on this over the preceding few years and brought the system into good control.

Several deviation investigation reports were selected for review and were found to be generally comprehensive and appropriate. Reports reviewed:

- [redacted] (Critical). [redacted] cycle does not match overlay due to extended ramp up.' The investigation and actions were acceptable however the executive summary included some conflicting information regarding the setpoint of the alarm.
- [redacted] (Major). [redacted] incorrect format for expiry date used.'
- [redacted] (Cancelled). Raised separately as an event therefore duplicate record cancelled.
- [redacted] (Cancelled). Documented under deviation [redacted]
- [redacted] (Major). 'Two sets of development samples labelled incorrectly.' The investigation was acceptable based on the samples involved (active and placebo) however the report did not consider the risk if samples for two active batches were mixed up and an issue was noted which could result in the wrong batch being accepted. This was discussed in detail and not raised as a deficiency as it was not a systemic issue and appropriate actions were implemented.
- [redacted] (Minor). 'Items issued to production whilst in quarantine.'
- [redacted] (Minor). 'Incorrect assay result used to calculate mass variation.'
- [redacted] (Minor). [redacted] magazine and shipper labels from previous batch found in waste.'

New product introduction and cleaning validation

A new product introduction process was in place, with a team meeting weekly to discuss proposed new projects. The cleaning assessments included review of PDEs, [redacted] of daily dose and the [redacted] limit, with the lowest of all of these being used for determining the cleaning limits. In addition, the lowest capacity of equipment such as mixing vessels was used even if batch sizes were all larger than that volume.

Cleaning of mixer vessels was via automated CIP, with the exception of two vessels [redacted] and [redacted] however it was indicated that it was the intent to transfer all products onto the vessels with automated cleaning and retire these two vessels. Intermediate vessels for transfer to the filling line (ISVs) and filling pumps and needles were subject to manual cleaning processes, and the validation of these manual processes was relied upon for all products, with no verification performed after campaigns of products with lower PDE values.

Several issues were noted with respect to the detail within the manual cleaning procedures and records and the PDE assessments. In addition, possible contra-indications were not formally included as part of the assessment for introduction to shared equipment and as a number of

molecules with low PDE values were handled on site, these were grouped into a major deficiency – refer to section D.

Batch review and release

SOP [redacted] Version [redacted] described the process for review and QP certification of bulk [redacted] commercial products and SOP [redacted] Version [redacted] related to the same for development products / IMPs. These were generally comprehensive, and the systems appeared to be in control.

Annual Product Quality Review

The PQR procedure was SOP [redacted] version [redacted] which was based on Catalent corporate policy procedure SOP [redacted] v [redacted] The Technical agreement and procedure required PQR reports to be completed within 3 months from end of review period. When completed there were 14 days given for internal review and approval then a further 14 days for external client review. SOP [redacted] ver [redacted] defined the procedure on consolidating information for the report. PQR's were tracked through [redacted] as a PR was raised for new product PQR's and a child PR was raised for annual PQR's. Control charts were created with [redacted] software. If the review period contained less than [redacted] batches then the previous review period was used for statistical calculations, if there were less than [redacted] batches then statistical analysis was not performed. P-value and cpk values were used to understand process control; cpk [redacted] highly capable, cpk of [redacted] equals [redacted] sigma. Several PQR's were reviewed during the inspection. [redacted] The conclusion was that the process was in control after statistical analysis of [redacted] batches. The PQR included a batch size increase and subsequent process validation batches. PQR for [redacted] showed the process was in control after statistical analysis of [redacted] batches. [redacted] for the period May 17 to April 18 was found to be in control after statistical analysis of [redacted] batches, however [redacted] batches were rejected after out of specification investigations found an API potency issue. The site now received the API in pre-dispensed aliquots.

Change Control

Change Control was governed by SOP [redacted] ver. [redacted] Change controls were initially reviewed by a review board and if approved for progression, was raised in [redacted] Urgent changes were allowed for safety or quality reasons, but these were retrospectively reviewed by the review board.

Several change controls were reviewed during the inspection and found to be generally acceptable. Change control [redacted] was raised for removal of routine status labelling of raw materials. It was opened 24 May 2019 and closed 29 Jan 2020. The project was to remove status labelling for raw materials only, finished products were not included. Rejected materials were also not included in the project. The status of raw materials was successfully changed over to [redacted] after procedural updates and training.

Customer Technical Agreements

Technical Agreement management was documented within SOP [redacted] ver. [redacted] The SOP clearly stated the required sections of the technical agreement and to ensured business terms were excluded from the Technical Agreement. The SOP described the additional requirements for an EU clinical trial manufacture technical agreement. Several technical agreements were reviewed and were found to be in compliance with the SOP and regulatory requirements.

C5 Personnel

The staff met during the inspection were knowledgeable of the procedures and processes and were an established team, particularly those in management positions. All staff interacted with were able to confidently describe their roles and the associated systems.

The site used curriculum-based training and was in the process of transitioning to the use of [redacted] for all staff which would enable progress to be easily managed and visible to both the employee and the management team. [redacted] software was used to record training.

It was noted that effectiveness checks for line clearance training had been changed from the 'live line clearance' style with items planted onto a line as part of the training to the use of real line clearances in production. The suitability of this approach to appropriately assess effectiveness of training was questioned and the site confirmed that this would be reviewed.

C6 Premises and Equipment

Storage Areas

There was sufficient space for all warehouse processes for incoming and outgoing materials. All goods were checked at goods-in against approved supplier lists as well as the standard incoming goods checks. It was noted that a check was not performed on whether the delivery vehicle was curtain sided. There were facilities for the storage of refrigerated and frozen API's. Data loggers were checked by the warehouse upon delivery receipt. Pallets were checked on arrival to ensure only heat-treated pallets entered the warehouse. This was detailed in SOP [redacted]

Goods out was transferred from manufacturing through to warehouse on a labelled pallet. Individual shippers weren't required to be labelled as whole pallet was shipped to customer.

Sampling

The warehouse contained a sampling booth that was divided into 2 sections, a holding area and a sampling room. It was used to sample all incoming materials according to [redacted]. Sampling was performed on one batch a time using disposable sampling tools. It was noted that procedures did not require the use of sampling thieves for larger containers. It was also noted that there was no defined limit to the number of samples that could be blended together to form a composite sample

The last material sampled was [redacted] the paperwork was reviewed during the lab inspection and was found to be satisfactory.

Digital Print Area

There was a newly established digit print area within the warehouse facility for the artwork printing of packaging base foil. The area was access controlled and designed as a cleanroom area to control contamination of the primary packaging material. Artwork was saved on the server as a security protected PDF document. The correct artwork (defined in the batch record) was uploaded to the printer, a secondary check performed and then used to print the primary packaging material. A 100% check was performed by camera which was challenged prior to commencement. There was a process defined in a procedure for the removal of expired artwork.

Air Fed Hoods

Procedure [redacted] ver [redacted] defined the Operation, Cleaning and Maintenance of [redacted] respirators. The filters used in the hoods were single use and disposed into an active waste bag at the end of the shift. The hoods were cleaned with [redacted] wipes after use.

Site Validation Master Plan

The Site validation master plan was defined in document [redacted] ver [redacted] and contained the following sections; Purpose, scope, responsibilities, Validation lifecycle, technical validation schedule, computer systems validation, analytical method validation & other areas. Analytical Method validation was discussed in [redacted] and [redacted] Cleaning Validation was contained in a separate document, [redacted]

HPLC Calibration

HPLC maintenance and calibration was governed by SOP [redacted] ver. [redacted] Before preventative maintenance and calibration, as-found checks were performed; pump flowrate, temperature control of the column oven and detector checked with a [redacted] filter. Any fails were reported to analytical support who would assess the impact of the failing check. The PM and calibration were then performed as per procedure. [redacted] last calibration by an [redacted] engineer was reviewed and found to be compliant with the procedure. Form [redacted] was then c0ompleted to allow the HPLC to be returned to routine use.

Freeze Dryer Number [redacted]

The qualification and maintenance documentation was reviewed for freezer dryer [redacted] The original qualification was performed in 1996 and despite the date, the documentation was readily available during the inspection. The site performed validation history reviews based on performance and unplanned maintenance and assigned a score to the equipment based on risk. The maintenance schedule was held on the [redacted] electronic database and was reviewed during the inspection. All tasks were performed on time without deviation to the schedule. When a task was due, a work order was printed from the system and completed by the engineer at the time of performing the task. The data was then transcribed into [redacted] database and saved. There was a second person check on the task and completion of the database.

Balances

Procedure [redacted] version [redacted] defined the [redacted] There was a 4 monthly contractor calibration as well as an annual maintenance event. The site used an external company to calibrate and maintain the balances. The balances were calibrated with either E2/F1/F2/M1 weights, determined by the balance capacity. Balances were first calibrated in the 'as found' state then only adjusted if the as found calibration failed. Eccentricity, linearity and range were checked during calibration. Min weigh was calculated as per United States Pharmacopoeia. The external contractor provided the site with certificates post calibration which were checked by an onsite engineer and signed if acceptable. During the inspection the calibration documentation for balance [redacted] asset number [redacted] was checked and found to be satisfactory.

Tray Marking System

The site is undertaking installation and qualification of a tray marking system for traceability of blister trays prior to being sealed and punched out into magazines. The improvement

programme was to prevent product mix up prior to the blister being printed with its variable data. The project was detailed in change control [redacted] opened 12 Feb 2019 and due for completion 31 Dec 20. The system would print a product/dose unique QR code on the base foil at the outer edge and then checked at following stages by a camera. The foil containing the QR code would then be cut off during the blister punch out stage.

The system employed was [redacted] Software version [redacted] supplied by [redacted] The project status at the time of the inspection was IOQ for each line, excluding Line [redacted] as a non-commercial line. The system will also link into the eBMR's at a future stage of the project.

The qualification documentation was not reviewed in detail at this inspection may be of interest at a future inspection.

C7 Documentation

An example batch record for [redacted] was reviewed. Separate sections were used for mixing, form/fill/freeze, drying and lidding. The bulk dried product could also be split into multiple final blister batches if required. The batch records were generally comprehensive and well designed.

C8 Production

The site contained the following production equipment; [redacted] development clinical line [redacted] , [redacted] commercial lines ([redacted] which consisted of a form filler, freezer tunnel, freeze drier and sealer), [redacted] development/clinical mixer [redacted] , [redacted] commercial mixers, Intermediate storage vessels (ISVs), refrigerated storage cabinets (RSCs) and dry storage cabinets.

Dispensing

The dispensing area was reviewed, and dispensing activities were acceptable. The [redacted] system was used to control the dispensing requirements for any given product. Dispensing was a 2-person operation; 1 person dispensed and 1 person checking the dispensed materials. The Team Leader then signed of the dispensing operation upon completion. The [redacted] report was verified electronically and QA signed off the report in the system. Dispensing operations typically was performed 24-48 hours in advance of the manufacturing slot.

There was a separate dispensing area containing 2 isolators for the dispensing of potent API's. Although there were 2 isolators, only one product was allowed into the area at any time. The API was dispensed into [redacted] which were detached from underneath the isolator and transferred into the manufacturing area. The isolators used a clean in place system with spray balls spaced out within the isolator. There was noticeable browning on the seals within the isolator, which was believed to be as a result from the API dispensed within the isolator.

Mixing Rooms - Mixer [redacted]

Mixer room [redacted] was reviewed. It was awaiting to be cleaned. Intermediate storage vessels were used in the area and transfer of material was transferred under vacuum using single use piping. [redacted] or paper-based records were used in this area. Operations were verified by the Team Leader with a full reconciliation at the end of the batch by weight check.

Line [redacted]

The form fill sealer was observed in use during the inspection. The line had a pin hole detector on the foil feed which was challenged at start and end of filling run. The filling line was dose checked during set up of the line. This employed the use of a balance that was connected to [redacted] The filled blisters travelled onto the freeze tunnel which quickly reduced the temperature of the product. The freeze tunnel had multiple temperature sensors on the length of the tunnel. The tunnel was cleaned post use with a jet washer.

One freezer unit was one fill of the freeze dryer and between [redacted] sub loads make up one batch. Once the cycle was complete, the sub batches were unloaded and placed into a dry store cabinet.

There was a post lyophilisation inspection of the filled blisters, typically 1 tray per load was 100% checked. QC sampling was performed across the batch to ensure homogeneity of the batch.

Line [redacted] was also observed during the inspection which was filling [redacted] batch number [redacted]. It was found to be acceptable.

Line [redacted] (development/clinical line)

Line [redacted] was contained in a separate area from the commercial lines and was operated by a separate team of manufacturing staff. Dispensing for line [redacted] was performed on the Line [redacted] dispensary and then transferred to Line [redacted] The mixing room contained an [redacted] mixer which was awaiting cleaning the time of inspection. Line [redacted] had a dedicated [redacted] for [redacted] due to low PDE limits. The [redacted] were cleaned straight after use as dirty hold times weren't validated for clinical products. Clean hold times were validated. All contact parts were dedicated for early phase clinical products and were etched with a code and stored in a sub room. As clinical products were scaled up, cleaning validation was performed before transferring into the commercial lines. The form filling room was adjacent to the mixing room. The operations screen for the line displayed an error message which implied data would be overwritten due to an error in a file path. This was explored further during the inspection and was rectified by the engineering team.

Line [redacted]

Line [redacted] was in a separate area with extra containment for the filling of pollens and allergen type products. The process in this area was manual compared to other areas within the manufacturing facility due to the small-scale nature of the products.

Washroom for Line [redacted]

[redacted] were cleaned manually with water using a high-pressure hose. One product; [redacted] used dedicated [redacted] at the request of [redacted]

[redacted] Sachet room

The room was used to sachet pack (secondary packaging) the blister for one product that was filled into PVC blister. The sachet machine printed the variable data which was challenged at start up and completion of packaging.

Line Clearance

Procedure [redacted] ver. [redacted] described the procedure for the clearance of manufacturing lines. Staff wore a blue waistcoat and placed a floor sign in the area to ensure they were not disturbed during line clearance. The line clearance checker was a different employee than those involved in the room cleaning. The start of batch line clearance ensured nothing was present in the room from the previous manufacture as well as a checked on the cleanliness of the equipment and room. There was also a quality line clearance audit performed by a separate quality function. Procedures for each specific line contained pictures and diagrams of notable hard to clean areas with specific guidance such as the use of a torch.

C9 Quality Control

Out of Specification

The procedure was described in [redacted] ver. [redacted] The Sop was found to be satisfactory. The procedure covered OOS/OOT and ATR and excluded multi-tier tests of the pharmacopoeias, R&D, method development, and microbiology (covered by SOP [redacted] and stability stress/accelerated studies where result is expected. Investigations were generally completed with 30 days of initiation. The [redacted] test was used to determine outliers.

Several investigations were chosen to review during the inspection.

[redacted] was raised for low Repeatability result (Analyst [redacted]), validation of Assay / Degradation of [redacted] method [redacted] Raised 16Nov18 and closed 20Dec18. The root cause was assigned as inadequate oversight/supervision.

[redacted] was raised form OOS Disintegration for [redacted] at 20 seconds for an expected disintegration time of 3-4 seconds. The investigation concluded that there were pinholes in the base foil which led to ingress of water. The batches were developmental and therefore non GMP packaging materials were used. A further OOS investigation [redacted] for OOS dissolution at 49% identified the same root cause. The site introduced a 100% visual inspection before QC analysis which identified blisters that contained pinholes and therefore not used for analysis.

[redacted] was raised for the Low recoveries for accuracy samples in [redacted] The investigation was opened on the 11 Dec 2019 and closed on 23Jan20. The root cause was assigned as being human error which concluded with a HR investigation as the employee had a pattern of not following instructions. An extensive investigation was performed which ensured there was no detrimental impact to other analysis performed.

[redacted] was raised for high OOS impurities obtained for [redacted] stability studies [redacted]. The OOS was raised 31 Aug 2018 and closed 12Jun19. The extended timeframe provided sufficient time for a full investigation of the root cause. Diode array analysis was performed, and the peak was found to be an excipient. A CAPA was implemented to prevent misidentification of the peak in future analysis.

[redacted] was raised for an OOS result for Stability on Marketing Samples [redacted] The report was opened 18 Mar 2019 and closed 16 May 2019. The water content at 24 months was

found to be OOS for one sample with a result of 12.04%. The investigation was thorough, and the root cause was assigned as being possible air in the [redacted] apparatus.

[redacted] was raised for [redacted] with a result above the action limit of 100cfu/ml. The investigation revealed that engineering works were performed on the water system prior to sampling which was thought to have dislodged a biofilm within the system. The engineering works was for the investigation of possible dead legs and non-turbulent flow within the system.

Laboratory

The laboratory was clean, modern and contained a large array of laboratory equipment. Samples were received and booked into the laboratory then assigned to an analyst. Chemicals were always controlled by a [redacted] system to ensure sufficient stock. Expiries were assigned as per the supplier's guidance or as per inhouse SOP. Reference standards were controlled by an assigned trained analyst. Primary and secondary standards were used depending on the customer requirements. EP/BP standards were checked monthly for validity of the lot. The reference standard for [redacted] was inspected against the customers supplied certificate of analysis and was found to be satisfactory.

[redacted] was being rolled out across the laboratory at the time of inspection. The site was using [redacted] and therefore the change of software was a major change for the laboratory in terms of relevant experience. The roll out was being supervised by a Catalent corporate team and therefore the support required by the site was available.

Analysis was written up into dedicated and uniquely identified hardbacked laboratory notebooks. A lab notebook was reviewed during the inspection for the finished product analysis of [redacted] and was found to be satisfactory.

Stability

The site had a range of stability cabinets; walk ins at 25/60 and 30/65 with reach-ins at 2-8°C and 40/75. Stabilities were set down by the QC team after creation of a protocol. Extra samples were taken if the stability study was part of a process validation. Ad hoc stability studies were performed for batch specific variation submissions. Samples were labelled with the timepoint once pulled and before sending to the laboratory for analysis.

A position paper, [redacted] was written by the site justifying stability trials in their primary packaging as opposed to the market pack as required by ICHQ1A (R2) 2.2.4. The site followed the Technical Agreement requirements for stability trials however, they wrote the paper to justify their actions.

[redacted] Laboratory

The [redacted] laboratory used to operate as a separate business entity, [redacted] (site number [redacted] but was amalgamated back into the Catalent Zydus business in 2018. The laboratory was dedicated to development (non GMP) work however some GMP work was performed in the laboratory such as method validation and registration stability studies. All non GMP work was clearly marked with yellow tape, however GMP standards were set across the laboratory as analysts worked in both areas. The laboratory was large, modern and well equipped.

Microbiology QC

The microbiology QC lab was responsible for testing of raw materials, finished products and site water systems. Most media used was purchased ready to use, however stocks of dehydrated

media were maintained as a backup and for some less frequently used media types and diluents such as peptone buffer and sterile water. Growth promotion was conducted on each delivery of each media used and this was performed using in-house prepared serial dilutions of the standard organisms. Two autoclaves were available, with cycles validated for smaller and larger volumes of media, plus a cycle for processing the manifold used for water testing. The autoclaves were air displacement design therefore were not appropriate for sterilisation of wrapped materials such as the manifold for water testing. A deficiency was not raised as there was no specific risk to product.

Environmental monitoring was also conducted in the manufacturing areas, using active air samples and contact plates on a monthly basis for each area. An in-house study of incubation conditions had been performed and had concluded using statistical analysis that [redacted] gave the best overall recovery of moulds from the facility.

All recoveries from product and raw materials were subject to identification, the extent of which was subject to a risk-based approach decision tree. Capability for Gram staining and use of purchased biochemical identification test kits was available in-house, with two contract laboratories available for identification by Maldi-TOF and nucleic acid sequencing if required.

The laboratory had replaced water baths for holding molten agar with metal bead baths. The temperature of the molten agar was not specifically measured prior to use for pour-plate analysis; however, a protocol had been followed to determine the appropriate duration between melting the agar in the boiling water bath and holding in the metal bead bath. The times determined had been included in the respective SOP.

SOP [redacted] ver. [redacted] described the procedure for Identification of Microorganisms. The procedure described the process for identification of any growth within a finished product, in process material or raw material. Environmental recoveries were identified if above the alert or action limits. Purified water system recoveries were identified if above the action limit.

C10 Outsourced Activities

[redacted] was described in SOP [redacted] ver. [redacted] The SOP was linked to the global procedure [redacted] Assessment of potential suppliers or changes to existing suppliers was managed through the change control procedure. Auditors were required to attend an auditor training course before performing a supplier audit under supervision. The type of audit was dependent on risk; high risk suppliers required a physical audit whereas low risk suppliers required a questionnaire and desktop audit. The quality manager and qualified person were responsible for closing out the audit report.

The audit of [redacted] for [redacted] was reviewed during the inspection. The audit was contracted to [redacted] The agreement and audit documentation were reviewed and found to be satisfactory. [redacted] were then added to the approved supplier security protected worksheet [redacted]

Supplier Complaint process was described in SOP [redacted] ver. [redacted]

Procedure [redacted] ver. [redacted] described the process for [redacted] The SOP was detailed in the requirements of a technical agreement and included a section on the requirements if a supplier insisted on using their own template.

C11 Complaints and Product Recall

Complaints SOP [redacted] Version [redacted] was generally comprehensive, and no specific issues were raised. Several complaint investigation reports were selected for review:

- [redacted] (Minor). Empty pockets (no sample received back).
- [redacted] (Major). Multiple empty blisters, including five total complaints for the batch and samples returned. A detailed investigation was performed, and an unusual causal chain was identified, with appropriate corrective actions implemented. It was however noted that the investigation report did not include consideration of whether a recall may have been necessary, for example the risk of a patient not having the medicine available.
- [redacted] (Minor). Pen marks on blisters.
- [redacted] (Major). Labelling error.

Recall SOP [redacted] Version [redacted] appropriately described the process required, taking into consideration that the site was not responsible for any finished medicinal products being certified and released to the market. A recall had been conducted in 2019 [redacted] reference [redacted] however this had been communicated to the previous site inspector and the report was provided at that time so this was not reviewed in any more detail during this inspection, apart from a review of the corrective actions, which were in control.

A mock recall was conducted in October 2018 and several issues were identified by the site regarding the out of hours capabilities. Appropriate actions were implemented and a follow up was performed in 2019.

C12 Self Inspection

A comprehensive self-inspection programme was in place, with evidence seen of good compliance to the intended schedule. In addition to specific areas being reviewed on a rolling 24-month cycle, four more details process audits were included for manufacturing (four times in 24 months), engineering (twice in 24 months), analytical (once in 24 months) and development (once in 24 months).

C13 Distribution and shipment (including WDA activities if relevant)

Procedure [redacted] ver. [redacted] related to Customer Specific Shipping Requirements. All materials were shipped in their primary packaging to client's site as was directed in the technical agreements. The product was shipped Ex works and under controlled temperatures. Despite this being the company's stated position, they were reminded that the MIA holder still has responsibility for ensuring products are shipped under appropriate conditions

The specification for shipping of [redacted] materials was reviewed and fund to describe all the requirements of the procedure.

The shipping paperwork for an [redacted] product shipment to Spain was reviewed and a few discrepancies was found. The specification from [redacted] stated that all shipments between May 1st and 30th September should be shipped under controlled conditions with data loggers. Outside this period, products were shipped noncontrolled. An October shipment to the client site in Spain was reviewed. The shipment was collected 11Oct19 and arrived in Alcobendas, Spain on the 13 Oct 2019. On the 11/12/13 Oct 2019, temperature according to [redacted] website was 25-28'C and therefore exceeded the specification storage condition of 20C° +/- 5°C. However, the site did not follow the client specification and shipped the product under controlled conditions with [redacted] as the weather forecast was checked by the site prior to arranging the shipment.

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

None

C15 Annexes attached

Annex 1 site risk rating

Section D List of Deficiencies

1. CRITICAL

None

2. MAJOR

2.1 **Technical and organisational measures to prevent contamination and cross contamination were deficient in that:**

2.1.1 Procedures for manual cleaning processes were not sufficiently clear to ensure consistency of the activities.

2.1.2 Records of routine manual cleaning of equipment comprised only a single signature to confirm that the cleaning method had been followed and did not include more detailed records of completion for significant steps in the process to ensure consistency with the validated state.

2.1.3 HBEL / PDE assessment reports were not all sufficiently detailed to support the reported values and conclusions. For example, the report for [redacted] did not include any justifications for the safety factors used in the calculations nor any supporting information relating to the toxicologist's qualifications or experience.

2.1.4 There was no consideration of potential contra-indications of the products handled on shared equipment.

2.1.5 Cleaning verification after each product campaign had not been considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products with low PDE values.

2.1.6 An example was observed where two mixing vessels ([redacted] and [redacted]) were deemed equivalent for revalidation purposes despite CIP cycle parameters differing between the vessels.

2.1.7 A purified water hose in the wash bay was not stored appropriately in that it remained connected to the supply and was not free-draining.

EU GMP C3.37, C3.38, C4.3, C4.8, C5.20, C5.21 Organisational Measures EMA/ CHMP/ CVMP/ SWP/169430/2012

3. OTHER

3.1 **Management of incoming materials was deficient as evidenced by but not limited to:**

3.1.2 Some APIs were received with no temperature control or monitoring and were accepted based on identification testing and the manufacturer's certificate of analysis. There was no supporting risk assessment or justification for this.

3.1.3 There was no formal requirement to confirm that materials had been received in an appropriate vehicle (e.g. hard-sided vs curtain sided) as applicable.

3.1.4 The number of individual samples which may be blended to form a composite sample had not been defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.

EU GMP C5.27, C5.28, A8.4

3.2 Complaint investigation [redacted] did not include consideration of patient impact of not having access to the product and due to the empty blisters and whether the implicated batch should have been subject to recall.

EU GMP C8.9(v)

4. COMMENT

4.1 It was discussed that stability studies were performed as per Technical Agreements with clients however the position paper on the use of primary packaged [redacted] drug product in stability studies did not take into account the requirements of ICH Q1 (R2) section 2.2.4 in that secondary packaging and container labels should be included as appropriate for finished product stability trials.

Section E Site Oversight Mechanism

Site referred or to be monitored by:	Tick (✓)	Referral date	Summary of basis for action
Risk Based Inspection Programme	✓		
Compliance Management Team			
Inspection Action Group			

Section F Summary and Evaluation

F1 Closing Meeting

The responses were communicated to the site and verbally accepted by all those present (see section B3 for list of persons).

F2 Assessment of response(s) to inspection report

The initial responses provided on 19 Mar 20 and after one round of requests, the final responses were received on the 31 Mar 2020 and were accepted by the inspectors.

F3 Documents or Samples taken

None

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

Based on the information provided, facilities observed, and commitments made after the inspection, the site is considered to operate in general compliance with the requirements of:

Compliance statement	Tick all statements that apply
Directive 2001/83/EC, Directive(s) 2003/94/EC and 2011/62/EU	✓
GMP as required by HMR 2012 (as amended)	
Directive 2001/20/EC	✓
Directive 2001/82/EC	
Article 84 and Article 85b(3) of Directive 2001/83/EC (GDP) and 2011/62/EU	

and is acceptable for the products in question.

Name of Inspector (s):

Lead Inspector: [redacted] **Date:** 21/04/2020

Accompanying Inspector: [redacted] **Date:** 21/04/2020

Annex 1

GMP Site Risk Rating

(a). Inspection Findings

Critical deficiencies this inspection:	0	Last inspection:	0
Major deficiencies this inspection:	1	Last inspection:	0
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.		

(c). Risk Assessment Inputs – discriminatory factors (✓applicable box)

[redacted]	None relevant (default)
	Significant concern over robustness of quality system to retain adequate control
	Significant failures to complete actions to close previous deficiencies raised at the last inspection
	Complex site
	Significant changes reported in Compliance Report
	Significant mitigating factors applied by the site
	Higher risk rating identified by other GxP and considered relevant to the GMP site
	Relevant site cause recalls, notifications to DMRC or rapid alerts since last inspection
	Nature of batch specific variations submitted since the last inspection give concern over the level of control
	Regulatory action related to the site
	Failure to submit interim update and/or failure to notify MHRA of significant change or slippage in commitments from post inspection action plan
	First Inspection by MHRA (does not require countersignature for RR II)
	Other discriminatory factor (record details and justify below)

(

[redacted]

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

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (✓)
0	Immediate (as soon as practicable)	[redacted]
I	6 monthly	
II	12 months	
III	24 months	
IV	30 months	
V	30 months with 50% reduction in duration of the next inspection	

(f). Basis for risk-based acceptance of specific matters arising during the inspection

[redacted]

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

[redacted]

(h). Conclusions

[redacted]

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

[redacted]

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

Risk Rating:	Next Inspection target date:
[redacted]	

Notes regarding re-inspection and GMP certificate validity

1. The inspection schedule is based upon risk and resource. This date may change at any time due to factors not pertaining to your site.
2. The GMP certificate does not 'expire' it is provisionally assigned 3-year validity date. For external questions regarding your validity thereafter; please advise that this can be confirmed by contacting the inspectorate at gmpinspectorate@mhra.gov.uk