HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

GMP INSPECTION REPORT

Report Reference No:	19373
Inspected Site(s):	Hovione Limited Loughbeg Ringaskiddy Co. Cork Ireland
Activities Carried Out:	Manufacture and Importation of Active Pharmaceutical Ingredients, Manufacture of Drug Product Intermediate Manufacture of Excipients
Inspection Date(s):	22/01/18 to 26/01/18
Inspector(s):	Richard O'Sullivan Catherine Neary
References:	M11208 IMP11207 ASR11447

Introduction

Hovione Limited (HE) was a contract manufacturing organisation, located on a large scale commercial manufacturing site (area of 115,461m2) which had been acquired from Pfizer in April 2009. The company's headquarters were located in Lisbon, Portugal, which also operated as a manufacturing site and another manufacturing site was located in Macau, China.

Date of Previous Inspection

11th – 15th May 2015

Inspectors on Previous Inspection

Catherine Neary & Alfred Hunt

Major Changes since Previous Inspection

- Installation of new processing equipment
    - Reactor Vessels: RE-01-10-1000, RE-10-12-1000,
    - Ultrafiltration Skid FT-01-112-1000
- Installation of new tank farm solvent tanks: TK21-02, TK21-08, TK21-22, TK21-04
- Commenced recommission activity of Building B02 (Ongoing at time of inspection)

Brief Report of the Inspection Activities Undertaken:

Scope of Inspection:

The objective of this inspection was to determine compliance of manufacture activities with Part 1 and Part 2 of the EU GMP guide.

Inspected Area(s):

Pharmaceutical Quality System
- Implementation of CAPAs for last inspection,
- Product Quality Reviews (PQRs),
- Deviation Management,
- Change Control,
- Quality Risk Management,
- Returns,

Personnel
- Personnel Hygiene,
- Training,

Premises and Equipment
- Drug Product Intermediate Manufacture,
- Active Pharmaceutical Ingredient Manufacture,
- Warehouse Operations,
- Equipment Qualification,
- Equipment Introduction, Calibration and Maintenance System,

Documentation

Production
- Batch Record Review,
- Supplier Qualification,
- New Product Introduction,
- Cleaning Processes,

Quality Control
- QC Laboratory Inspection,
- Laboratory Investigations,

Outsourced Activities

Complaints, Quality Defects and Product Recalls,
- Complaints,
- Quality Defects,
- Recall,

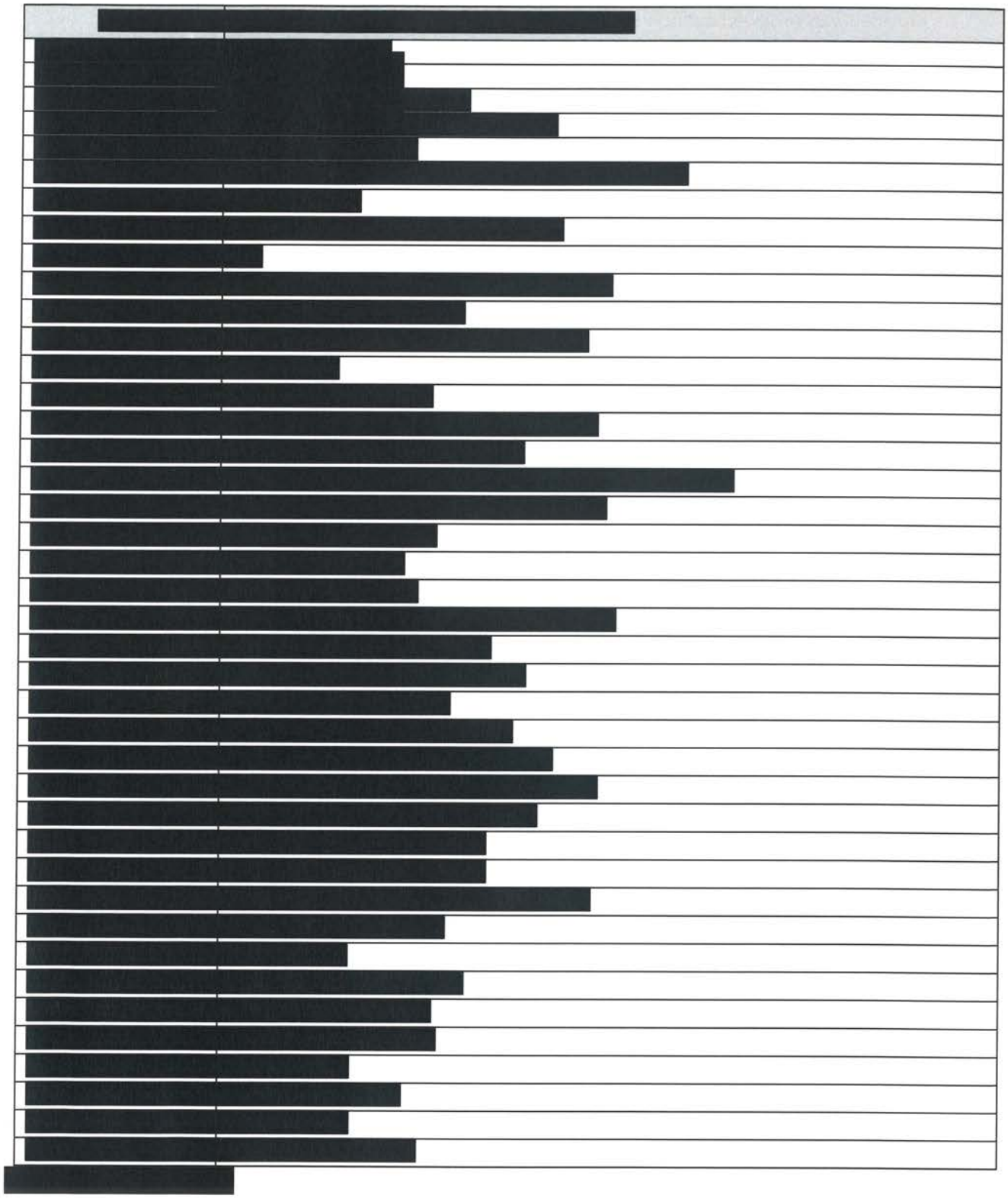
Self Inspection

Activities not Inspected

Process Validation

- A detailed review of process validation activities was not performed as part of this inspection.

Personnel met during the Inspection:



Inspector's Findings and Observations:

Pharmaceutical Quality System

Implementation of CAPAs from previous inspections

Implementation of CAPAs related to the sites oversight and management of contracted service providers was reviewed during the inspection. A data integrity (DI) breach which concerned a contracted calibration service provider had been identified at the site in 2014, following which two inspections were conducted by the HPRA - a for-cause inspection on the 11th July 2014 (inspection reference 7876) and a follow-up inspection on the 22nd – 23rd April 2015 (inspection reference 8741). The for-cause inspection was triggered by a report from Hovione to the HPRA that calibration certificates had been issued for instruments, that were found not to exist at the site, and that calibration certificates had been issued for instruments which subsequent review of process control systems indicated had not been calibrated. The follow-up inspection included a review of the final outcome and CAPAs put in place in relation to the reported falsification of data and verification of the actions taken by the company to investigate and assess the impact of the non-compliance. During this inspection implementation of CAPAs from the April 2015 inspection were reviewed.

[redacted]

of this report (i.e. Deviation #52127).

A commitment had been provided in response to the April 2015 inspection that Delta V trends would be attached to calibration certificates for equipment connected to the Delta V system at the time of review. However, it was apparent that this was not the case for weighing scales installed in the warehouse and manufacturing areas (as evident from deviation #52127) and an action to incorporate a requirement for the printing of the Delta V trends for the weighing scales connected to the Delta V system, remained outstanding at the time of the inspection. The company stated that the earlier CAPA had not incorporated the weighing scales as this equipment had not been implicated in the previous DI breach investigated in 2014. The company also stated that only a small number of weighing scales were connected to the Delta V system (approx. 10 out of ~53 in total).

The risk assessment conducted on the calibration procedure to identify and mitigate against risks of falsification in response to the HPRA inspection in April 2015 had excluded calibration service providers related to weighing scales (& other equipment) without appropriate justification. It was observed that the risk assessment conducted was not 'formal' in the sense that no standard process/format/risk

[redacted]

reasons; e.g. weighing scales were verified by production pre-use, total organic carbon (TOC) weekly checks carried out by QC on the water quality, no issues detected to date with the vendors.

These were identified as deficiencies and were cited as part of a major deficiency related to deviation management at the site. Additional details are included in the section on *Deviation Management*.

The calibration procedure, HE.DQ.SOP169.3.EN, effective 09.10.2015 was reviewed. According to its scope, the procedure was applicable to instruments installed at Hovione that were used for cGMP manufacturing. Analytical instruments/equipment was not within the scope. Under the section related to calibration records a requirement for a copy of the trend from the Delta V (or OSI PI) to accompany

the calibration record where trending was available, was included. Where trending of data was not available on Delta V, the procedure called for at least five calibrations each month to be repeated (carried out by a different technician) as an exercise in oversight of calibrations integrity. A risk based approach was required when selecting instruments that were to be re-checked which included consideration of the criticality of the instruments to be calibrated.

Calibration records with the accompanying Delta V trend were reviewed – i.e. temperature transmitter, TT-01-14-6520, 23.01.2017, with Delta V printout attached; flow transmitter, FT-0100166550, 23.06.2016, with Delta V printout attached; level transmitter, LIT-0100076561, 21.12.2015, with Delta V printout attached.

Records for the random independent repeat calibration checks on equipment not on the Delta V system were reviewed – i.e. differential pressure indicator, DPI-01-22-1682, 22.03.2017; temperature transmitter, TT-23-00-6521, 06.07.2016; differential pressure indicator, DPI-01-22-6515, 13.04.2016.

The calibration requirements for the production and warehouse weighing instruments, were captured in a separate procedure entitled 'Management of Production and Warehouse Weighing Instruments', SOP HE.DQ.SOP168.5.EN, effective 17.02.2017. There were no provisions in this procedure for oversight of calibrations integrity by the sites management. It was acknowledged that the sites management had executed due diligence in conducting the checks against the Delta V trends in September 2016 which had led to the identification of the DI breach.

It had been noted during the April 2015 inspection that the primary record for recording temperature and humidity in B10 production areas was a manual record made by operators in areas where humidity sensitive products were being handled. A point to note had been included in the inspection report at that time that consideration should be given to providing temperature and humidity monitors with records and alarm functions in areas where products sensitive to humidity were being processed. It had been noted at that time that there was a project to allow monitoring of the temperature and humidity via the Delta V system. The company's response to the point raised was that the action was being implemented and tracked through a site project and was being controlled through the site change control system (PdA No. 6519). Follow up in this regard was requested during this inspection and it was found that the action had not been implemented. PdA 6519 which related to the B10 SDD BMS proposal to connect to Delta V for the purpose of monitoring trends, alarms and events related to environmental parameters of B10 rooms had been cancelled on the 11.05.2016. The reason for cancellation was that all the BMS relevant GMP data was being recorded manually as per RF1117 and following the Delta V upgrade, the requirements of the change control had changed due to new technologies available. The closure of this change control was not considered justified and the required open action was not documented under any other aspect of the sites quality system and this was highlighted as a deficiency. It was stated that the action would be progressed as part of the 2016 – 2020 automation upgrade plan for the site.

Product Quality Reviews (PQRs)/ Annual Reviews (ARs)

An overview of the PQR process was provided. PQRs were required to be approved by the Quality Manager within 3 months of the review period. It was stated that due to business demands and to ensure a timely review of PQRs that the company had implemented a change to the PQR process. Prior to 2017 the review period for all PQRs was the fiscal year (April 1st – March 31st). However this has since changed since the last inspection, in that the review period for PQRs will be staggered to

assist in timely completion. The requirement for the approval of PQRs within three months of the review period was maintained.

[redacted]

A deficiency was cited with respect to the content of PQR HE.QSR.AR221.1.EN as the analytical data review did not allow for an accurate assessment of the control status of the process. While the content validation and conclusion sections were not considered an accurate reflection of the control status of the validated process as they conflicted with the detail of event 49360.

[redacted]

comment/assessment was made in the PQR with respect to this OOT result. A deficiency is cited relating to this also.

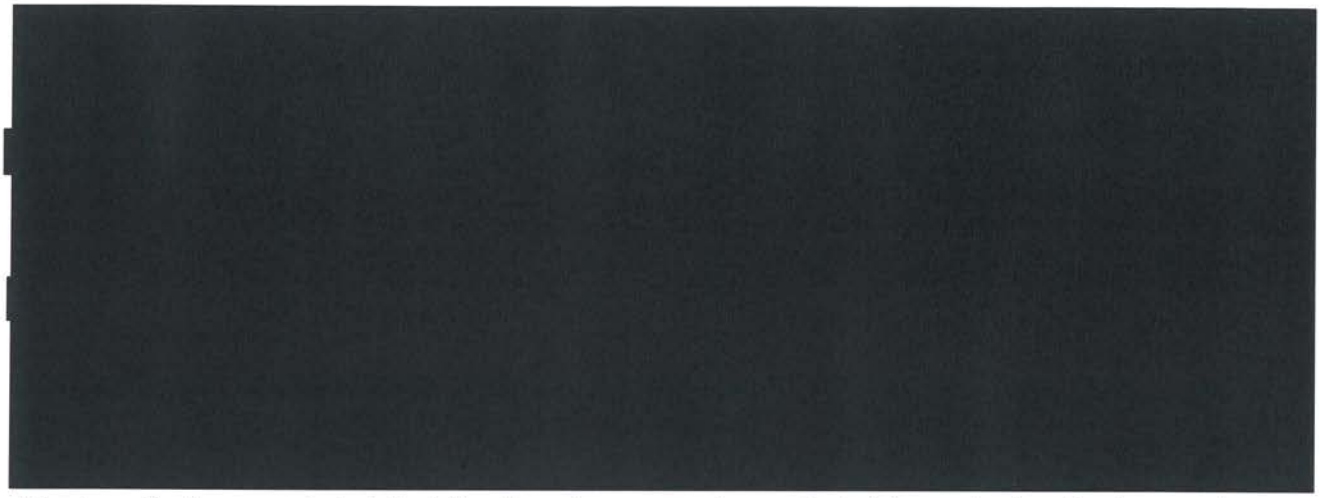
Deviation Management

A bespoke electronic system referred to as the "CAPA" system was implemented for deviation and CAPA management.

The listing of deviations raised in the period since the last HPRA inspection in May 2015 was reviewed as were records related to the following deviations - #63217, #62943, #62941, #62802, #62028, #61941, #59703, #52127, #48187 and #43143.

It was noted from the listing that a number of deviations related to 'as found' instrument calibration failures had been raised in the period, in particular during December 2017. The company was asked if there was any on-going open investigation in this regard and if any DI breaches had been identified in 2017. It was clarified by the company that no DI related issues had been identified in this period.

A major deficiency was cited in relation to deviation investigations, associated records and CAPAs.



The investigation concluded that the breach concerned one technician only; for the impacted calibrations identified, calibration had been carried out on the dates specified but not using all of the required weights across the range. Results had been recorded on the certificates for specific weights which had not been physically placed on the scales according to the Delta V trends. [redacted] no longer worked for [redacted] had last attended the Hovione site on the 29th September 2016, as verified from records generated from the site's 'CORE' system, which tracked the movement of personnel on the site.

A copy of a letter from the UK Weighing Federation dated 14.11.2016 included in the deviation records included a statement indicating that it had 'no hesitation in recommending' [redacted] and that the issues encountered were down to an individual member of staff failing to carry out instructions.

As the Delta V trends related to the earlier calibrations conducted in March 2016 had not been reviewed until September 2016, the company was asked to clarify if this requirement had been implemented in the quality system as committed to following the April 2015 inspection. The company stated that the CAPA agreed to, back in 2015, regarding the printing of the Delta V trends to accompany the calibration certificates had not been routinely implemented for weighing scales, as this equipment had been out of scope of the duties performed by the previous service provider involved in the DI issue in 2014. It appeared that only the equipment calibrated by the previous service provider had been included in the scope of the CAPAs and not all equipment calibrated by other service providers. A number of deficiencies were identified related to this investigation. No formal risk assessment had been conducted; the listing of weighing scales equipment within the scope of the deviation had not been recorded or attached; the Delta V trends related to the March 2016 calibrations were not reviewed until September 2016; the risk assessment conducted on the calibration procedure to identify and mitigate against risks of falsification in response to the HPRA inspection in April 2015 had excluded calibration service providers related to weighing scales (& other equipment) without appropriate justification. It was also

observed that the risk assessment which had been conducted was not 'formal' in the sense that no standard process/format/risk management tools had been executed; an action to incorporate a requirement for the printing of the Delta V trends for the weighing scales connected to this system had not been identified as part of this investigation, the action had been identified in December 2017 and its implementation remained outstanding at the time of the inspection.

In relation to deviation #61941 raised in September 2017 which concerned foreign matter contamination of API originating from tie wraps, the lengthy timeframe of the 17 February 2018 proposed for completion of CAPA #61264 to implement a reconciliation document for full tie wraps to be accounted for was not considered justified. In addition, guidance related to criteria to be used in proposing CAPA completion dates was not provided for under the quality system. These were identified as deficiencies.

Deviation #62028 raised on the 02.11.2017 related to re-swabbing of IBCs for [redacted] due to interference in the blank swab prior to analysis of the original swab samples. The minimal quality impact concluded as a result of test results from repeat swabs was not considered justified as the re-swabs may not have accurately reflected the state of cleanliness of the equipment, as the initial swabs may have removed any residues present. This was identified as a deficiency.

Deviation #62802 was raised on the 02.12.2017 related to a flow meter (FIT 10-22-6542; [redacted] It was stated that the calibration errors were observed only at volumes below 3000 litres and therefore did not impact on the routine operations; however, no calibration checks above 3000 litres had been conducted. The CAPA required a work order (WO) to be raised for re-calibration up to a maximum of 12,000 litres before the 2nd March 2018. This approach was not considered justified, it was not known why calibration volumes were not reflective of routine operations and when discovered, why calibration at the routine volume had not been verified. This was identified as a deficiency.

Deviation #62941 raised on the 07.12.2017 related to a weighing scales (WIT 01-0067_6602) in B01 which had failed its 'as found' 6-month calibration test. The calibration had been done by a technician from [redacted] t had failed at 50Kg, 100Kg, 150Kg & 200Kg and was found to be within specification limits in the 0 -20Kg range. It was adjusted to within limits with the most probable root cause recorded as 'error due to drift'. No product quality impact had been concluded based on the requirement for pre-use verification checks to be conducted on all weighing scales.

Deviation #62943 raised on the 07.12.2017 related to an incorrect user login on pH Meter PH10, in the QC laboratory. An analyst had performed the test whilst another user was still logged onto the instrument and this had been identified from the data printout. [redacted] No immediate action for correction of the raw data printout was recorded or implemented and the preventative action proposed to put in place more visual signage in the location of pH meters was not considered a robust solution as signage had previously been in place and had proven not to be effective and this was identified as a deficiency.

Deviation #63217 raised on the 14.12.2017 related to a differential pressure instrument (DPI) in B10 (DPI 10-0075-8001) which had failed its 'as found' calibration test. It had been adjusted to within calibration 'as left'. This instrument was classified as non-critical and had no previous calibration failures identified; it measured the differential pressure across an F9 bag filter (FT6491) on AHU 10-75-1000; it was stated that the bag filter was also fitted with a differential pressure switch which alarmed on the BMS system if the filter became blocked. The records indicated that this AHU served non-GMP areas. As a CAPA an action plan (event #63565) was raised to assess all DPIs in B10 with the intent of any identified as having

a quality impact to be classified as 'C1' and to require calibration after each change of line; all others were to be classified as 'C3' and were to remain on the current annual schedule. [redacted]

The deviation procedure, SOP HQ.CCO.COP014.11.EP dated 21.11.2016 was reviewed. The company stated that this procedure was under review at the time of the inspection and that a number of improvements had been identified internally and would be included in the updated revision.

There were no planned deviations, all changes were handled under the site change control procedures. Reference was made in the procedure to 'Quality Incidents' which were governed under a separate procedure. It was noted that the procedure permitted deviation records to be raised within two working days from the date of occurrence; the company was informed that the deviation should be recorded at the time of occurrence and within one working day and that this point should be addressed in its procedure update which was underway at the time of inspection. The procedure indicated that quality related deviations were required to be closed by the QA Unit except for QC related non-critical deviations which may be closed by the QC Unit. When this was queried, the company stated that the site did not avail of this option, which was allowed under the corporate quality system.

The procedure governing incidents, SOP HE.QC.IOP101.1.EN dated 22.12.2017 was briefly reviewed. It was stated that QC at the site did not raise QC incidents as permitted by the procedure and that deviations were raised instead.

Change Control:

Change Control (CC) procedure HQ.CCO.COP027.7.EN was reviewed as part of this inspection. Changes were classed as minor or major. Description of the following types of changes were detailed: Changes to procedures involving GMP and HSE, Other business changes, Changes triggered by CAPA, Emergency changes, Temporary changes.

Changes were required to be handled in the following stages:

- Phase 1: Description of Change,
- Phase 2: Impact assessment of Change,
- Phase 3: Implementation Plan Proposal,
- Phase 4: Decision on Change Request Implementation,
- Phase 5 Evaluation after implementation
- Phase 6: CC closure

The change control procedure made reference to the use of formalised quality risk management tools to assess complex changes.

The following CC records were reviewed as part of this inspection:

- CC#7873: Introduction of [redacted] process at Hovione,
- CC#8196: [redacted] Installation changes required for Building 01 at Hovione Ireland,

Both change control records related to the introduction of [redacted] process at Hovione. An overview of both change records was provided on the change stream CC software. The CC records identified the need to perform Installation qualification and operational qualification of the [redacted] process equipment train. These records were reviewed and are discussed in the equipment qualification section of this report.

An overview of the Change Stream software using the above two CC records CC#7873 and CC#8196 was provided. In general the records reviewed were considered suitable. However, it was noted that no formal Quality Risk Management (QRM) processes were observed during review of CC records.

Quality Risk Management (QRM)

The procedure for Risk Management, COP047.2.EN was reviewed and was considered in general to be satisfactory. It indicated that the use of formal tools was not mandatory and there was no guidance regarding situations when formal tools should be implemented, e.g. critical deviations, quality defects, change management etc. In addition, requirements regarding the application of formal quality risk management tools to certain aspects of the quality system were not documented under the relevant system procedures, e.g. deviation management, change management, complaint management and this was highlighted as a deficiency.

Returns

[redacted]

The site had been inspected by the US FDA on two occasions since the last HPRA inspection in May 2015. The most recent inspection took place on the 18 - 22 December 2017; this was a general GMP inspection during which no 483 was issued. A pre-approval inspection by US FDA related to [redacted] took place on the 16 – 20 May 2016, during which some observations had been cited on a 483 form. This inspection was closed and the Establishment Inspection Report (EIR) had been received by the site on the 5th December 2016.

The site's B10 had been inspected by the Ministry of Industry and Trade of the Russian Federation on the 29 - 30 June 2017 following which a GMP Certificate had been issued (GMP-00358/17/IE). The certificate was issued with a 3-year validity included within its scope manufacturing of intermediate product, powder for further processing, packaging, chemical / physical testing and listed the inspected [redacted]

Personnel

Personnel Hygiene

In relation to personnel gowning and hygiene practices it was noted that there were no instructions under the quality system for personnel to use hand-washing facilities (e.g. prior to sampling and

dispensing operations and other operations conducted in clean rooms). Hand sanitiser dispensers were installed and in use. It was noted that hand washing facilities were not installed in the warehouse building and that the facilities installed in the B01 clean room personnel entry lobby had been disconnected from the water supply; the facilities were not labelled as out of use. In the personnel exit lobby of B01, the hand washing facilities remained connected to the water supply; these facilities were not used in practice according to the company personnel. Gowning requirements were not displayed in the personnel entry gowning lobby in B01 as indicated was a company requirement. It appeared that the SOP had recently been updated and the display version had not been issued. These were identified as deficiencies. The company initiated an investigation relating to the above findings during the inspection and presented a CAPA plan on the last day of the inspection.

Training

Training records for [redacted] were reviewed. The start date for this contractor was recorded on the 'CORE' system as the 17.02.2015. The person's status was verified as 'Inactive' on the CORE records which were presented, with the last date on site recorded as the 29.09.2016. The records included a 'Signed Declaration of Principles and Commitment' dated 17.02.2015 which included a section on quality including performance of work with integrity. It was understood from the discussions with the company that the contract service providers were required to undergo cGMP induction training prior to engaging in GMP related activities at the site. When requested, records of attendance at cGMP induction training or refresher cGMP training were not available for the concerned technician and this was identified as a deficiency. The company stated that the induction training record could not be located during the inspection and that it may have been removed from the persons file at some time during the investigation. Requirements related to provision of refresher cGMP training to relevant contractors was queried with the company and it stated that this requirement was implemented in December 2017. However, instructions related to this requirement were unclear as it could not be determined from the matrix presented, which modules were required for the contractors and at what frequency (i.e.COP007_A3.3EN), this was identified as a deficiency.

Premises and Equipment

Drug Product Intermediate Manufacture

Building B10:

Drug product intermediate production took place in building B10. The main operations which took place in B10 included; dispensing, excipient and API mixing, spray drying and secondary cone drying.

this tour and it was noted that additional gowning requirements were required in order to reduce the risk of; contamination to product and prevent cross contamination within B10.

Processing in building 10 was directed by the paper batch production record. A Delta V system was used to allow operator interface with processing equipment. Each floor had at least one Delta V control Panel, while in the control rooms activities could be monitored and controlled by operators also. It was noted that processing recipes were not utilised to control production. Instead operators manually inputted/adjusted process parameters as defined by the batch processing record. All Delta V processing data was stored on the Delta V historian. The Delta V system provided a trend report of this data which allowed for process engineers and quality to review the parameters under which a batch was manufactured. During review of the Delta V system it was noted that batch numbers were not recorded for batches. It was stated that the time stamps of the Delta V and the time entries recorded by operators in the batch processing record (BPR) allowed for traceability between the BPR and Delta V.

The following areas of Building 10 were visited during this inspection:

- Room 414: IBC Docking area for mixing tanks,
- Room 313: Mixing vessel/tanks room,
- Room 309: Cone Dryer (Mikato Plate Dryer room),
- Room 219: Bottom of Mixing vessels,
- Control Room,
- Room 116: Cone Dryer Discharge room/ Product pack off room,
- B10 Purified Water System

In general the premises and equipment observed during the site tour were considered suitable. However a number of issues were observed during the site tour, a description of which is detailed as an 'other deficiency' in the deficiency section of this report.

[redacted]

reflected activities described on the site tour. See the production section of this report for further information.

API Manufacturing

Building B01

The B01 API manufacturing facilities were installed across three floors – service floor, reactor floor and [redacted]

a blow with Nitrogen. Deficiencies were identified in the gowning facilities of the clean rooms and are described in the deficiency section of the report. The company initiated an investigation relating to the findings during the inspection and presented a CAPA plan on the last day of the inspection.

Delta V Automation System

It was apparent that a number of different versions of the Delta V system was installed throughout the building and across the site. Upgrade from version 8 to version 12 of the software had been completed in some areas and this updated version was supported by the service provider [redacted] Version 5 of the software was installed in certain areas of the facilities including the tank farm.

The data from the Delta V system was trended on the continuous historian and backed up. [redacted] ecipe driven processes and it was indicated that the site strategy was to use this mode when processes were sufficiently developed with appropriate supporting data.

The sites automation upgrade plans for the Delta V system were discussed and the company presented a copy of a presentation entitled 'HE Automation Upgrade Plan – executive summary 2016 – 2020' dated [redacted] systems upgrades. Key milestones included the update of the B01 Delta V from v8.4.1 to v8.4.2 in August [redacted] working on the upgrade of the B02 OCM Delta V at the time of the inspection under the March 2017 B02 "Bring back to life" and upgrade study and report.

In relation to the Delta V upgrade the following deficiencies were identified:-

- Corporate Automation Strategy – Annex A1 – Systems Inventory and Risk Assessment – (HQ.QSD.IMP059-A1.0.EN) was not current at the time of approval on the 03.12.2015 and was not subjected to periodic review (the versions of software to which it related were not indicated and not accurately reflected);
- The HE Automation Upgrade plan 2016 – 2020 was not documented under the quality system, e.g. no change control was captured in the quality system for phase 2 of the upgrade which was outstanding at the time of inspection;
- B01 Delta V automation system v8 to v12 migration performance qualification report (HE:QSR:EQ434.0.EN) did not include any records as evidence of what constituted the incident/deviation review actually executed in support of statements that no related incidents/deviations had been raised in the period.

Building B04:

[redacted] standards. Level 2H standards differed to Grade D clean room standards in that no microbiological room monitoring was performed. The company stated it took this approach as [redacted] with no microbiological specification. During the review of the of the Glatt dryer process it was noted that the personnel airlock for B04 was not operating correctly and a deficiency was cited relating to this.

Building B02– Construction Zone

[redacted] zone' at the time of inspection. The company anticipated that it would be ready to commence

production in mid-2018; the plan was to bring on-line approximately half of the capabilities of the [redacted]

Warehouse Operations:

SAP was installed for inventory management and material status control which included barcode scanning technology.

[redacted] was engaged as the pest control service provider and bait boxes and electric fly killers were evident in the areas inspected.

The Approved Supplier List (ASL) was maintained on the bespoke electronic MASQ supplier qualification system. There was an interface installed between this MASQ system and SAP, which provided controls related to purchase orders in that they could only be placed for approved materials from approved suppliers.

Warehouse personnel were responsible for sampling operations. All materials for use in B10 required all containers received to be sampled for identification purposes. In relation to the sampling booth, there was no requirement under the quality system to check that all gauges were reading in the green zone prior to conducting sampling operations and it was noted at the time of inspection that the supply HEPA filter gauge was reading in the red zone. This was identified as a deficiency. The company indicated that the gauge located external to the booth itself was required to be checked in advance of sampling operations; however, the significance of this check was not provided or explained at the time of inspection. Sampling activities were not observed in operation during the inspection.

The environmental conditions in the warehouse were not controlled; they were monitored. It was stated that temperature and humidity mapping studies had been completed by the service provider Hanley's and that the next 3-yearly study was imminent. Records related to temperature mapping were not reviewed during the inspection.

[redacted]

for monitoring of relative humidity levels in the storage areas. It was noted that batch HE00059 in the shipment preparation area at the time of the inspection had been manufactured in March 2016 so had been in storage at the site for almost 2 years. The company stated that a study had been performed in this regard, a copy of which was requested to be provided as a point requiring clarification in this report.

Processes related to the temperature monitoring of the cold stores were inspected and deficiencies were identified.

A locked caged area was installed for storage of 'reject and recalled' materials. Containers of [redacted] were present in this area and it was stated that the company was in discussion with the customer and awaited the disposal notification. It was stated that the material had been rejected due to burst bellows in B10.

Drum Store/Cold Chain Storage area:

The 'Drum Store' was a secondary warehouse area which housed the cold chain refrigerator FR-23-05-4000. The Drum store acted as an over flow storage area for the primary warehouse. Materials were required to be receipted to the site in the primary warehouse prior to being receipted in the drum store. Drum store materials were also required to be sent to the primary warehouse to undergo disposition from the site. The controls for the drums store were identical to the controls described for the primary warehouse (detailed above) and no issues were identified in the ambient areas of the drum store.

FR-23-05-4000 was entered during this inspection. At the time of the inspection FR-23-05-4000 was acting as the primary 2-8^{0}C storage location for [redacted] As with other warehouse locations the FR-23-05-4000 storage locations were each labelled with a SAP storage location which allowed traceability of the movement of materials. Two temperature probes were observed in the refrigerator for the monitoring of temperature conditions. The probes were connected to the Delta V system and alarmed to the warehouse office in the event of a temperature excursion. The company stated as well as Out of Specification alarms, control alarms were also set up on the alarm system to highlight to warehouse personnel if a the temperature was approaching 2-8^{0}C limits. The fridge temperature was maintained using a single Air handling unit.

A review of the latest temperature mapping study for FR-23-05-4000 (Protocol# HCS.18093.001.RT) was also performed as part of this inspection. The subject matter expert (SME) for this study stated that the probe locations in the fridge was based on the highest and lowest temperature locations identified over a 24Hour mapping period using in use conditions. The company stated that temperature mapping for the fridge on empty and capacity had been performed on initial qualification of the fridge. However, during the site tour it was noted that the max storage height for materials in the floor space of the refrigerator had was not defined for operators and no procedure stated the max storage height in the fridge. A deficiency was cited relating to this. During inspection of 17BB01 drums it was noted that several labels were found to be peeling. A deficiency was also cited relating to this.

Bulk Solvent Tank Farm:

The unloading of Ethanol Bulk Solvent lot HE000053 [redacted] was observed as part of this inspection. The process for the receipt and offloading of bulk solvents included:

- Certificate of analysis (CofA) for solvent, Certificate of cleaning for mobile tanker were checked.
- A one litre sample of material in the mobile vessel was taken.
- The CofA, Certificate of Cleaning and sample were sent to QC for testing and release.
- If all documentation and testing complied with requirements, QC performed an approval of the bulk solvent which allowed for the transfer of materials from mobile tank to bulk tank.
- Once approval was granted the warehouse operator used a dedicated ethanol transfer hose and recorded the mobile tanker number and bulk storage tank number between which the ethanol was being transferred.
- A second operator was required to inspect the setup of the transfer line and sign to verify the setup was correct.
- The transfer then proceeded using an overpressure of nitrogen to perform the transfer.

- Following transfer the bulk storage tank storage location on SAP quantities were updated to reflect the delivery of ethanol.

A review of Bulk Tanker unloading procedure form HE.WH.IOP037-A.10.EN was reviewed as part of the bulk solvent unloading overview. No issues were identified.

Since the last inspection Hovione had replaced 5 bulk storage tanks with like for like tanks. An inspection of one of these new tanks TK-21-02-1000 was performed. Each bulk storage tank was individually vented to atmosphere.

No issues were identified during review of Bulk solvent storage practices.

Equipment Qualification:

[redacted]

The user requirements specifications (URS) (HE. QSD.URS- 454) for the reactor vessel RE-01-12-1000 was reviewed The URS was detailed and clearly defined the required vessel characteristics. The company had generated 'trace matrix' HE.QSR.RE725.1EN which recorded a check that all URS requirements were achieved. The trace matrix referenced several reports which demonstrated that URS requirements were met.

[redacted]

reviewed. During commissioning of reactor 01-12-100, operators noted that baffles within the reactor vessel was 904 Stainless Steel (SS) instead of Hastelloy. Deviation 55909 was raised. The output of this

[redacted]

The Installation Qualification (IQ) report: HE.QSP.EQ026.7.EN for new direct impacting equipment RE-01-12-1000 was also reviewed. During review it was noted that the IQ acceptance criteria was not met. However, deviation 55944 was raised to investigate and assess the failed acceptance criteria. The IQ records reviewed were considered suitable.

The company segregated the equipment qualification for manual portions of the equipment and automated portions of the equipment. Equipment operational qualification (EOQ) was performed for automated portions of the equipment train. The EOQ for RE-01-12-1000 (HE.QSP.EQ1027-A4.1.EN) was reviewed. This EOQ included an operational qualification of temperature control and agitator speed. The following acceptance criteria were defined:

[redacted]

The content of EOQ HE.QSP.EQ1027-A4.1.EN was considered suitable.

Equipment Introduction, Calibration and Maintenance System:

SAP equipment maintenance module was in use at Hovione. Using RE-01-12-1000 as an example, an overview of the addition of new equipment to the SAP module and the creation of a preventative maintenance program was provided.

The maintenance department were alerted to new equipment as part of the change control process as a task. Each new piece of equipment was given a unique SAP identification number. Hastelloy reactor RE-01-12-1000 had been given unique SAP number 6052814. The SAP record for 6052814 was reviewed. The SAP record detailed the following:

- Equipment Manufacturer, Model number and Serial number,
- Activation date: November 2016,
- A list of associated SAP equipment IDs, which represented minor equipment associated with the reactor. For example 6029811 was a Level transmitter,
- The calibration frequency and location for 6029811 was also visible in the SAP records.

Procedure SOP169 detailed the process for generating calibration frequency of equipment. Items that were identified as process critical were required to be calibrated at least once per year. An overview of the preventative maintenance of Reactor Vessel RE-01-12-1000 and calibration frequency of Level transmitter 6029811 was reviewed on the SAP system. The reactor vessel required preventative maintenance (PM) annually, and the level transmitter required calibration annually also.

An overview of the PM for equipment 6022347 (Reactor 12 Pump) performed in February 2017 was provided. The SAP PM was executed in the following format:

- A list of equipment maintenance task was stored on the SAP system and associated to the equipment.
- SAP administrator and SAP planner scheduled the PM Work Order and issued the paper based Work Order (WO) task list to maintenance. For completion.
- The maintenance technician recorded paper based PM record and also recorded the completion of PM activities on the SAP system.
- Maintenance supervisor reviewed the paper WO and signed off the paper based to confirm the work was done appropriately.
- The completed WO was then sent to the SAP administrator who on receipt of a double signed paper based WO signs of the PM WO as completed on SAP.
- Paper based records were then archived in the document archive.

It was stated that Equipment calibration was handled in an identical way to PM.

As part of the SAP Maintenance system review an overview of the following processes was provided:

- The generation and maintenance of out of service equipment list.
- The raising and performance of non-routine work orders.
- Planning and Scheduling PM and calibration schedules (scheduled 6-8 weeks in advance).
- Control of equipment stock items (consumables such as o-rings/seals).

The control equipment maintenance and calibration activities were considered suitable.

Documentation

Documentation reviewed during the inspection included:

[redacted]

Production

Batch Record Review:

Batch records were referred to as 'Batch Production Records (BPRs)' at HE. BPRs at HE were manual entry records. Delta V trends were attached to the BPR. BPRs underwent review by a Production Engineer, QA representative and QP (for drug product intermediates). During the tour of Building B10

[redacted]

The following critical process parameters (CPPs) and in-process controls (IPCs) were established for

[redacted]

No issues were identified during review of the batch processing record.

Supplier Qualification

The bespoke electronic system "MASQ" was implemented for supplier qualification.

Records related to the qualification and approval of Globeweigh as a provider of calibration services for weighing scales were reviewed. Records reviewed included MASQ Record 5401 & MASQ Record 7445. Details noted included the following:-

- Scope of the services provided - calibration of scales (manufacturing & warehouse)
- Risk assessment ID:2134, % risk 61%, 18.07.2014

- Due diligence - authorised verifiers awarded contract to verify trade approved scales on behalf of NSAI
- Audit 05.09.2014
- Company had been providing satisfactory service on site for the past 5 years; good service history; qualified up until 02.03.2018
- 16.03.2017 request from quality & maintenance to block supplier due to DI issue as documented in deviation #52127; no longer to be used, CAPA 53668
- Audit trail record for blocked status on MASQ, 16.03.2017
- Quality Agreement (QA00074), July 2014
- Master Services Agreement MSA00087 – 28.06.16 - commercial agreement

Records related to the qualification and approval of [redacted] were reviewed. Records reviewed included MASQ Record 9528. Details noted included the following:-

- 26.05.2017, chosen by end user to replace [redacted]
- Calibration of scales (manufacturing and warehouse)
- Audit 18.05.2017
- Qualified 12.06.2017
- Training certificates for technicians
- Supplier Qualification Questionnaire completed
- Quality Agreement QA00182, 12 December 2017
- Master Services Agreement, MSA00169, 31 August 2017

The procedure for Contractor Management, SOP 176.1.EN, 12.12.2017, was reviewed. This required all contractors to be approved through the MASQ Supplier Approval System. On induction completion, the Hovione contact was required to sign the Access Authorization Form and to notify security of any additional access level requirements. Reference was made to the Hovione Contractor Management Logbook and a requirement for failure of the contractor to perform satisfactorily to be reported on the CAPA system and to site management.

The procedure for Supplier Qualification, SOP 105.6.EN 24.05.2016, was reviewed, was found to be comprehensive and was considered in general to be satisfactory. The scope included manufacturers and service providers, suppliers of raw materials, packaging materials, machinery, equipment, spare parts. It required a risk assessment of the material/service to be conducted. Four phases were outlined - selection, approval, qualification & monitoring. The approval stage required an audit as a prerequisite. The qualification stage required a Quality Agreement to put in place; continuous assessment & improvement requirements included Quality/HSE audits, key performance indicator (KPI) evaluation, supplier development. A validity date was required to be assigned which was inputted into the SAP Source List and this permitted Purchase Orders to be issued to that supplier for the specific material/service during the validity period. High risk materials required full supply chain to be known (e.g. APIs, calibration, outsourcing of analytical testing, HVAC testing). High risk services required their quality system to be accredited or a GMP certificate issued; reference was made to the Falsified Medicines Directive and the requirement for written confirmations. The frequency for routine audits was 3 years and could be brought forward; for suppliers listed in drug master files (DMFs) the recommended frequency was 1 year. A 5 year frequency was stated as acceptable for suppliers of materials other than API, e.g. starting materials for which there was evidence of good performance. The procedure also provided for supplier disqualification.

It was noted that there was no reference in the site quality system to the Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use (2015/C 95/02) and assessments were not available. A point to note is included in the report in this regard.

New Product Introduction (NPI)

The NPI procedure, SOP172-A1.4.EN, 24.03.2016, was reviewed and was considered in general to be satisfactory.

Process Validation

Process validation reports for the new APIs introduced to the site had not been approved at the time of the inspection and were not reviewed. The new APIs were [redacted]

Cleaning

A review of cleaning practices in Building B10 (Drug product intermediate manufacturing facility) was performed as part of this inspection. Matcon Intermediate Bulk Containers (IBCs) and cone valves were utilised during processing in building B10. A focused review of cleaning practices with respect to IBC/Cone valves was performed.

The company stated that they did not employ a matrixed cleaning approach based on worst case materials. Instead they performed cleaning assessment and calculated Maximum Allowable Carryover (MACO) Limits for each type of Product A and Product B combination. It was stated that equipment to be used was identified prior to commencing a campaign and as part of the equipment selection each piece of equipment was assessed for; the material it was used to manufacture, MACO levels calculated and cleaning verification performed.

During review of the cleaning at HE, the following documents were reviewed:

- TBALGERALHE.54: Cleaning matrix
- HE.TS.CAM00007.1.EN: Cleaning Assessment Memo for 19WG08A-50,
- RF822-18-01: Cleaning Assessment form post 19WG08A-50 campaign, pre 19PJ01A-25 campaign
- HE.CLD.VP1130-A54.1.EN Protocol to determine the sampling swabbing locations of process equipment annex – Annex A54

TBALGERALHE.54 detailed a list of all materials (raw materials, detergents) which came in contact with product contact surfaces of processing equipment. For each material the following was listed; Cleaning agent to be used, Cleaning verification agent, Analysis Technique for cleaning verification, Test Method number, Method Validation reference, Limit of Detection test method reference, Limit of Quantification test method reference, % Recovery report and the % recovery identified for product contact materials. During review of TBALGERALHE.54 it was noted that % recovery for 19WG08A had only been assessed for stainless steel surfaces. This was not considered suitable as during the site tour EPDM product contact surfaces were observed on IBC containers and Cone valves. No assessment of [redacted]rom EPDM services had been performed by the company. A deficiency was cited relating to this.

Cleaning Assessment Memo for [redacted] No issues were observed with this document.

During review of RF822-18-01 it was noted that four options were available for the calculation of MACO limits (daily therapeutic dose MACO, Observable Effect Limit (OEL) MACO, No OEL MACO, or [redacted] deficiency was cited as HE had failed to implement the requirements of *'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'* for any products/materials.

During review of HE.CLD.VP1130-A54.1.EN and discussions with the company the following was noted:

- No formalised risk assessment process was performed to identify the worst case swab locations of IBCs.
- The top of the IBC was selected as a swab location based on it 'being easy to reach', this was not considered suitable. The swab site selection assessment did not assess the material height in the IBC and did not assess if the area swabbed had come in contact with process materials.
- All swab locations were smooth stainless steel locations. The rationale for swabbing only the smooth stainless steel surface of the cone valve and not the ridged areas i.e between the EPDM and Stainless steel materials on the cone valve was not available.
- No analytical verification of cleaning of the EPDM product contact surfaces of the IBC had been performed. No study data was available to support this approach.
- The company stated that they did not perform analytical cleaning verification for product contact seals removed from process equipment which underwent manual cleaning. The company stated that they performed visual inspection only. Justification for this approach was not available.

A deficiency relating to cleaning practices capturing these issues is detailed in the deficiency section of this report.

Quality Control

QC Laboratory Inspection:

The QC laboratory was located in Building 31. The lab was organised with a primary lab area which was open plan. The open plan area was segregated into nine working bays. The open plan was surrounded by office spaces, a balance room, waste area, glassware washing area, and glassware store room. The layout and organisation of the QC laboratory was considered suitable.

The following aspects of the QC laboratory were inspected:

- Sample Receipt
- Weigh Balance calibration/verification
- High Performance Liquid Chromatography (HPLC)
- FTIR
- Reference Standards

Sample Receipt:

Samples were delivered to the QC lab by warehouse (Raw material) or Production (Finished product). Upon delivery samples were placed in the 'InQ' box and warehouse/production completed an entry in the respective logbook, recording the delivery of samples. Lab personnel then entered samples on LIMs and moved samples to the 'In Test' box. Samples were then scheduled for testing. Following testing samples were then placed into the 'For-Review' box. Following review of testing samples were moved to the sample disposal box and processed for destruction. It was noted that cold chain 17BB01 samples were placed directly in the QC lab fridge by warehouse/production personnel upon delivery to the lab. A review of the following sample receipt logbooks was performed:

- QC Finished Product Sample Receipt Logbook #3,
- QC In Process Control (IPC) QC-PROD-LOG-28,

In general the control of samples within the Hovione QC lab was considered suitable.

Weigh Balance Calibration/verification:
A review of the calibration/verification logbook for lab balance #12 was reviewed. The usage range of the balance was 20mg -200mg. The balance underwent a five point monthly calibration which included weights at the minimum and maximum limits of the balance operating range. The scales also underwent a one point daily verification using a 100mg weight. No issues were identified during review of the logbook for balance #12.

High Performance Liquid Chromatography (HPLC):
Analytical software Empower 3 was used at HE. An overview of the Empower 3 system was performed. The software had four access level: QC Analyst, Reviewer, Manager, and Administrator. It was noted that no lab personnel had administrator level access rights. No lab personnel had the capability to delete data. Empower data was backed up nightly onto the Hovione 'Empower Server', only IT had access to this server. During review of the Empower system it was noted that manual integration of peaks was allowed in circumstances defined in HQ.CO.SOP121.1.EN section 5.4.1.2.

[redacted]

(LIMS# 68507) were reviewed as part of this inspection. Sample preparation records were recorded as manual entries in the equipment logbook for HPLC#21. Samples were prepared and tested as per test method: HE. CR.LC4268.4.EN. A review of the sample preparation records and Empower records for sample 68507 against the test method was performed. No issues were identified.

Fourier-transform infrared spectroscopy (FTIR):
FTIR was used for identification testing at Hovione. FTIR-03 was Thermoscientific Nicolet iS10 Spectrometer. The spectrometer underwent monthly calibration. Access to the FTIR software-Omnic was password controlled. Access rights available on the Omnic software was similar to the Empower system, with Analyst, Reviewer, Manager and IT administrator profiles available. The company had installed 'Deskman' computer software to prevent the deletion of FTIR software. An overview of FTIR analysis was performed. It was noted that operators were required to overlay 'reference spectra' on

sample spectra to ensure conformity. The company stated that depending on the product/customer that critical peak maxima were sometimes identified for some test methods while, for others they were not. A point for clarification is detailed relating to the nonstandard methods for reviewing FTIR spectra.

Reference Standards:

[redacted]

Laboratory Events/Investigations:

Laboratory Events and investigations were recorded and managed as part of the deviations management system as described in 'deviation management' section of this report. A list of QC deviations raised since the last inspection was reviewed and a number of records selected. Trends relating to; delays in Stability sampling/testing, lab calibration issues and the presence of contamination/unknown peaks were observed.

The following laboratory events were reviewed as part of this inspection:

- [redacted]
- [redacted]
- 58143: PIP05 Failed as found calibration in lab
- 59656: Suspected OOS Assay results obtained for RM.0109822.HE00005/HE00006,
- 60900: Atypical Spectrum was discovered upon analysis of the sample and viewing the resulting spectrum on the OMNIC FTIR software,
- 62256: Incorrect Monthly Calibration on BAL 17 (XPE205),

In relation to recurrent laboratory events relating stability testing issues, the company provided evidence that a CAPA was underway at the time of the inspection relating to a corporate re-structuring and the establishment of a corporate stability team with responsibility to coordinate stability testing programs. A site stability coordinator which liaised with the corporate stability entity had also been introduced. At the time of the inspection the company was only in the process of transferring stability programs to the corporate entity. HE stated they expect the transfer process to be completed and new stability system to be fully operational by end of 2019.

No issues were identified from the laboratory records reviewed.

Outsourced Activities

Management of outsourced activities was inspected and is included in the sections entitled *Supplier Qualification* and *Implementation of CAPAs from previous inspections.*

[redacted]

company presented a summary document, a copy of which was obtained for the file. The investigation had been recorded under deviation #53646, a copy of which had been previously provided to the HPRA. The potentially impacted systems had been identified in the period from 2009 – 2016 and the impact of the irregularities had been assessed for each system. No issues had been identified which would lead to an incorrect result being generated. The CAPAs identified had been completed. [redacted]

Complaints, Quality Defects and Product Recalls

Complaints

The listing of complaints raised in the period since the last HPRA inspection was reviewed as were the records related to the following complaint investigations – #44153, #46084, #49279, #54369 and #59840. The records reviewed were in general considered to be satisfactory.

[redacted]

the customer for trial use. Validation of the intermediates stages for this API was underway at the site at the time of the inspection. The complaint records related to this API were not reviewed during the inspection.

[redacted]

was indicated that the nylon particles may have originated from bag ties; the entry of the pieces of bag tie to the API at the Cork site had been concluded by the site team to be low risk and the potential that it may have entered the product at the formulation site was also considered.

[redacted]

#7549 and that the process train had been cleaned prior to restarting the process. The investigation had concluded that the material was inert, would not react with product and the material was of food grade. This certification was not reviewed during the inspection.

[redacted]

Quality Defects

[redacted]

provide an explanation for the increased levels observed on stability, taking into consideration the potential impact for those batches for which the impurity was found to be OOS during stability analysis and within specification at the time of release.

Correspondence between the company and the Market Compliance section of the HPRA had been ongoing in the period since the May 2015 inspection with the most recent update provided on the 7th December 2017. Follow up was conducted during this inspection to obtain a status update regarding the status at the time of the inspection. The company provided a summary document, a copy of which was obtained for the file. The summary indicated the following:-

[redacted]

Recalls

It was stated that no recalls had occurred. The recall procedure was not reviewed.

Self Inspection

Self inspection plans for 2015, 2016 and 2017 and the associated procedure, SOP HQ.DQ.SOP098.7.EN, 28.03.2017, were reviewed and were considered to be satisfactory. Evidence of completion of inspections in line with the plans were presented. Audits of the contractor management system were included on the plans and had been executed on the 15.01.2018, 24.06.2016 and the 11.01.2016

Distribution and Shipment
Not reviewed during this inspection

Questions Relating to the Assessment of a Marketing Authorisation
N/A

Other specific issues identified
N/A

[redacted]

Miscellaneous
N/A

Annexes Attached
None

List of Deficiencies

I Critical Deficiency

None were identified during the inspection

II Major Deficiency

Pharmaceutical Quality System

1. Investigations, records and CAPAs related to deviations were deficient as evidenced by the following examples:-
   1.1. In relation to deviation #52127 which concerned data integrity issues in 2016 involving a contracted calibration service engineer:-
      1.1.1. No formal risk assessment had been conducted;
      1.1.2. The listing of [redacted] equipment within the scope of the deviation had not been recorded or attached;
      1.1.3. The Delta V trends related to the March 2016 calibrations were not reviewed until September 2016 (*It was noted that a commitment had been provided following a previous HPRA inspection in April 2015 that Delta V trends would be attached to calibration certificates for equipment connected to the Delta V system at the time of review. The company stated that the earlier CAPA had not incorporated the weighing scales as this equipment had not been implicated in the previous DI breach investigated in 2014*);
      The risk assessment conducted on the calibration procedure to identify and mitigate against risks of falsification in response to the HPRA inspection in April 2015 had excluded calibration service providers related to [redacted] (& other equipment) without appropriate justification. It was observed that the risk assessment conducted was not 'formal' in the sense that no standard process/format/risk management tools had been executed;
      1.1.4. An action to incorporate a requirement for the printing of the Delta V trends for the weighing scales connected to this system had not been identified as part of this investigation; the action had been identified in December 2017 and its implementation remained outstanding at the time of the inspection;
      1.1.5. There were no provisions in procedure SOP HE.DQ.SOP168.5.EN for oversight of calibrations integrity by the sites management for production and warehouse weighing instruments;
      1.1.6. Records of attendance at cGMP induction training or refresher cGMP training were not available for the concerned engineer (*The company stated that the induction training record could not be located during the inspection and that it may have been removed from the persons file at some time during the investigation*);
      1.1.7. Instructions related to the requirement for provision of refresher cGMP training modules to contractors implemented in December 2017 were unclear as it could not be determined from the matrix which modules were required for the contractors and at what frequency (i.e.COP007_A3.3EN);

1.2. In relation to deviation #62943 concerning incorrect user login on QC pH Meter pH10; this was the third occurrence of this deviation and the first time a CAPA was proposed. No immediate action for correction of the raw data printout was recorded or implemented. The preventative action proposed to put in place more visual signage in the location of pH meters was not considered a robust solution as signage had previously been in place and had proven not to be effective.

1.3. [redacted] process, routinely charged volume 12,392 litres), it was stated that the calibration errors were observed only at volumes below 3000 litres and therefore did not impact on the routine operations; however, no calibration checks above 3000 litres had been conducted. The CAPA required a WO to be raised for re-calibration up to maximum of 12,000 litres before 2 March 2018. This approach was not considered justified, it was not known why calibration volumes were not reflective of routine operations and when discovered, why calibration at the routine volume had not been verified.

1.4. [redacted] residue in B10 due to interference in the blank swab prior to analysis of the original swab samples; the minimal quality impact concluded as a result of test results from repeat swabs was not considered justified as the re-swabs may not have accurately reflected the state of cleanliness of the equipment as the initial swabs may have removed any residues present.

1.5. In relation to deviation #61941 raised in September 2017 which concerned foreign matter contamination of API originating from tie wraps, the lengthy timeframe of 17 Feb 2018 proposed for completion of CAPA 61264 to implement a reconciliation document for full tie wraps to be accounted for was not considered justified. In addition, guidance related to criteria to be used in proposing CAPA completion dates was not provided for under the quality system.

Reference: GMP Guide, Part 1, Chapter 1, Principle & Paragraphs 1.4 (xiv), 1.8 (vii), 1.9 (iv); Chapter 7, Principle & Paragraph 7.7

III Other Deficiency

Pharmaceutical Quality System

1. Requirements regarding the application of formal quality risk management tools to certain aspects of the quality system were not documented under the relevant system procedures, e.g. deviation management, change management, complaint management.

Reference: GMP Guide, Part 1, Chapter 1, Principle & Paragraphs 1.3, 1.4 (xiv); Annex 15, Paragraph 11.4; Chapter 8, Principle & Paragraphs 8.10, 8.13

2. The cancellation of PdA 6519 which related to the B10 SDD BMS proposal to connect to Delta V for the purpose of monitoring trends, alarms and events related to environmental parameters of B10 rooms was not considered justified and the action which was still a requirement, was not documented in any other aspect of the sites quality system.

Reference: GMP Guide, Part 1, Annex 15, Principle & Paragraph 11.1

3. PQR HE.QSR.AR221.1.EN was considered deficient in that:
   3.1. [redacted]
   3.2. [redacted]
   3.3. The content of the validations and qualification section of the report was not accurate as it stated 'No improvements and/or actions were deemed necessary to maintain the validation status for the time period covered in this PQR. This conflicted with Event 49360 which concluded that current validated process was not robust with respect to [redacted] 51429 was open to assess the suitability of parameters relating to [redacted].
   3.4. The content of the 'Conclusion' section of this PQR was not accurate in that it states: 'The statistical analysis of the QC test results within this PQR was created to address the statistical control of th[redacted] process. The contents of analysis confirms the [redacted] batches are in statistical control.'

Reference EU GMP Guide Part 2: Section 2.19, 2.60 & 2.61

Personnel

4. In relation to gowning and hygiene practices:-
   4.1. There were no instructions under the quality system for personnel to use hand-washing facilities (e.g. prior to sampling and dispensing operations and other operations conducted in clean rooms). It was noted that hand washing facilities were not installed in the warehouse building and that the facilities installed in the B01 clean room personnel entry lobby had been disconnected from the water supply; the facilities were not labelled as out of use. In the personnel exit lobby of B01, the hand washing facilities remained connected to the water supply; these facilities were not used in practice according to the company personnel;
   4.2. Gowning requirements were not displayed in the personnel entry gowning lobby in B01 as was indicated was a company requirement. It appeared that the SOP had recently been updated and the display version had not been issued.
   4.3. In the personnel exit lobby in B01:-
      4.3.1. There was no lighting installed;
      4.3.2. A spare door was present in the area and appeared to have remained there for a number of months;
      4.3.3. An empty mauser/drum was present for which there was no explanation

(*It is acknowledged that the company initiated an investigation relating to the above findings during the inspection and presented a CAPA plan on the last day of the inspection*)

Reference: GMP Guide, Part 1, Chapter 2, Paragraphs 2.15, 2.19, 2.21

Premises and Equipment

5. The following deficiencies were observed during the site tour:
   5.1. Waste flow was not reflected on Drawing 01-A-004, issue 03, for ground floor B01.
   5.2. The Blank/Lid of the Spray Dryer lance connection was observed to be left resting on a walkway on top of the spray dryer. This was not considered an appropriate place for storing the blank.
   5.3. The Internal light of the spray dryer was not operational at the time of the inspection. The light was required to allow operators to check the spray consistency during change of line.
   5.4. The roof access panel to non-GMP void space was open in Room R309 at the time of the inspection. The room was in clean state following cleaning. (Noted: This was addressed during the course of the inspection.)
   5.5. [redacted] to be peeling.
   5.6. The interlock on entry to GMP area of building 4 was not operating as defined at the time of the inspection.
   5.7. The maximum storage height in the cold chain refrigerator FR-23-05-1000 was not defined.
   5.8. In relation to the sampling booth, there was no requirement to check all gauges were reading in the green zone prior to conducting sampling operations. It was noted at the time of inspection that the supply HEPA filter gauge was reading in the red zone.
   5.9. Maintenance activities with respect to HEPA filtered air handling system were considered deficient in that:
      5.9.1. There was no risk assessment which demonstrated that once yearly review of HEPA filter performance was frequent enough and a suitable level of monitoring for HEPA filters.
      5.9.2. No minimum differential pressure across HEPA filters was defined. During the site tour it was noted that the Magnahelic HEPA filter differential pressure gauges indicated that a differential pressure of 0Pa was acceptable (Green).

Reference EU GMP Guide Part 1: Chapter 3 Principle and Sections 3.1, 3.2, 3.19, 3.34, 3.36, Chapter 5, Paragraph 5.21

6. Cleaning Practices were considered deficient in that:
   6.1. The company had not implemented the 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'.
      6.1.1. The acceptable residue limit calculated for the MACO calculations reviewed for Product [redacted] using 10ppm method and not based on toxicological data.
      6.1.2. The company stated that currently toxicology data was not used to perform MACO calculations, MACO calculations defaulted to the 10ppm method. This was not considered suitable.
   6.2. The selection of worst case swab locations for cleaning verification detailed in HE.CLD.VP1130-A54.1.EN was considered deficient in that:
      6.2.1. No formalised risk assessment process was performed to identify the worst case locations.
      6.2.2. The selection of the top of the IBC based on it 'being easy to reach' was not considered suitable. The assessment did not assess the material height in the IBC, if area swabbed would come in contact with material.

6.2.3. The rationale for swabbing only the smooth stainless steel surface of the cone valve and not the ridged areas i.e. between the EPDM and Stainless steel materials on the cone valve was not available.

6.2.4. No analytical verification of cleaning of the EPDM product contact surfaces of the IBC had been performed. No study data was available to support this approach.

6.2.5. It was stated by the company that they only performed visual inspection verification for seals that are removed from processing equipment and undergo manual cleaning. No analytical verification was routinely performed and no study had been performed to support this approach.

6.3. During review of recovery study QSR.CR172 and document of TBALGERALHE.54 it was noted [redacted] material only. There was no justification for this as other product contact materials such as such as EPDM were present in the equipment train.

Reference EU GMP Guide Chapter 5 section 5.19Annex 15 section 10.1, 10.5, 10.6, 10.11, 10.12, 10.15

7. In relation to the Delta V upgrade:-

7.1. Corporate Automation Strategy – Annex A1 – Systems Inventory and Risk Assessment – (HQ.QSD.IMP059-A1.0.EN) was not current at the time of approval on the 03.12.2015 and was not subjected to periodic review (the versions of software to which it related were not indicated and not accurately reflected);

7.2. The HE Automation Upgrade plan 2016 – 2020 was not documented under the quality system, e.g. no change control was captured in the quality system for phase 2 of the upgrade which was outstanding at the time of inspection;

7.3. B01 Delta V automation system v8 to v12 migration performance qualification report (HE:QSR:EQ434.0.EN) did not include any records as evidence of what constituted the incident/deviation review actually conducted in support of statements that no related incidents/deviations had been raised in the period.

Reference: GMP Guide, Part 1, Annex 11, Paragraphs 1, 11

8. Processes related to the temperature monitoring of the cold stores were deficient for the following reasons:

8.1. Temperature excursions were permitted up to 10^0C for 30 minute durations, for which no rationale was available at the time of inspection;

8.2. The logbook containing records of daily temperature monitoring checks as required by procedure IOP41 had not been completed since December 2017;

8.3. There were anomalies between procedure IOP41 and the DCS system relating to alarm icons; the procedure indicated that red flashing icons were triggered at 1.4^0C and 8.5^0C; however at the time of inspection a red flashing icon on the DCS screen appeared to be triggered by a reading of 3.4^0C;

8.4. The annual trend summary reports for the period 2017 were not available;

8.5. The annual trend summary reports for the period 2016 had been approved in December 2017. The reports did not include any discussion related to excursions which had occurred or any reference to any deviations, incidents etc. in the period;

8.6. Instructions/guidance related to generation and content of the annual trend reports including timeframes for completion were not captured under the quality system;

8.7. In relation to cold store FR 23-05-3000, it was observed from the trends that the storage condition had changed in September 2016 from $15^0C/25^0C$ to 5^0C for which there was no explanation documented nor a reference to a change control. In addition, the trend data had been calculated using the mean of both data sets.

Reference: GMP Guide, Part 1, Chapter 3, Principle & Paragraph 3.19

Quality Control

9. [redacted] was noted that USP monograph for [redacted] primary (against which the secondary standard was qualified) stated that [redacted] reference standards were for single use unless justified for multiple use by the company.

Reference EU GMP Guide Part 1: Chapter 6 Section 6.20

IV Points for Clarification

1. The company is requested to provide an update regarding its plans for transfer of temperature/humidity monitoring from the BMS to the Delta V system.
2. [redacted] requirement for monitoring of relative humidity levels in the storage area. It was noted that batch HE00059 in the shipment preparation area had been manufactured in March 2016 so had been in storage at the site for almost 2 years. It was stated that a study had been performed in this regard. Please forward a copy of the study report with the response to the inspection.
3. The company is asked to provide justification for not establishing critical peak maxima for all FTIR test methods.

V Points to Note

1. Requirements regarding notification of significant deviations identified internally by contracted service providers relating to services provided to Hovione, should be captured within the Hovione contractor/supplier management procedures and corresponding quality agreement templates.
2. The company was reminded of the Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use (2015/C 95/02) and informed that assessments/responsibilities in this regard should be documented under the quality system.

Recommendations

N/A

Summary and conclusions

The inspection will be concluded following receipt and approval of proposals/corrective actions and target dates for completion of the above deficiencies. Renewed GMP certificates will be issued to the company on receipt of a satisfactory response to this inspection report.

Signature of Inspector: _____ **Date:** _____

Richard O'Sullivan
GMP Inspector, HPRA

Signature of Inspector: _____ **Date:** _____

Catherine Neary
GMP Inspector, HPRA

Organisation: Hovione Limited, Loughbeg, Ringaskiddy, Cork, Ireland

Distribution: Hovione Limited, Loughbeg, Ringaskiddy, Cork, Ireland
Health Products Regulatory Authority

ANNEX 1 DEFINITION OF SIGNIFICANT DEFICIENCIES
(Reference: Compilation of Community Procedures on Inspections and Exchange of Information)

1 Critical deficiency

A deficiency which has produced, or leads to a significant risk of producing, either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

2 Major deficiency

A non-critical deficiency:
which has produced or may produce a product, which does not comply with its marketing authorisation;
or
which indicates a major deviation from EU Good Manufacturing Practice;
or
(within EU) which indicates a major deviation from the terms of the manufacturing authorisation;
or
which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;
or
a combination of several 'other' deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

3 Other deficiency

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.
(A deficiency may be 'other' either because it is judged as minor, or because there is insufficient information to classify it as a major or critical).

Annexes
None